

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

**PETITION FOR POST-GRANT REVIEW
UNDER 35 U.S.C. §§ 321-329 AND 37 C.F.R. § 42.1 et seq**

TABLE OF CONTENTS

I.	INTRODUCTION	1
II.	MANDATORY NOTICES UNDER 37 C.F.R. § 42.8.....	6
	A. Real Party-In-Interest	6
	B. Related Matters.....	6
	1. United States Patent & Trademark Office	6
	2. United States Patent Trial and Appeal Board	7
	C. Lead and Back-up Counsel and Service Information.....	7
III.	REQUIREMENTS FOR POST-GRANT REVIEW	8
	A. Grounds for Standing	8
	B. Identification of Challenge	8
	1. The '109 Patent is Eligible for PGR	9
	2. Statutory Grounds on Which the Challenge is Based	12
IV.	BACKGROUND	12
	A. Technology of the '109 Patent	12
	B. The Challenged Claims	14
	C. The Prosecution History of the '109 Patent	14
V.	THE BOARD SHOULD NOT EXERCISE ITS DISCRETION TO DENY INSTITUTION.	17
	A. There Is No Basis for Discretionary Denial Under 35 U.S.C. § 325(d).....	17
	1. The § 112 Written Description Arguments in Ground 1 Are Not the Same Or Substantially the Same as Arguments Considered During Prosecution.....	18
	2. The § 112 Enablement Arguments in Ground 2 Are Not the Same Or Substantially the Same As Arguments Considered During Prosecution.....	19
	3. The Anticipation Argument in Ground 3 Is Not the Same or Substantially the Same As Any Argument Considered During Prosecution.	20

B. There Is No Basis for Discretionary Denial Under 35 U.S.C. § 324(a).....	22
VI. LEVEL OF ORDINARY SKILL IN THE ART	22
VII. CLAIM INTERPRETATION	22
VIII. GROUND 1: Claims 1-10 are UNPATENTABLE for failing to meet the written description requirement.	23
A. The Written Description Inquiry Asks Whether An Inventor Possessed the Full Scope of the Claims As of the Claimed Effective Filing Date.	23
B. As of December 10, 2013, The '109 Patent Inventors Did Not Possess The Full Scope of the Methods of Challenged Claim 1.....	25
1. Challenged Claims 1 and 10 Define a Genus of Endotoxin Assay Agents and Methods For Making the Same That Broadly Cover 3,456 Possible Options.	25
2. The '767 Application Does Not Describe a Single Species or Example Within The Genus of Claim 1 or Claim 10.....	29
3. The '767 Application Provides No Identification of Structural Features Common to the 3,456 Members of the Claimed Genus.	33
C. As of December 10, 2013, the '109 Patent Inventors Did Not Possess The Full Scope of the Methods of Challenged Dependent Claims 2-9.....	36
IX. GROUND 2: Claims 1-10 are UNPATENTABLE for failing to meet the enablement requirement of § 112(A).....	38
A. The '767 Application Fails To Explain How A POSA Could Make and Use The Thousands of Possible Combinations of Recited Components, Assembled Into the Claimed Assay, Without Undue Experimentation.....	38
1. Legal Standard for Enablement.....	38
2. Wands Factor Analysis.....	40
B. Claim 10 is Not Enabled For The Same Reasons as Claim 1.	54
C. None of Challenged Claims 2-9 Are Enabled by the Disclosure of the '767 Application.	55
1. Claims 2 and 3	56

2. Claim 4	57
3. Claims 5-9	58
X. GROUND 3: The '629 publication anticipates claims 1-10 of the '109 patent.....	60
A. The '629 Publication Is Prior Art To The Challenged Claims As Those Claims Are Not Entitled To An Effective Filing Date Earlier Than The Actual Filing Date of the '109 Patent (July 3, 2023).....	61
B. The '629 Publication Anticipates Challenged Claim 1.....	61
1. [1PRE.A] “A method for producing an endotoxin assay agent”	61
2. [1PRE.B] “comprising a horseshoe crab Factor C, a horseshoe crab Factor B, and a horseshoe crab Pro-clotting enzyme, the method comprising”	62
3. [1A] “expressing the horseshoe crab Factor C in a Chinese Hamster Ovary cell or a Human Embryonic Kidney cell as a host cell,”	62
4. [1B] “secreting the horseshoe crab Factor C into an extracellular culture supernatant,”	63
5. [1C] “and recovering the horseshoe crab Factor C in the culture supernatant,”	64
6. [1D] “wherein the recovered horseshoe Factor C has activity of Factor C, and”	65
7. [1E] “wherein the horseshoe crab Factor C is a <i>Tachypleus tridentatus</i> Factor C or a <i>Limulus polyphemus</i> Factor C,”	66
8. [1F] “expressing the horseshoe crab Factor B having activity of Factor B in a mammalian cell as a host cell”	67
9. [1G] “expressing the horseshoe crab Pro-clotting enzyme having activity of Pro-clotting enzyme in a mammalian cell as a host cell, and”	68
10. [1H] “producing an endotoxin assay agent comprising the horseshoe crab Factor C, the horseshoe crab Factor B, and the horseshoe crab Pro-clotting enzyme,”	69
11. [1I] “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.”	70
C. The ’629 Publication Discloses Every Limitation of Independent Claim 10.	71
1. [10PRE] “A method for measuring endotoxin in a test specimen”	71
2. The ’629 Publication Discloses Limitations [10A]-[10H] and [10K] For The Same Reasons Discussed Above Regarding Limitations [1A]-[1I].....	72
3. The ’629 Publication Discloses Limitations [10I] and [10J]	73
D. The ’629 Publication Discloses Every Limitation of Challenged Claims 2-10.....	75
1. Claim 2	75
2. Claim 3	76
3. Claim 4	77
4. Claim 5	77
5. Claim 6	80
6. Claim 7	82
7. Claim 8	82
8. Claim 9	83
E. The ’629 Publication Is Enabled	84
XI. CONCLUSION.....	86
APPENDIX A: CLAIM LISTING	87

TABLE OF AUTHORITIES

CASES

<i>Advanced Bionics, LLC v. Med-El Elektromedizinische Gerate GMBH</i> , IPR2019-01469, Paper 6 (PTAB Feb. 13, 2020)	17
<i>ALZA Corp. v. Andrx Pharms., LLC</i> , 603 F.3d 935 (Fed. Cir. 2010)	45
<i>Amgen Inc. v. Sanofi</i> , 598 U.S. 594 (2023)	40, 41, 45
<i>Amgen Inc. v. Sanofi, Aventisub LLC</i> , 987 F.3d 1080 (Fed. Cir. 2021)	41
<i>Apple Inc. v. Fintiv, Inc.</i> , IPR2020-00019, Paper 11 (PTAB Mar. 20, 2020)	22
<i>Apple v. MPH Technologies Oy</i> , IPR2019-00819, Paper 10 (PTAB Sept. 27, 2019)	22
<i>Ariad Pharms., Inc. v. Eli Lilly & Co.</i> , 598 F.3d 1336 (Fed. Cir. 2010)	passim
<i>Biogen Int’l GMBH v. Mylan Pharms. Inc.</i> , 18 F.4th 1333 (Fed. Cir. 2021)	24
<i>Boston Sci. Corp. v. Johnson & Johnson Inc.</i> , 647 F.3d 1353 (Fed. Cir. 2011)	30, 35
<i>Carnegie Mellon University v. Hoffmann-La Roche, Inc.</i> , 541 F.3d 1115 (Fed. Cir. 2008)	30
<i>Cellco P’ship v. Huawei Device Co.</i> , IPR2020-01117, Paper 10 (PTAB Feb. 3, 2021)	21, 22
<i>Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.</i> , 800 F.3d 1375 (Fed. Cir. 2015)	85
<i>Enzo Life Scis., Inc. v. Roche Molecular Sys., Inc.</i> , 928 F.3d 1340 (Fed. Cir. 2019)	47

<i>Genentech Inc. v. Novo Nordisk A/S</i> , 108 F.3d 1361 (Fed. Cir. 1997)	39
<i>Idenix Pharms. LLC v. Gilead Scis. Inc.</i> , 941 F.3d 1149 (Fed. Cir. 2019)	46
<i>Impax Labs., Inc. v. Aventis Pharms., Inc.</i> , 545 F.3d 1312 (Fed. Cir. 2008)	84
<i>In re Antor Media Corp.</i> , 689 F.3d 1282 (Fed. Cir. 2012)	84, 85
<i>In re Gleave</i> , 560 F.3d 1331 (Fed. Cir. 2009)	85
<i>In re Wands</i> , 858 F.2d 731 (Fed. Cir. 1988)	39
<i>In re Wertheim</i> , 541 F.2d 257, (C.C.P.A. 1976)	23
<i>Inari Agriculture, Inc. v. Pioneer Hi-Bred Int’l, Inc.</i> , PGR2023-00022, Paper 50 (PTAB Oct. 10, 2024)	54
<i>Juno Therapeutics, Inc. v. Kite Pharma, Inc.</i> , 10 F.4th 1330 (Fed. Cir. 2021)	24
<i>Lifescan Global Corp. v. Ikeda Food Rsch. Co.</i> , PGR2019-00032, Paper 11 (PTAB Aug. 15, 2019)	19
<i>Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.</i> , 868 F.3d 1013 (Fed. Cir. 2017)	23
<i>Nrg Energy, Inc. v. Midwest Energy Emissions Corp.</i> , IPR2020-00832, 2020 WL 6277239, (PTAB Oct. 26, 2020)	21
<i>Pfizer, Inc. v. Genentech, Inc.</i> , IPR2017-02019, Paper 16 (PTAB Feb. 12, 2018)	84
<i>Phillips v. AWH Corp.</i> , 415 F.3d 1303 (Fed. Cir. 2005)	23

<i>Puma North America v. Nike</i> , IPR2019-01058, Paper 10 (PTAB Oct. 31, 2019).....	22
<i>Samsung Elecs. Co. v. Queen’s Univ. at Kingston</i> , IPR2015-00584, Paper 53 (PTAB July 27, 2016).....	84, 85
<i>Schering Corp. v. Geneva Pharms.</i> , 339 F.3d 1373 (Fed. Cir. 2003)	80
<i>Schul Int’l Co., LLC v. Emseal Joints Sys., Ltd.</i> , PGR2018-00034, Paper 7 (PTAB Aug. 22, 2018).....	11
<i>Sitrick v. Dreamworks, LLC</i> , 516 F.3d 993 (Fed. Cir. 2008)	39
<i>SmithKline Beecham Corp. v. Apotex Corp.</i> , 403 F.3d 1331 (Fed. Cir. 2005)	79
<i>The Gillette Company LLC v. Sphere USA, LLC</i> , PGR2022-00030, Paper 8 (PTAB Sept. 23, 2022).....	21
<i>University Of Rochester v. G.D. Searle & Co.</i> , 358 F.3d 916 (Fed. Cir. 2004)	33
<i>US Endodontics, LLC v. Gold Standard Instruments, LLC</i> , PGR2015-00019, Paper 54 (PTAB Dec. 28, 2016)	11
<i>Wedeco UV Techs., Inc. v. Calgon Carbon Corp.</i> , No. 01-924 (JAG), 2006 WL 1867201 (D.N.J. 2006)	79
<i>Wedeco UV Techs., Inc. v. Calgon Carbon Corp.</i> , 223 F. App’x 982 (Fed. Cir. 2007).....	79
<i>Wyeth & Cordis Corps. v. Abbott Lab’ys</i> , 720 F.3d 1380 (Fed. Cir. 2013)	39, 47

STATUTES

35 U.S.C. § 102(a)	61
35 U.S.C. § 102(b)	61
35 U.S.C. § 112	passim

35 U.S.C. § 112(a)	39
35 U.S.C. § 282(b)	23
35 U.S.C. § 324(a)	22
35 U.S.C. § 325(d)	17, 19, 20, 22

REGULATIONS

37 C.F.R. § 42.200(b)	23
37 C.F.R. § 42.204(a).....	8
37 C.F.R. § 42.204(b)	8, 12
37 C.F.R. § 42.8(b)(1).....	6

OTHER AUTHORITIES

Patent Trial and Appeal Board Rules of Practice for Briefing Discretionary Denial Issues, and Rules for 325(d) Considerations, Instituting Parallel and Serial Petitions, and Termination Due to Settlement Agreement, 89 Fed. Reg. 28693 (April 19, 2024)	18
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APPENDIX LISTING OF EXHIBITS

Exhibit	Description
1001	U.S. Patent No. 11,959,109
1002	Prosecution History of U.S. Patent No. 11,959,109 (Application No. 18/346,420)
1003	Declaration of Siddhartha Jain, Ph.D., PMP (“Jain”)
1004	Curriculum Vitae of Dr. Siddhartha Jain, Ph.D., PMP
1005	International Patent Publication No. WO 2018/074498 A1
1006	Higdon et al., “Modeling sequence and function similarity between proteins for protein functional annotation,” <i>Proc Int Symp High Perform Distrib Comput.</i> 2010: 499–502.
1007	Kobayashi et al., “Factor B Is the Second Lipopolysaccharide-binding Protease Zymogen in the Horseshoe Crab Coagulation Cascade,” <i>J Biol Chem.</i> 2015 Jun 24; 290(31):19379–19386.
1008	Japanese Priority Application No. JP2012-269840 (certified translation)
1009	U.S. Patent No. 5,716,834
1010	Muta et al., “Limulus Factor C. An endotoxin-sensitive serine protease zymogen with a mosaic structure of complement-like, epidermal growth factor-like, and lectin-like domains,” <i>J Biol Chem.</i> 1991 Apr 5; 266(10):6554-61.
1011	Karen McClymont, Ph.D. Thesis, submitted in fulfilment of the requirements for the Degree of Doctor of Philosophy from the University of Glasgow, Institute of Molecular, Cell and Systems Biology College of Medical, Veterinary and Life Sciences, March, 2017
1012	U.S. Patent Application Publication No. 2021/0363564
1013	Declaration of Dr. Mary K. Bolin
1014	RESERVED
1015	U.S. Patent Application Publication No. 2019/0241629
1016	U.S. Patent Application Publication No. 2015/0307864
1017	U.S. Patent Application No. 14/650,767, as filed June 9, 2015
1018	RESERVED
1019	Shi et al., “Protein N-Glycosylation in the Baculovirus-Insect Cell System,” <i>Curr Drug Targets.</i> 2007 Oct; 8(10): 1116–1125.
1020	RESERVED
1021	RESERVED
1022	Transition Certification for U.S. Patent Application No. 15/983,725, filed May 31, 2019.

1023	RESERVED
1024	RESERVED
1025	Tokunaga, F., et al. "Further studies on lipopolysaccharide-sensitive serine protease zymogen (Factor C): Its isolation from <i>Limulus polyphemus</i> hemocytes and identification as an intracellular zymogen activated by α -chymotrypsin, not by trypsin," <i>J. Biochem.</i> 1991 Jan; 109(1):150-7.
1026	Dwarakanath, R.S. et al., "Recombinant COS-1 cells express <i>Carcinoscorpius rotundicuada</i> Factor C," <i>Biotechnology Letters.</i> 1997 April; 19(4):357-61.
1027	Wang, J. et al., "Functional expression of full length <i>Limulus</i> Factor C in stably transformed Sf9 cells," <i>Biotechnology Letters.</i> 2001; 23:71-76.
1028	RESERVED
1029	RESERVED
1030	Barrabes, S. et al., "Effect of sialic acid content on glycoprotein p/ analyzed by two-dimensional electrophoresis," <i>Electrophoresis.</i> 2010 Sep; 31(17):2903-12.
1031	Palomares, L.A., "Production of Recombinant Proteins: Challenges and Solutions," From: <i>Methods in Molecular Biology</i> , vol. 267: <i>Recombinant Gene Expression: Reviews and Protocols</i> , Second Edition Edited by: P. Balbás and A. Lorence © 2004 Humana Press Inc., Totowa, NJ, pp. 15-51.
1032	RESERVED
1033	RESERVED
1034	RESERVED
1035	RESERVED
1036	RESERVED
1037	RESERVED
1038	Sekiguchi, K. and Shuster, C.N., "Limits on the Global Distribution of Horseshoe Crabs (<i>Limulacea</i>): Lessons Learned from Two Lifetimes of Observations: Asia and America," <i>Biology and Conservation of Horseshoe Crabs</i> , 2009.
1039	Hossler et al., "Optimal and consistent protein glycosylation in mammalian cell culture," <i>Glycobiology.</i> 2009 Sep; 19(9):936-4.
1040	File History of United States Application No. 16/399,386
1041	ExpiCHO™ Expression System - USER GUIDE – For transfection of ExpiCHO-S™ in a defined, serum-free medium. Catalog Number A29133, Publication Number MAN0014337 Revision D.0 (May 25, 2018).

I. INTRODUCTION

Charles River Laboratories, Inc. (“Petitioner”) respectfully requests Post-Grant Review (“PGR”) and cancellation of claims 1-10 (the “challenged claims”) of U.S. Patent No. 11,959,109 (“the ’109 patent”) (EX1001) in accordance with §§ 321-329 and § 42.200 et seq.¹

The ’109 patent relates to methods of testing—and methods of making assays to test—for the presence of biologically harmful substances (endotoxins) that contaminate medical products. The claims of the ’109 patent recite methods for producing an endotoxin detection assay by recombinantly generating three proteins—recombinant Factor C, recombinant Factor B, and recombinant Pro-clotting enzyme (known as “zymogen proteins”)—which are otherwise naturally found in the hemolymph (blood) of horseshoe crabs and which naturally undergo a clotting cascade reaction when combined together in the presence of endotoxin. “Recombinant” protein production involves using the genetic information for a particular protein (either the gene sequence or the amino acid sequence of that protein), and “programming” a host cell with this information such that the host cell produces (or expresses) the protein *in vitro* (in a lab).

¹ Section cites are to 35 U.S.C. or 37 C.F.R. as context indicates, and all emphasis and annotations are added unless otherwise noted.

Ground 1 of this Petition demonstrates that claims 1-10 are not adequately described as required by 35 U.S.C. § 112. Each of these claims defines a genus of endotoxin detection assays and methods for making the same requiring the recombinant production of all three of Factor C, Factor B, and Pro-clotting enzyme and their assembly into a functioning enzymatic cascade to detect endotoxin. The challenged claims require all three proteins but allow for a series of options with respect to how such recombinant proteins are produced, including (1) the species of horseshoe crab from which genetic and protein information is sourced, (2) the recombinant expression system to be used, and (3) the means for recovering the recombinant proteins once produced. The challenged claims also allow for each of these three components to be produced from different expression systems or using different species of horseshoe crab and combined together to produce the resulting assay. Conservatively, and in view of the limitations set forth in challenged claim 1, these claims cover a genus of 3,456 different options for making the claimed assay. The disclosure to which the '109 patent claims priority (the representative "'767 Application"), however, does not describe a single example of such an assembled assay or any method for making the same. This is because, for example, while the challenged claims require that Factor B and Pro-clotting enzyme be expressed "in a mammalian cell as a host cell" the '767 Application *only* describes the recombinant production of these proteins in insect cell (Sf9) systems. The '767

Application provides no disclosure or guidance of common structural features or any explanation recognizable by a person of ordinary skill in the art (“POSA”) for why these thousands of combinations of recombinant proteins can be assembled into a functional endotoxin detection assay using the same or different expression systems or the same or different species sequence information, as claimed. Because a sufficient description of a genus requires the specification to disclose “either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can ‘visualize or recognize’ the members of the genus” and because the ’767 Application discloses neither, challenged claims 1-10 are unpatentable for failure to satisfy the written description requirement. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1350 (Fed. Cir. 2010) (*en banc*).

Ground 2 of this Petition demonstrates that claims 1-10 are unpatentable because the full scope of those claims are not enabled as required by 35 U.S.C. § 112. As noted above, the challenged claims encompass a genus of at least 3,456 different combinations of recombinant proteins for producing an endotoxin assay or for measuring endotoxin. The ’767 Application, however, provides no guidance regarding how a POSA would make and use all of these possible recombinant protein components and combine them to generate a functioning assay for detecting endotoxin. In fact, while the challenged claims require that for all of the

claimed combinations, Factor B and Pro-clotting enzyme are recombinantly expressed in mammalian cell hosts, the '767 Application does not explain how to make or use recombinant Factor B or Pro-clotting enzyme from any mammalian cell line at all. Instead, the '767 Application only provides working examples of the claimed three-protein assay using Pro-clotting enzyme and Factor B from *insect* cells, which the '767 Application specifically *distinguishes* from the claimed mammalian cell lines. EX1017, 89-96.

Moreover, while the challenged claims recite that the host cells for expressing the three zymogen proteins “may be the same or different,” there is no guidance, instruction, or example in the '767 Application regarding how to make the claimed assay from proteins expressed by *different* mammalian cells. In order to do so a POSA would have to undertake significant experimentation to generate all three proteins in different mammalian cells (when the '767 Application doesn't even provide guidance on this for Factor B or Pro-clotting enzyme) and then work to ensure endotoxin detection function from a combination of proteins expressed in completely different mammalian cell lines, which rely on different biological mechanisms and follow from different experimental protocols.

The challenged claims also allow for the three zymogen proteins to be produced from the same or different horseshoe crab species sequence information and combined to produce an assay agent. Again, a POSA would be left with their

own undue experimentation to determine whether such mixing and matching of proteins across different species would work to detect endotoxin. Finally, while claiming methods of making endotoxin assay agents by recombinantly expressing zymogen proteins from the horseshoe crab *Limulus polyphemus*, the '767 Application did not enable a POSA to make such proteins as of the priority date of December 10, 2013 because, by the inventors' own admission, the gene and sequence information for such proteins from *Limulus polyphemus* was not yet known or disclosed. Instead, these inventors claimed as inventive recombinant *Limulus polyphemus* proteins and methods of using the same to detect endotoxin ***nearly four years later*** on October 18, 2017. As such, the experimentation required of a POSA to make and use the full scope of the claimed assay in view of this stark absence of guidance about how to generate and combine different recombinant components as claimed would be extraordinary and undue. The '767 Application fails to enable the full scope of challenged claim 1-10.

To the extent Patent Owner pivots from the priority claim of the '109 patent and argues that its specification as filed on July 3, 2023, in view of the advancement of the art over the preceding decade adequately describes and enables such claims, those claims are anticipated by intervening prior art such as U.S. Pat. Publication No. 2019/0241629 ("the '629 Publication") published on August 8, 2019 which describes the production (via a CHO expression system) of a

recombinant horseshoe crab three-factor composition including recombinant horseshoe crab factor C, recombinant horseshoe crab factor B, and recombinant horseshoe crab Pro-clotting enzyme for detection of endotoxin. **Ground 3** explains how the '629 Publication explicitly discloses each and every feature of, and therefore anticipates, the challenged claims of the '109 patent.

II. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8

A. Real Party-In-Interest

Pursuant to 37 C.F.R. § 42.8(b)(1), Petitioner identifies Charles River Laboratories, Inc. as the Real Party-in-Interest. No other party had access to or control over the present Petition, and no other party funded or participated in preparation of the present Petition.

B. Related Matters

A decision in this proceeding could affect or be affected by the following:

1. United States Patent & Trademark Office

Per the face of the '109 patent, the application from which it issued, U.S. Application No. 18/346,420, 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 (U.S. Patent No. 11,236,318), filed April 30, 2019, which is a Continuation of U.S. Patent Application No. 15/983,725 (U.S. Patent No. 10,982,202), filed May 18, 2018, which is a Continuation of U.S. Patent

Application No. 14/650,767 (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.

2. United States Patent Trial and Appeal Board

There are no proceedings before the PTAB that could affect or be affected
by a decision in this proceeding.

C. Lead and Back-up Counsel and Service Information

Lead Counsel	Scott A. McKeown, Reg. No. 42,866
Backup Counsel	Flora Luo, Reg. No. 78,667 Chelsea A. Loughran, pending admission <i>pro hac vice</i>
Service Information	<u>E-mail:</u> SMcKeown-PTAB@wolfgreenfield.com FLuo-PTAB@wolfgreenfield.com CLoughran-PTAB@wolfgreenfield.com <u>Post and hand delivery:</u> Wolf, Greenfield & Sacks, P.C. 600 Atlantic Avenue Boston, MA 02210-2206 <u>Telephone:</u> 617-646-8000 <u>Facsimile:</u> 617-646-8646

A power of attorney is submitted with the Petition. Counsel for Petitioner
consents to service of all documents via electronic mail.

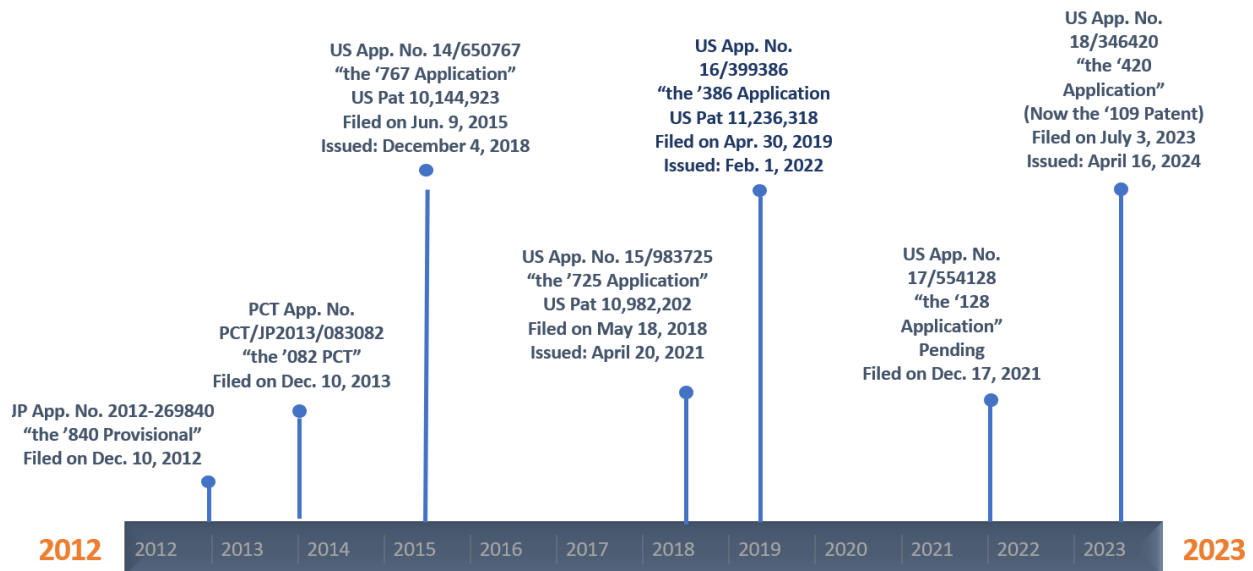
III. REQUIREMENTS FOR POST-GRANT REVIEW

A. Grounds for Standing

Pursuant to 37 C.F.R. § 42.204(a), Petitioner certifies that the '109 patent is available for PGR and that Petitioner is not barred or estopped from requesting PGR of the challenged claims of the '109 patent on the grounds identified herein. The '109 patent issued on April 16, 2024, and this Petition is being filed within nine months of that issue date (January 16, 2025). *See also* § III.B.1, *infra* (regarding eligibility for PGR).

B. Identification of Challenge

Pursuant to 37 C.F.R. §§ 42.204(b) and (b)(1), Petitioner requests PGR of the challenged claims (1-10) and that the Board cancel the same as unpatentable. The '109 patent matured from U.S. Patent Application No. 18/345,420, filed on July 3, 2023 (“the '420 Application”). As shown in the figure below, the '109 patent further claims priority to U.S. Application Nos. 17/554,128 (“the '128 Application,” filed December 17, 2021), 16/399,386 (“the '386 Application,” filed April 30, 2019), 15/983,725 (“the '725 Application,” filed May 18, 2018), and 14/650,767 (“the '767 Application,” filed June 9, 2015) which is the U.S. National Phase Entry of PCT/JP2013/083082 (“the '082 PCT, filed December 10, 2013). The '082 PCT claims foreign priority to a JP Priority Application (JP2012-269840, “the '840 JP Priority Application”) filed on December 10, 2012. Jain, ¶33.



1. The '109 Patent is Eligible for PGR

Although the '109 patent claims priority to a pre-AIA application, during prosecution of the great grand-parent application to the '109 patent (App. No. 15/983,725), Patent Owner filed a "Statement Under 37 C.F.R. § 1.55 or § 1.78 for AIA (First Inventor to File) Transition Applications." EX1022, 1. The Office then examined the '725 Application and all subsequent applications in the continuity chain (including the challenged claims) under AIA law. In view of this Patent Owner admission and subsequent AIA treatment, the '109 patent is PGR-eligible.

Even beyond this admission, the challenged claims include limitations that both lack a proper written description and are not enabled by the '840 JP Priority Application and its U.S. progeny as discussed in Sections VIII and IX below. Accordingly, and without conceding that either the '109 patent specification or any other prior application in its priority chain describes or enables the challenged

claims, in no event are such claims entitled to an effective filing date of earlier than December 10, 2013. The '109 patent is therefore eligible for PGR because it is an AIA "first-to-file" patent, filed on or after March 16, 2013.

The '840 JP Priority Application is incorporated by reference into each application in the '109 patent priority chain. It discloses less than the later-filed utility applications. *See generally*, EX1008. Jain, ¶50. Upon U.S. entry of the '082 PCT with the filing of the '767 Application on June 9, 2015, Patent Owner amended the specification to add a paragraph describing the zymogen cascade. EX1017, 132-33. This paragraph appears in the subsequent '725, '386, '128 and '420 Applications in the '109 patent family, and in the '109 patent specification itself. Therefore all the disclosures of the parent applications (to which the '109 patent claims to be continuations) including the '840 JP Priority Application are, *at best*, the same as the disclosure found in the specification of the '767 Application (including the additional noted paragraph). Because this representative '767 Application fails to support and/or enable the '109 patent claims, as explained in detail in Sections VIII and IX below, its parent applications (including the '840 JP Priority Application) fail to do so for the same reasons.

Regarding the '840 JP Priority Application specifically, it provides no disclosure or guidance regarding how a POSA would make or use the assay of exemplary challenged claim 1 with Factor B or Pro-clotting enzyme recombinantly

produced in a mammalian expression system as claimed. The '840 JP Priority Application does not discuss or teach the recombinant production of such proteins via any system other than Sf9 insect cells. EX1008, ¶¶0112-14; *see also* §§ VIII, IX, *infra*. Nor does the '840 JP Priority Application disclose or teach how to generate the claimed assay agent via three functional recombinantly produced zymogen proteins expressed via *different* mammalian cell lines or with sequence information from *different* species of horseshoe crabs as claimed. *See generally*, EX1008; Jain, ¶140. For all of these deficiencies, the '840 JP Application and its U.S. progeny neither describe nor enable the challenged claims. The challenged claims are not entitled to claim priority to the '840 JP Priority Application (December 10, 2012) and so, in addition to the Patent Owner's admission to the same effect, the '109 patent is eligible for PGR.² Jain, ¶¶34, 140.

² *See, e.g., US Endodontics, LLC v. Gold Standard Instruments, LLC*, PGR2015-00019, Paper 54, at 6-12 (PTAB Dec. 28, 2016) (finding PGR eligibility for patent issuing from transition application, holding that where “neither the [reviewed patent's] application nor any of the earlier applications adequately supports [the] claims..., the effective filing date for those claims is the actual filing date”); *see also Schul Int'l Co., LLC v. Emseal Joints Sys., Ltd.*, PGR2018-00034, Paper 7, at 10-16 (PTAB Aug. 22, 2018).

2. Statutory Grounds on Which the Challenge is Based

Petition respectfully requests cancellation of the challenged claims on the following grounds:

Ground Number and Statute		Claims
1	35 U.S.C. § 112 (written description) (AIA-law)	1-10
2	35 U.S.C. § 112 (enablement) (AIA-law)	1-10
3	35 U.S.C. § 102(a)(1) (AIA-law)	1-10

The information required by Sections 42.204(b)(4)-(5) is provided in Sections VIII-X. This Petition is supported by the Declaration of Dr. Siddhartha S. Jain (EX1003) (“Jain”).

IV. BACKGROUND

A. Technology of the ’109 Patent

The ’109 patent relates to endotoxin testing for the quality assurance of medical products (medical devices and pharmaceuticals) and for other product and environmental safety applications. Specifically, it claims methods of making enzyme-based assays to test (and methods of testing) for the presence of a harmful bacterial substance known as endotoxin where such tests comprise recombinantly produced versions of Factor C proteins, recombinant Factor B proteins, and recombinant Pro-clotting enzymes—“zymogen” proteins otherwise naturally sourced from the hemolymph (invertebrate equivalent of blood) of horseshoe crabs

which had been discovered to undergo a clotting reaction in the presence of endotoxin. EX1001, 1:57-2:11; Jain, ¶31.

The clotting cascade includes these three serine protease zymogens and one clottable protein (coagulogen). Endotoxin initiates the cascade by binding to and activating the first serine protease, Factor C. Factor C then cleaves and activates Factor B, which in turn converts Pro-clotting enzyme to clotting enzyme. Clotting enzyme cleaves coagulogen, which forms coagulin gel, giving rise to clotting. EX1001, 1:66-2:11, 13:36-49, FIG. 1; Jain, ¶32.

The '109 patent discusses the production of recombinant Factor C proteins from commonly used mammalian cell lines, while saying far less about the production of recombinant Factor B and Pro-clotting enzyme. According to the specification, expression of Factor C from known industrial production strains, including Chinese Hamster Ovary ("CHO") and Human Embryonic Kidney ("HEK"), purportedly solves the problem of ion interference with the Factor C signaling cascade that limits endotoxin recovery (thus underestimating endotoxin levels). EX1001, 3:10-31. While the '109 patent provides examples involving the "Expression of Factor C in Mammalian Cells" (*id.*, 30:52-32:5), it describes "Preparation of Recombinant Factor B and Recombinant Pro-Clotting Enzyme" via expression of these proteins in an insect (Sf9) host cell only. *Id.*, 32:29-59; Jain, ¶¶35-36.

The gene and amino acid sequences of Factor C proteins from certain species of horseshoe crab (including *Tachypleus tridentatus* Factor C and *Carcinoscorpius rotundicauda*) were known prior to the earliest claimed priority date of the '109 patent, however the sequences encoding Factor C, Factor B, and Pro-clotting enzyme for the horseshoe crab species *Limulus polyphemus* had **not** been described or fully characterized until much more recently. EX1009, EX1010³, EX1011 (2017, disclosing full protein sequences for Factor C in *Limulus polyphemus* horseshoe crabs); *see also* EX1005, pp. 49-75 (SEQ ID NOS. 1-22); EX1012, ¶¶0334-35, 0339-41, 0344-45, 0350-51 (*Limulus polyphemus* sequences for Factor B, Factor C, Pro-clotting enzyme); Jain, ¶37.

B. The Challenged Claims

The challenged claims of the '109 patent include two independent and 8 dependent claims. They are reproduced in Appendix A.

C. The Prosecution History of the '109 Patent

Prosecution of the '109 patent was brief (a Track One request was granted on September 1, 2023) and failed to address the expansive scope of the then-pending claims. Original claim 1 recited:

³ The Declaration of Dr. Mary K. Bolin (EX1013) authenticates EX1006, EX1010, EX1019, EX1025-1027, EX1031, EX1038-1039, and EX1041.

1. A method for producing an endotoxin assay agent comprising a horseshoe crab Factor C, a horseshoe crab Factor B, and a horseshoe crab Pro-clotting enzyme, the method comprising:

expressing the horseshoe crab Factor C in a Chinese Hamster Ovary cell or a Human Embryonic Kidney cell as a host cell, and recovering a culture supernatant comprising the horseshoe crab Factor C having activity of Factor C,

expressing the horseshoe crab Factor B in a mammalian cell as a host cell, and recovering a culture supernatant comprising the horseshoe crab Factor B having activity of Factor B,

expressing the horseshoe crab Pro-clotting enzyme in a mammalian cell as a host cell, and recovering a culture supernatant comprising the horseshoe crab Pro-clotting enzyme having activity of Pro-clotting enzyme, and

formulating the endotoxin assay agent comprising the horseshoe crab Factor C, the horseshoe crab Factor B, and the horseshoe crab Pro-clotting enzyme.

EX1002, 462. Jain, ¶¶39-40.

On September 15, 2023, the Examiner rejected all claims 1-10 as obvious over Ding-1 et al., (U.S. Patent No. 5,858,706) in view of Tamura et al. (U.S. Patent Application No. 2009/0208995). EX1002, 182-86. The Examiner also found

claims 1-10 to be obvious over Ding-2 (U.S. Patent No. 5,716,834) in view of Tamura. *Id.*, 187-91. Jain, ¶¶41-42.

On November 24, 2023, Patent Owner amended the claims to add the limitation of “secreting the horseshoe crab Factor C into an extracellular culture supernatant and recovering the horseshoe crab Factor C having activity of Factor C secreted in the” culture supernatant, and also added that the recombinant Factor C is “a *Tachypleus tridentatus* Factor C or a *Limulus polyphemus* Factor C.”

EX1002, 119-121. Patent Owner also amended the claims to recite expressing Factor B “having activity of Factor B” and Pro-clotting enzyme “having activity of Pro-clotting enzyme.” *Id.* Finally, Patent Owner added the last limitation to claim 1: “producing an endotoxin assay agent...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.” *Id.* Jain, ¶¶43-44.

Patent Owner argued that “culture supernatant” as recited in the claims was different than “a supernatant by centrifuging cultured and lysed host cells” as recited in Ding-1 and that neither Ding-1 nor Ding-2 recite “secreting” recombinant Factor C “into an extracellular supernatant, and recovering” the secreted protein. *Id.*, 124-25. Patent Owner submitted a contemporaneous declaration from inventor, Dr. Mizumura, purportedly showing that while no

Factor C activity was observed in the cellular fraction from Ding-1 or Ding-2 (Factor C sourced from [the mammalian] Cos-1 expressed cell lysate), “excellent Factor C activity was observed in the culture supernatant as described in the Examples and Fig. 6 of the present application [using CHO and HEK cells].” *Id.*, 124-29. Jain, ¶45-46.

On December 20, 2023, the Examiner amended the claims to specify that the “recovered horseshoe Factor C has activity of Factor C,” amended several other pending claims, and allowed them. *Id.*, 67-79. Jain, ¶47.

V. THE BOARD SHOULD NOT EXERCISE ITS DISCRETION TO DENY INSTITUTION.

The Board should not exercise its discretion to deny institution under Sections 325(d) or 324(a).

A. There Is No Basis for Discretionary Denial Under 35 U.S.C. § 325(d).

Considering the two-part framework discussed in *Advanced Bionics, LLC v. Med-El Elektromedizinische Gerate GMBH*, the Board should not exercise its § 325(d) discretion to deny institution based on any written description, enablement, or prior art arguments herein. IPR2019-01469, Paper 6, at 8-9 (PTAB Feb. 13, 2020). As the Director recently noted in a notice of proposed rulemaking, “application of section 325(d) should be limited to situations in which the prior art or arguments were meaningfully addressed by the Office”—meaning that the

Office “articulated its consideration of the art or arguments in the record.” 89 Fed. Reg. 28693, 28700 (Apr. 19, 2024). The record here lacks any such articulation. *See generally* EX1002.

1. The § 112 Written Description Arguments in Ground 1 Are Not the Same Or Substantially the Same as Arguments Considered During Prosecution.

The Examiner never rejected the challenged claims based on inadequate written description in view of the disclosure found in the '420 Application (or in any of the other applications filed in the priority chain of that patent). As discussed in Section IV.C, above, the Examiner’s sole rejection of the pending claims was for obviousness over the prior art as applied to the earliest claimed priority date of the '109 patent. But, as discussed in Section VIII, below, the disclosure provided in the '420 Application (identical to the '767 Application, and encompassing the disclosures of each application in the priority chain of that application tracing back to the '840 JP Priority Application) fails to describe a *single* example falling within the genus of over 3,400 claimed options for producing a cascade of recombinant zymogen components (Factors B, C, and Pro-clotting enzyme) to detect endotoxin. While the Examiner looked for and applied prior art falling within the scope of such claims, the Examiner did not recognize that such claims were insufficiently described as of their priority date under 35 U.S.C. § 112. Petitioner presents new

evidence never considered by the Examiner demonstrating that Patent Owner did not possess the full scope of the claimed invention.⁴

2. The § 112 Enablement Arguments in Ground 2 Are Not the Same Or Substantially the Same As Arguments Considered During Prosecution.

No rejections were made under the enablement requirement of § 112. The Examiner never discussed how a POSA would be able to make and use the full scope of the claimed invention, nor did the Examiner discuss whether undue experimentation would be required to make and use the full scope of the claimed invention. Nor did the Examiner analyze the claimed invention in view of the *Wands* factors. The Board should not exercise its § 325(d) discretion to deny institution based on the enablement arguments herein. *See Lifescan Global Corp. v. Ikeda Food Rsch. Co.*, PGR2019-00032, Paper 11, at 14 (PTAB Aug. 15, 2019) (declining to deny institution under § 325(d) where enablement arguments presented in the petition were not previously considered and “beyond the

⁴ While a written description rejection was brought against pending claims in the ’386 Application (grandparent to the ’109 patent), those claims were of markedly different scope and content than the challenged claims here (EX1040, 515-519, 371-376) such that the respective written description arguments are not the same or substantially similar.

consideration given to all allowed claims for compliance with the requirements of 35 U.S.C. § 112,” also holding that “the mere absence of a rejection does not reflect that the Examiner already considered the specific arguments presented in the Petition”).

The enablement arguments in this Petition include a detailed analysis of the *Wands* factors that speak to the amount of experimentation required to practice the full scope of the claimed invention. *See* § IX.A.2, *infra*. The Examiner never considered evidence relating to these factors, nor how a POSA would practice the broad scope of the claimed invention or, consequently, the amount of undue experimentation that a POSA would require to make and use that invention. The Examiner did not have before him the Jain Declaration (EX1003), which describes, *inter alia*, the state of the prior art and its unpredictable nature. As the Examiner did not specifically consider how a POSA would practice the invention or the undue experimentation such practice would require, the Board should not exercise its § 325(d) discretion to deny institution based on the enablement arguments herein.

3. The Anticipation Argument in Ground 3 Is Not the Same or Substantially the Same As Any Argument Considered During Prosecution.

Ground 3 of this Petition argues that if the challenged claims are entitled to an effective filing date of no earlier than their actual filing date (July 3, 2023), such

claims are anticipated by the '629 Publication. The '629 Publication was never cited, analyzed, considered, or applied against the pending claims at any point during the prosecution history of the '109 patent because the Examiner never considered whether the '109 patent was entitled to its earliest claimed priority date. The Examiner therefore never considered the '629 Publication as applicable prior art against the challenged claims, even though it discloses precisely what Patent Owner later claimed. Even if the Board were to find the '629 Publication to be similar to the art cited or applied during prosecution of the '109 patent, the Examiner plainly “misapprehend[ed] or overlook[ed] specific teachings of the relevant prior art where those teachings impact patentability of the challenged claims.” *Cellco P’ship v. Huawei Device Co.*, IPR2020-01117, Paper 10, at 12 (PTAB Feb. 3, 2021); *The Gillette Company LLC v. Sphere USA, LLC*, PGR2022-00030, Paper 8, at 40-41 (PTAB Sept. 23, 2022) (finding the Office erred “to the extent that the Office assumed that the claims were entitled to a priority date as claimed in the application”); *Nrg Energy, Inc. v. Midwest Energy Emissions Corp.*, No. IPR2020-00832, 2020 WL 6277239, at *6-7 (PTAB Oct. 26, 2020) (declining to deny institution under § 325 where the Examiner failed to consider whether priority applications provided written description support for the claims).

The “fact that [the references in the Petition were] not the basis of rejection weighs strongly against exercising [the Board’s] discretion to deny institution

under 35 U.S.C. § 325(d).” *Cellco*, IPR2020-01117, Paper 10, at 13; *Puma North America v. Nike*, IPR2019-01058, Paper 10, at 19 (PTAB Oct. 31, 2019)

(instituting where petition presented “new non-cumulative evidence...probative to issues of patentability and helpful to our consideration of a prior art combination that was not before the Examiner”); *Apple v. MPH Techs. Oy*, IPR2019-00819, Paper 10, at 16-17 (PTAB Sept. 27, 2019) (similar).

B. There Is No Basis for Discretionary Denial Under 35 U.S.C. § 324(a).

There is no co-pending litigation involving the ’109 patent that would warrant discretionary denial of this Petition based on the factors in *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 (PTAB Mar. 20, 2020).

VI. LEVEL OF ORDINARY SKILL IN THE ART

A POSA in the technical field relating to the ’109 patent would have 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. More education could substitute for experience to a certain extent, and vice versa. Jain, ¶¶48-53.

VII. CLAIM INTERPRETATION

Claim terms subject to PGR are to be “construed using the same claim construction standard that would be used to construe the claim in a civil action

under 35 U.S.C. [§] 282(b), including construing the claim in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent.” § 42.200(b). Only terms necessary to resolve the controversy need to be construed and should be given their plain and ordinary meaning. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017).⁵ Jain, ¶54.

VIII. GROUND 1: CLAIMS 1-10 ARE UNPATENTABLE FOR FAILING TO MEET THE WRITTEN DESCRIPTION REQUIREMENT.

A. The Written Description Inquiry Asks Whether An Inventor Possessed the Full Scope of the Claims As of the Claimed Effective Filing Date.

The written description requirement of 35 U.S.C. § 112 exists “to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him.” *In re Wertheim*, 541 F.2d 257, 262, (C.C.P.A. 1976). Thus, to assess the written description support of claims such as those challenged herein which were sought in an application filed in 2023 but claim a priority date of a 2012 JP Priority Application and a PCT filing on

⁵ See generally *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005); 37 C.F.R. § 42.200(b). This claim-construction analysis is not a concession as to the scope of any claim term in litigation, or a waiver of any argument regarding indefiniteness, invalidity, or unpatentability.

December 10, 2013,⁶ the question is whether a POSA would understand the inventors to have been in possession of the full scope of such claims in 2013. *Ariad Pharms.*, 598 F.3d at 1351 (inadequate written description where disclosure failed to “reasonably convey [] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.”); *see also Biogen Int’l GMBH v. Mylan Pharms. Inc.* 18 F.4th 1333, 1342-44 (Fed. Cir. 2021) (no written description for claims directed to a method of treating with DMF at 480mg/day—“written description is judged based on the state of the art as of the priority date....That Biogen later established the therapeutic efficacy of DMF480 is of no import to the written-description analysis.”); *see also Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 10 F.4th 1330, 1341 (Fed. Cir. 2021) (improper for patentee to

⁶ The ’109 patent claims priority to the ’840 JP Priority Application (filed Dec. 10, 2012) but the content of that Application does not support the challenged claims (*see* §VIII.B, *infra*) and is encompassed by the disclosure of the ’767 Application. If the disclosure of the ’767 Application (identical to the December 10, 2013 ’082 PCT filing but including an additional paragraph added with the U.S. entry of that application (*see* EX1017, 132-33)) does not demonstrate that the inventors possessed the full scope of the challenged claims, the same is true for the ’840 JP Priority Application. Jain, ¶¶50-51.

rely on post-filing evidence to show that the disclosure of two species in the specification provide adequate written description for the broad genus that was claimed).

“A sufficient description of a genus [] requires the disclosure of either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can ‘visualize or recognize’ the members of the genus.” *Ariad*, 598 F.3d at 1350. “[M]erely drawing a fence around the outer limits of a purported genus is not an adequate substitute for describing a variety of materials constituting the genus and showing that one has invented a genus and not just a species.” *Id.*

B. As of December 10, 2013, The '109 Patent Inventors Did Not Possess The Full Scope of the Methods of Challenged Claim 1.

1. Challenged Claims 1 and 10 Define a Genus of Endotoxin Assay Agents and Methods For Making the Same That Broadly Cover 3,456 Possible Options.

Independent challenged claims 1 and 10 broadly encompass making an endotoxin detection assay by expressing recombinant Factor C, recombinant Factor B, and recombinant Pro-clotting enzyme, each of which has the “activity of” each protein so as to act in a functioning cascade for the detection of endotoxin. While these claims recite certain limitations on the recombinant production of Factor C,

they are broader with respect to the recombinant expression of the other zymogen proteins (Factor B and Pro-clotting enzyme). Jain, ¶55.

For Factor C, the recombinant protein must come from either *Tachypleus tridentatus* or *Limulus polyphemus* species, must be expressed in either HEK or CHO cells, and must be secreted into the extracellular culture supernatant for protein retrieval. For Factor B and Pro-clotting enzyme the recombinant protein can come from any species of horseshoe crab, can be expressed in any mammalian host cell (the '767 Application lists CHO DG 44, CHO K1, and HEK293 as non-limiting examples), and can be retrieved after secretion into the extracellular supernatant or by any other method. EX1017, 53-54(¶¶0036-39). These claims are also explicit that the assay can be created with recombinant proteins from the same or from different host cells. They also allow for the recombinant proteins to be produced from gene or amino acid sequences from the same or different species of horseshoe crabs. EX1001, cls. Jain, ¶¶56-57

Thus, per challenged claims 1 and 10, the assay of the claimed method can comprise all three proteins recombinantly produced in a certain CHO cell line, or all three proteins recombinantly produced in a certain HEK cell line, or with a variety of mix-and-matching proteins where Factor C is from the *Tachypleus tridentatus* species of crab and expressed in CHO cells, but Factor B and Pro-clotting enzyme is produced via any **other** mammalian expression system and from

any *other* species of horseshoe crab. The result of these optional combinations is a claim that, even by a conservative estimate, broadly recites a genus of thousands of possible methods for producing the claimed endotoxin assay agent. Jain, ¶58.

Challenged Claims 1 and 10				
	Expression System	Horseshoe Crab Species	Recovery	Options
Factor B	“Mammalian” (could include), at least: ⁷ • CHO DG44 • CHO K1 • HEK293	• <i>Tachypleus tridentatus</i> • <i>Tachypleus gigas</i> • <i>Limulus polyphemus</i> • <i>Carcinoscorpius rotundicauda</i>	• Secreted into extra-cellular culture supernatant • Not secreted (i.e., lyse cells and recover)	At least 24 options
Factor C	• CHO DG44 • CHO K1 • HEK293	• <i>Tachypleus tridentatus</i> • <i>Limulus polyphemus</i>	• Secreted into extra-cellular culture supernatant	At least 6 options
Pro-Clotting Enzyme	“Mammalian” (could include), at least: • CHO DG44 • CHO K1 • HEK293	• <i>Tachypleus tridentatus</i> • <i>Tachypleus gigas</i> • <i>Limulus polyphemus</i> • <i>Carcinoscorpius rotundicauda</i>	• Secreted into extra-cellular culture supernatant • Not secreted (i.e., lyse cells and recover)	At least 24 options
				At least 3,456 possible combinations

2. The '767 Application Does Not Describe a Single Species or Example Within The Genus of Claim 1 or Claim 10.

While the '109 patent inventors claimed a method for producing an endotoxin detection assay broadly encompassing thousands of possible options for assembling the claimed components thereof, they did *not describe in the '767 Application a single example of the making of such an assay*. Jain, ¶59.

Amongst the minimal limitations on the breadth of challenged claims 1 and 10, both claims explicitly require that Factor B and Pro-clotting enzyme are expressed “in a mammalian cell as the host cell.” However the '767 Application only describes the recombinant production of *Tachypleus tridentatus* Factor B and Pro-clotting enzyme *via the Sf9 insect cell expression system*. EX1017, 89-90(¶¶0117-120); Jain, ¶60. Aside from a generic mention that the descriptions of recombinant Factor C in mammalian cells can be applied to these other proteins, there is no discussion, data, or reference to the inventors' production of either of these zymogen proteins via a “mammalian cell as the host cell” to make a functioning endotoxin detection assay as claimed. Jain, ¶61. Thus, while the genus of 3,456 possible combinations set forth above requires that Factor B and Pro-clotting enzyme be recombinantly produced in a mammalian expression system in

⁷ The '767 Application defines “mammalian cells” broadly. These three options are a conservative estimate based on the specific examples disclosed. Ex. 1017, 53-54.

all cases, the '767 Application never describes a single species falling within this genus. *Boston Sci. Corp. v. Johnson & Johnson Inc.*, 647 F.3d 1353, 1364 (Fed. Cir. 2011) (for claims directed to macrocyclic lactone analogs of rapamycin, affirming no written description where, “[t]he shared specification lists ‘Agents: Rapamycin (sirolimus) structural analogs (macrocyclic lactones) and inhibitors of cell cycle progression.’ Then four experimental delivery methods using only rapamycin are detailed. No experiments are detailed using macrocyclic lactone analogs nor does the specification even indicate performance of any such experiments....[The shared specification] does not evidence possession of the genus of macrocyclic lactone analogs of rapamycin in the claimed invention to inhibit restenosis.”); *Carnegie Mellon University v. Hoffmann-La Roche, Inc.*, 541 F.3d 1115, 1125-26 (Fed. Cir. 2008) (affirming no written description where claims encompassed a genus of recombinant plasmids, but specification disclosed only one coding sequence from one bacterial source—“To satisfy the written description requirement in the case of a chemical or biotechnological genus, more than a statement of the genus is normally required. One must show that one has possession, as described in the application, of sufficient species to show that he or she invented and disclosed the totality of the genus.”). Jain, ¶62.

In addition, challenged claims 1 and 10 require that the claimed endotoxin detection assay be produced in such a manner “wherein the host cell for expressing

the horseshoe crab Factor C, the host cell for expressing the horseshoe crab Factor B, and the horseshoe crab for expressing Pro-clotting enzyme *may be the same or different.*” EX1001, cls. However the ’767 Application provides no example of the production of any assay where the three zymogen proteins are expressed via the same mammalian expression host cells. Again, the only working assay described in the ’767 Application used Factor B and Pro-clotting enzyme expressed via insect cells. EX1017, Ex. 1017, 89-90(¶¶0117-120). And the ’767 Application makes no discussion or mention whatsoever of producing a functioning endotoxin detection assay where the three zymogen proteins are expressed via *different* mammalian host cells. The ’109 patent inventors did not possess a method for producing a functioning endotoxin assay agent comprising three recombinant proteins able to function in an enzymatic cascade in such a mix-and-match fashion. Jain, ¶¶63-65.

While challenged claim 1 explicitly recites using *Limulus polyphemus* Factor C for the production of recombinant Factor C (and places no species limitation on the recombinant production of Factor B or Pro-clotting enzyme), 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. Jain, ¶¶66; EX1011, 36; EX1015, ¶¶0004-13.

The inventors themselves admitted to the United States Patent Office in an unrelated patent filing on October 18, 2017 (publishing on August 8, 2019) that the field had struggled to sequence and structurally and functionally characterize the *Limulus polyphemus* species of horseshoe crab. EX1015 (“the ’629 Publication”), ¶¶0007-12 (“in *Limulus polyphemus*, complete identification of these proteins and genes from both structural and functional aspects has not been achieved even though 20 years or more has passed since the reports regarding the genus *Tachypleus* described above were published. ***This is because accurate determination of the full-length sequence structures and elucidation of the expression and functions of these proteins and genes could not be achieved by general techniques due to various differences in biomolecules, diversities, etc. because of differences in genera or species of horseshoe crabs.***”); EX1005, ¶¶0010-12; *see also* EX1038, 6-7, 10-15 (discussing discreteness of Family Limulidae and Family Tachypleinae); Jain, ¶67.

Finally, while the challenged claims encompass producing the endotoxin assay agent from three recombinant zymogen proteins where each of those proteins are generated from ***different*** species of horseshoe crab and then mixed together, the ’767 Application makes no mention, disclosure, or example of making a functioning endotoxin assay agent this way. EX1001, cls.; Jain, ¶68.

Challenged claims 1 and 10 define at least 3,456 possibilities for making an endotoxin detection assay, however, the '767 Application fails to describe a single example of the three zymogen proteins recombinantly produced per the claimed limitations and assembled together into a functioning enzymatic cascade to detect endotoxin as claimed. *University Of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 918, 926 (Fed. Cir. 2004) (affirming summary judgment of no written description where claim required use of a non-steroidal compound as treatment and patentee only described the compound by the functions it was to achieve and a general statement that such a compound might be found by trial and error through a large pool of possible compounds, but did not identify even a specific single compound that would achieve the recited function). For at least these reasons, the '767 Application does not demonstrate that the inventors possessed the purported invention of challenged claims 1 and 10 as of December 10, 2013. Jain, ¶69.

3. The '767 Application Provides No Identification of Structural Features Common to the 3,456 Members of the Claimed Genus.

In addition to providing no example of a method of making an endotoxin assay agent within the scope of the claimed genus, the '767 Application provides no explanation or common structural feature that would be present in all of the at least 54 proteins (24 Factor B, 6 Factor C, and 24 Pro-clotting Enzyme) that result in 3,456 possible zymogen protein combinations making up this genus that would

result in a functioning assay. Jain, ¶70. While claims 1 and 10 require that all three zymogen proteins are expressed in mammalian cells, the '767 Application provides no common structural feature present in all such proteins that would, for example, allow them to be combined in a functioning endotoxin detection assay in the scenario where each protein were expressed in a *different* mammalian cell and/or from *different* species of horseshoe crabs. The '767 Application provides no disclosure of whether or how such could be accomplished. Jain, ¶71.

Moreover, it was known by 2013 that the four existing species of horseshoe crabs fell into two distinct taxonomic families (Limulidae and Tachypleinae), with different physiological and genetic features based on geographical separation. EX1038, 6-7, 10-15 (discussing the discreteness of Family Limulidae and Family Tachypleinae). Given these known differences, a POSA would not have understood the '109 patent inventors to be in possession of a method of producing an endotoxin assay agent comprised of all three zymogen proteins expressed from different species of horseshoe crabs and certainly no group had reported the accomplishment of that feat by 2013. Jain, ¶71-72.

The '767 Application posits that endotoxin detection function is enhanced in mammalian cell expression (as opposed to non-mammalian cell expression) because of the addition of a post-translation (α -2,3) terminal sialic acid in mammalian cell expression in contrast to, for example, insect cell expression. Ex.

1017, 99, 105-107(¶¶0138,0149-154). However, the inventors abandoned their theory regarding the significance of this structural feature to endotoxin detection function during prosecution of the grandparent application to the '109 patent (App. No. 16/399,386). EX1040, 77, 85-86 (“[S]uperior salt tolerance can be reproduced *irrespective* of (α-2,3)-linked terminal sialic acid, at least for *Limulus* Factor C recombinantly produced by using HEK 293 cell as a host.”); Jain, ¶73.

While challenged claims 1 and 10 draw a broad fence around a variety of mix-and-match features for producing an endotoxin assay agent, the '109 patent inventors did not describe and were not in possession of any single claimed example or any structural rationale or explanation for how and why the members of such genus could be produced to work, as claimed, in a cascade to detect endotoxin. Because the structure of each protein is critical to its function and because the claims encompass over 3,400 combinations of recombinant proteins functioning together in an enzymatic cascade to detect endotoxin, 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. The '767 Application does neither and so the challenged claims do not meet the written description requirement. *Ariad*, 598 F.3d at 1350; *Boston Sci.*, 647 F.3d at 1366-67 (no written description where specification failed to show a correlation

between the structure of the claimed analog and the function it was described as performing); Jain, ¶¶74-76.

C. As of December 10, 2013, the '109 Patent Inventors Did Not Possess The Full Scope of the Methods of Challenged Dependent Claims 2-9.

Dependent claims 2-9 are likewise not adequately described by the '767 Application for the same reasons set forth above for challenged claims 1 and 10 in Section VIII.B, above. In particular, none of the additional limitations recited in these claims serve to narrow or limit such claims to a scope which is adequately described by the '767 Application. Instead, most of these claims encompass the exact same exceedingly broad genus of endotoxin detection assays and methods for making or testing for the same (or a slightly narrower one), but as with challenged claims 1 and 10, the '767 Application fails to disclose even a single example of this genus or any common structural features of the genus giving rise to an assembled functioning endotoxin detection assay. Jain, ¶77.

While dependent claims 2 and 3 limit the mammalian expression of Factor B and Pro-clotting enzyme, respectively, to CHO and HEK Cells, these options are coextensive with the conservatively estimated three options (CHO DG44, CHO K1, and HEK293, recited in the '767 Application (EX1017, 53-54(¶0038)) described above for calculating the size of the genus of claim 1. Jain, ¶78.

Claim 4 limits the species of Factor B and Pro-clotting enzymes to *Tachypleus tridentatus* and *Limulus polyphemus*. While this narrowing of species options reduces the genus of endotoxin detection assays to 864, the '767 Application still fails to describe a single example of making such an assay because, again, claim 4 requires that Factor B and Pro-clotting enzyme are recombinantly expressed in a mammalian cell as a host cell and the '767 Application only describes an example of recombinant expression of these two zymogen proteins from insect cells. Ex. 1017, 89-90(¶0118). Claim 4 is also broad enough to encompass production of the endotoxin assay wherein the three zymogen proteins are expressed in the same or different host cells, and from the same or different horseshoe crab species, but as discussed in Section VIII.B.2 and 3, above, the '767 Application provides no example of any of these scenarios. And claim 4 recites production of *Tachypleus tridentatus* and *Limulus polyphemus* zymogen proteins, but the gene and amino acid sequences for such proteins from the *Limulus polyphemus* species of horseshoe crab was not yet known or disclosed. See Section VIII.B.2, *supra*. For the same reasons that the '767 Application does not adequately describe the genus of challenged claim 1, it also does not adequately describe the slightly narrower genus of claim 4. Jain, ¶¶79-81.

Dependent claims 5-9 recite additional limitations on the method of producing an endotoxin assay agent of challenged claim 1 but none of these

additional limitations narrow the exceedingly broad genus of claim 1 in a manner whereby the disclosure of the '767 Application demonstrates the inventors had possession of such genus. Instead, each of these dependent claims recites a further characteristic of the zymogen proteins (claim 5, Factor C containing (α -2,3)-linked terminal sialic acid; claim 6, molecular weight of Factor C) or a further step in the process for making certain of the zymogen proteins (claim 7, filtering the culture supernatant for Factor C; claim 9, expressing all three zymogen proteins in individually established host cells), or specifies an additional characteristic of the assay agent itself (claim 8, formulated as a solid, liquid, or gel).

Because none of these dependent claims narrow the claimed genus of challenged claim 1 in any way that align with what the '109 patent inventors actually possessed as their invention, and for the same reasons that the '767 Application does not adequately describe the genus of challenged claim 1, it also does not adequately describe dependent claims 2-9. Jain, ¶¶82-83.

IX. GROUND 2: CLAIMS 1-10 ARE UNPATENTABLE FOR FAILING TO MEET THE ENABLEMENT REQUIREMENT OF § 112(A).

A. The '767 Application Fails To Explain How A POSA Could Make and Use The Thousands of Possible Combinations of Recited Components, Assembled Into the Claimed Assay, Without Undue Experimentation.

1. Legal Standard for Enablement

Section 112(a) contains an enablement requirement separate from the written description requirement. *Ariad*, 598 F.3d at 1344. To satisfy the enablement

requirement of § 112(a), “the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without ‘undue experimentation.’” *Genentech Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997). “Claims are not enabled when, at the effective filing date of the patent, one of ordinary skill in the art could not practice their full scope without undue experimentation.” *Wyeth & Cordis Corps. v. Abbott Lab’ys*, 720 F.3d 1380, 1384 (Fed. Cir. 2013). “It is the specification, not the knowledge of [a POSA], that must supply the novel aspects of an invention in order to constitute adequate enablement.” *Genentech*, 108 F.3d at 1366.

Undue experimentation factors include “(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.” *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). “A patentee who chooses broad claim language must make sure the broad claims are fully enabled.” *Sitrick v. Dreamworks, LLC*, 516 F.3d 993, 999 (Fed. Cir. 2008).

As the Supreme Court has instructed, enablement is not satisfied where a disclosure demands a POSA to engage in a trial-and-error methodology to weed through many possible combinations to determine which such combinations satisfy

the function claimed. *Amgen Inc. v. Sanofi*, 598 U.S. 594, 614-15 (2023)

(“Through trial and error, imagine that an inventor finds and discloses 26 different successful lock combinations.’ But imagine, too, ‘that the inventor tries to claim much more, namely all successful combinations,’ while instructing others ‘to randomly try a large set of combinations and then record the successful ones.’ Sure enough, that kind of ‘roadmap’ would produce functional combinations. But it would not enable others to make and use functional combinations; it would instead leave them to ‘random trial-and-error discovery.’”).

Because the ’767 Application likewise leaves a POSA to engage in random trial-and-error discovery to assemble functional claimed assays from the myriad of options covered by challenged claim 1, it fails to enable the challenged claims under *Amgen*.

2. Wands Factor Analysis

a. Claim 1 is Broad (Factor 8).

As discussed in Section VIII.B.1, above, challenged claim 1 broadly requires that all three zymogen protein components claimed are recombinantly produced, but based on the parameters of the claim, as of 2013, there were various options for carrying out the method of claim 1 (from a number of possible horseshoe crab species, in a number of possible expression systems, and by secreting or not secreting such proteins into the culture supernatant). Jain, ¶84. In total, the method

of claim 1 broadly encompasses a genus of 3,456 possible options for producing the claimed assay agent. *See* § VIII.B.1, *supra*; Jain, ¶85.

Such breadth requires a commensurate enabling teaching such that a POSA is able, from the disclosure, to make and use the full scope of the invention.

Amgen, 598 U.S. at 613 (“[I]f our cases teach anything, it is that the more a party claims, the broader the monopoly it demands, the more it must enable.”).

Moreover, all of the challenged claims require that the claimed combination of recombinantly produced proteins result in a functional assay or method for detecting endotoxin. The Federal Circuit, however, has cautioned that where, as here, the asserted claims include a functional requirement, the Court’s enablement inquiry must consider “the quantity of experimentation that would be required to make and use, not only the limited number of embodiments that the patent discloses, but also the full scope of the claim.” *Amgen Inc. v. Sanofi, Aventisub LLC*, 987 F.3d 1080, 1086 (Fed. Cir. 2021).

As discussed in Section IX.A.2.d, below, however, the ’767 Application does not describe making or using a single one of these claimed combinations, let alone how to make or use all 3,456 such combinations into a functioning endotoxin assay agent. Jain, ¶86.

b. The Nature of the Invention, Lack of Information in the Prior Art, and Unpredictability in the Field Renders Production of the Claimed Assay Subject to Significant Uncertainty (Factors 4, 5, 7).

Claim 1 covers over 3,400 options for making recombinant Factor C, Factor B, and Pro-clotting enzyme including that of the *Limulus polyphemus* species to produce an endotoxin assay agent. However, per the '109 patent inventors' own admission years after the '767 Application was filed, the field had struggled to sequence and recombinantly produce a significant proportion of these options—those involving *Limulus polyphemus* zymogen proteins. As the '629 Publication describes, “in *Limulus polyphemus*, even though more than 20 years have passed since the report in the genus *Tachypleus*, complete identification of these proteins and genes in terms of both structure and function has not been achieved. This is because due to the various differences and diversity of biomolecules depending on the genus and species of horseshoe crab, it has not been possible to accurately determine the full-length sequence structure, expression, and function of these proteins and genes using conventional methods.” EX1005, ¶¶0010-12; *see also* EX1038, 6-7, 10-15 (discussing the geographic and genetic discreteness of Family Limulidae and Family Tachypleinae); Jain, ¶¶87-88.

Likewise, while recombinant technology was not new as of 2013, a significant amount of research and experimentation was required to generate a particular protein, with the ability to detect endotoxin, across a number of different

expression systems. Jain, ¶89; *see* EX1031, 15-27; EX1039, 936. The '767 Application itself explains the difficulties faced by scientists in the field with generating recombinant zymogen proteins (such as Factor C) that were capable of detecting endotoxin when produced via mammalian expression systems. Ex. 1017, 14(¶011) (“[F]actor C derived from the Singaporean horseshoe crab (*Carcinoscorpius rotundicauda*) was expressed in COS-1, which is a cell line derived from African green monkey kidney cells, as host cells. However, it has been reported that when COS-1 was used as a host, the expressed Factor C was insoluble (Non-Patent Documents 3 and 4)”)”; Jain, ¶90.

Finally, as of December 10, 2013, there had been no reports of successful recombinant production of Factors B or Pro-clotting enzyme for any species of horseshoe crab, in any mammalian expression system. There had likewise been no reports of the production of a functioning endotoxin detection assay using recombinant proteins each from different species of horseshoe crabs. Jain, ¶¶91.

In view of this admitted uncertainty and failure to express such proteins in certain mammalian expression systems, and in view of the lack of guidance in the '767 Application for making any example of a claimed assay, a POSA would not have been able to make or use (as of 2013) and without undue experimentation, the 3,456 possible protein combinations encompassed by claim 1 into a functioning endotoxin assay agent. Jain, ¶¶92-93.

c. The Required Level of Skill To Practice The Challenged Claims Is Higher than the Level of Ordinary Skill in the Art (Factor 6).

The level of skill required to practice the purported invention given the absence of disclosure in the '767 Application is higher than the level of ordinary skill in the art in this field. As noted in Section VI, above, an ordinarily skilled artisan would have had 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 Factor C (lysate, purified native and/or recombinantly produced) for endotoxin detection and quantitation. Jain, ¶¶52, 94-95.

Designing, expressing, and testing recombinant proteins is laborious, time-consuming, complicated, and highly unpredictable due to the many effects that variations in gene and amino acid sequence can have on protein structure and function. EX1031, 16-27; EX1006, Abstract. Additionally, making a recombinant Factor C protein and a recombinant Factor B protein, and a recombinant Pro-clotting enzyme that work as a cascade to result in a desired activity (i.e., ability to detect endotoxin) was known to be difficult in view of challenges, for example, with getting Factor C to be secreted by the host cells themselves. EX1026, 360; EX1027, 71. In view of this, making a series of recombinant zymogen proteins with endotoxin detection function was highly speculative, particularly where there

is no example of recombinantly producing Factor B and Pro-clotting enzyme in mammalian cells as claimed. Jain, ¶96. As a result, a POSA is left with no more than an iterative trial-and-error process, figuring out how to express the claimed zymogen proteins in the various combinations set forth in the challenged claims and then determining whether such function to detect endotoxin. Jain, ¶97.

While the level of skill typically required to practice in this field is already high, because of the lack of guidance in the '767 Application itself and elsewhere in the prior art, as discussed in at least Section VIII, above, even such highly skilled individuals who *attempt* to practice the claimed invention may *still* be left with nothing but a “research assignment[]” for generating endotoxin detection assays across the full scope of claim 1. *Amgen*, 598 U.S. at 614. Thus, reaching the full scope of claim 1 would require a higher than ordinary level of skill in the relevant art. *See ALZA Corp. v. Andrx Pharms., LLC*, 603 F.3d 935, 939-41 (Fed. Cir. 2010) (affirming finding of lack of enablement where practice of claims would have required undue experimentation beyond the level of ordinary skill in the art— “[Patentee] cannot simply rely on the knowledge of a [POSA] to serve as a substitute for the missing information in the specification...[particularly where] even [Patentee] concedes that a [POSA] would have been required to engage in an iterative, trial-and-error process to practice the claimed invention even with the help of the [patent] specification.”); Jain, ¶98.

d. The Absence of Guidance or Examples in the '767 Application Necessitates Extensive and Undue Experimentation to Practice the Full Scope of Claim 1 (Factors 1-3).

Reaching the full scope of claim 1 requires undue experimentation to produce a *functioning* assay for detecting endotoxin assembled with the three required “active” protein components produced using the various optional horseshoe crab species, various optional expression systems, and various optional recovery methods allowed by the claims. *E.g.*, Ex. 1017, 53-54, 57-58, 76-78(¶¶0037-38, 0044-47, 0086-90). Due to the functional requirements of these claims, namely, that they are directed to “producing an endotoxin assay agent” (which the specification indicates is a testing method for the detection of endotoxin (Ex. 1017, 56-57(¶¶0043-44)) or a “method of measuring endotoxin,” an enabling disclosure must teach a POSA how to make and use the full scope of the claimed components together such that they are able to detect endotoxin. Jain, ¶¶99-100.

For claims that state certain structural requirements and also require performance of some function (*e.g.*, efficacy for a certain purpose), courts consistently find that undue experimentation can include undue experimentation in identifying, from among the many concretely identified compounds that meet the structural requirements, the compounds that *satisfy* the functional requirement. *See, e.g., Idenix Pharms. LLC v. Gilead Scis. Inc.*, 941 F.3d 1149, 1155-56 (Fed. Cir. 2019) (affirming no enablement where, for claims requiring structural features

and functional efficacy, challenger failed to demonstrate that a POSA would know, without undue experimentation, which structures would result in such efficacy); *Enzo Life Scis., Inc. v. Roche Molecular Sys., Inc.*, 928 F.3d 1340, 1346-47, 1349 (Fed. Cir. 2019) (affirming summary judgment of invalidity for lack of enablement where claims were broadly directed to hybridizable polynucleotides and specification failed to explain how all possible variables in structure for polynucleotides would impact their functionality); *Wyeth*, 720 F.3d at 1384, 1387 (affirming grant of summary judgment holding asserted claims invalid for lack of enablement undue experimentation was required to determine which compounds in the claimed class would have the required immunosuppressive functionality).

The '767 Application provides no identification of which claimed combinations would work to detect endotoxin. Jain, ¶¶101-102.

i. Production of Recombinant Factor B From Any Horseshoe Crab Species in Any Mammalian Expression System as of 2013 Would Have Required Undue Experimentation.

Claim 1 requires the assay agent to comprise any horseshoe crab Factor B having activity of Factor B from *any* species of horseshoe crab and in *any* mammalian cell as a host cell. The '767 Application falls well short of enabling the full scope of this aspect of claim 1 because it provides no information about how to make recombinant Factor B across the full scope of the claim. Jain, ¶103.

The '767 Application indicates that “[t]he Factor B of the present invention may be a variant of any of the aforementioned horseshoe crab Factor B proteins” and that “[t]he gene encoding the Factor B of the present invention is not particularly limited,” but defines the boundaries of what would count as a Factor B protein as among such “variants” only functionally—“so long as the variant has activity of Factor B.” Ex. 1017, 58-59(¶¶0048). The '767 Application provides no guidance on how to make and use the full scope of such Factor B proteins and variants for purposes of combining them with the other components claimed to yield a functioning endotoxin-detection assay. Jain, ¶¶104-06.

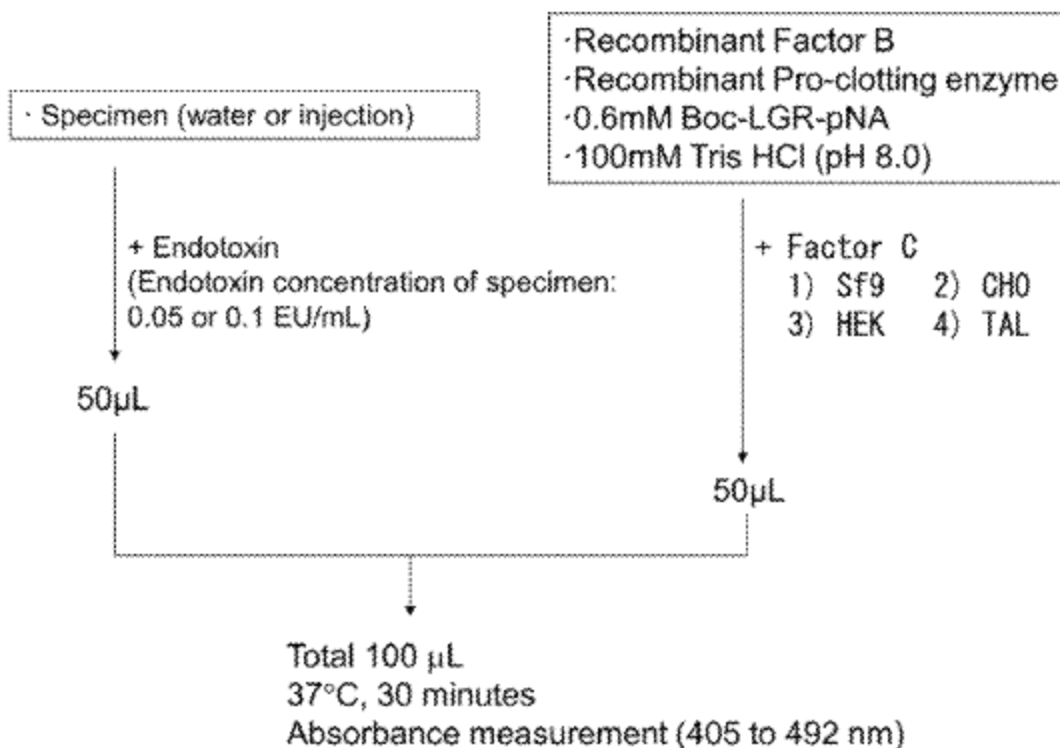
Aside from generically stating that Factor B proteins can be produced in similar fashion to those described for production of Factor C, the '767 Application only describes “[p]reparation of recombinant Factor B” using DNA encoding the *Tachypleus tridentatus* species of horseshoe crab and expression of this protein in Sf9 insect cells. EX1017 63, 89-90(¶¶0057-58, 0118-120). The '767 Application explains that the nucleotide sequence provided for Factor B is “optimized for expression in insect cells.” *Id.*, 89-90(¶¶0118). Jain, ¶¶107.

If anything, Patent Owner relied heavily on the distinction between mammalian expression systems and insect expression systems in order to **distinguish** the present alleged invention from prior art. *Id.*, (¶¶0137) (“In contrast, recombinant Factor C (Sf9) was most susceptible to reaction inhibition in many

injections.’’), 107(¶0154). And Patent Owner explained that recombinant expression of zymogen proteins in *some* mammalian cells do not work, highlighting the trial-and-error nature of expression of such proteins. *Id.*, 14(¶0010). Jain, ¶¶108-09.

The ’767 Application provides no other guidance about the preparation of Factor B for any species of horseshoe crab other than *Tachypleus tridentatus* in any expression system other than Sf9. When measuring the “activity” of these cascade proteins, the ’767 Application states only that “each of the above-prepared four types of Factor C was combined with *other factors* and activity measurement was carried out through the following procedure. Fig. 4 shows the scheme of activity measurement.” Ex. 1017, 93-96(¶¶0128-133), 119 (Fig. 4). Figure 4, however, is non-specific as to the species or expression system of the utilized Factor B protein:

[Fig. 4]



Aside from the disclosure of recombinant production of *Tachypleus tridentatus* Factor B expressed via insect cells (Sf9) (which is not within the scope of claim 1), the '767 Application provides no guidance or teaching whatsoever as to how a POSA would make or use Factor B proteins within, let alone across, the full scope of those contemplated by the claims of the '109 patent, nor any additional guidance as to how any of these various Factor B proteins would work with the other claimed components of such claims to generate a functional assay capable of detecting endotoxin. Jain, ¶¶110-11.

In view of this, a POSA would have had to engage in significant trial-and-error experimentation to identify all of the possible gene/amino acid sequences for

the various species of horseshoe crab (while such information for *Limulus polyphemus* was not even then known), would have had to work to express such proteins in all varieties of mammalian expression systems (at a minimum CHO and HEK), and would have had to ensure that such Factor B proteins worked with the other possible varieties of recombinant Factor C and Pro-clotting enzyme (from the same or different species of horseshoe crabs and expressed via the same or different host cell types) to detect endotoxin. Such experimentation would have been undue and unreasonable for a POSA as of 2013. Jain, ¶112.

ii. Production of Recombinant Pro-clotting Enzyme From Any Horseshoe Crab Species in Any Mammalian Expression System as of 2013 Would Have Required Undue Experimentation.

As with Factor B, claim 1 of the '109 patent requires the assay agent to comprise *any* horseshoe Pro-clotting enzyme having activity of Pro-clotting enzyme from *any* species of horseshoe crab and expressed in *any* mammalian cell as a host cell. As with Factor B, the '767 Application falls well short of enabling the full scope of this aspect of claim 1. Jain, ¶113-14.

The '767 Application also posits that the Pro-clotting enzyme of the “present invention” can be variants of such sequences “so long as the variant has activity of Pro-clotting enzyme” (Ex. 1017, 59-60(¶0049-50)), which can be confirmed by “combining the Pro-clotting enzyme of the present invention with a suitable Factor C and a suitable Factor B in the presence of endotoxin, and detecting the progress

of the cascade reaction.” Ex. 1017, 60-61(¶¶0051-52). As with Factor B, the only instruction provided in the ’767 Application regarding generating recombinant Pro-clotting enzyme is an example where the inventors purportedly prepared recombinant Pro-clotting enzyme using DNA encoding Pro-clotting enzyme from the *Tachypleus tridentatus* species of horseshoe crab, expressed in an insect cell (Sf9) expression system. Ex. 1017, 89-90(¶¶0118-120). The ’767 Application provides no guidance or teaching whatsoever as to how a POSA would make or use Pro-clotting enzymes across the full scope of those contemplated by claim 1 of the ’109 patent, nor any additional guidance as to how any of these various Pro-clotting enzymes would work with the other claimed components of such claims to generate a functional assay able to detect endotoxin. Jain, ¶¶115-17.

As with Factor B, a POSA would have had to engage in significant trial-and-error experimentation to identify all of the possible gene/amino acid sequences for the various species of horseshoe crab (while such information for *Limulus polyphemus* was not even then known), would have had to work to express such enzymes in all varieties of mammalian expression systems (at a minimum CHO and HEK), and would have had to ensure that such Pro-clotting enzymes worked with the other possible varieties of recombinant Factor C and Factor B (from the same or different species of horseshoe crabs and expressed via the same or

different host cell types) to detect endotoxin. Such experimentation would have been undue and unreasonable for a POSA as of 2013. Jain, ¶118.

iii. Combining Any of the Above Possibilities In Any One of At Least 3,456 Possible Assemblies of Challenged Claim 1 Would Have Required Undue Experimentation.

Based on the disclosures provided in the '767 Application regarding options for species of horseshoe crab and options for mammalian expression systems, challenged claim 1 encompasses at least 3,456 different possible combinations of the three required components (Factor C, Factor B, Pro-clotting enzyme).

However, as discussed above, the '767 Application *does not provide a single example* of any of these combinations. Instead, the only example of recombinant production of Factor B or Pro-clotting enzyme provided in the '767 Application is via the *insect* (Sf9) expression system. Ex. 1017, 89-90(¶0118-120). And in describing the measurement of activity of Factor C, the '767 Application states only generically that “Each of the above-prepared four types of Factor C was combined with other factors.” Ex. 1017, 93(¶0128). Jain, ¶¶119-120

Preparing and assembling the assay of challenged claim 1 for detection of endotoxin would have required a POSA to engage in an unreasonable and undue level of experimentation both in determining how to assemble *even one example* of the thousands of possible combinations of proteins required by claim 1, but also in determining which such combinations yield a functional assay across the full

scope of possibilities. The disclosure in '767 Application falls short of the enablement requirement. *Inari Agriculture, Inc. v. Pioneer Hi-Bred Int'l, Inc.*, PGR2023-00022, Paper 50, at 32 (PTAB Oct. 10, 2024) (no enablement where claims covered broad swath of polypeptides with particular function but disclosure provided no means for knowing which polypeptides would meet such function without trial-and-error testing—"The central problem with Patent Owner's position is that *any* dual herbicide-degrading activity falls within the claim scope, but Patent Owner has not disclosed more than general indications of which amino acids might be involved in creating such activity despite claiming a broad swath of highly identical polypeptides. The Specification includes no disclosure that explains how one may reliably distinguish sequences that will result in polypeptides retaining dual herbicide-degrading activity short of preparing the polypeptides and testing their activity in the various scope of plant cells that fall within the scope of the claims."). Jain, ¶121-22.

B. Claim 10 is Not Enabled For The Same Reasons as Claim 1.

As noted above, independent claim 10 is near-identical to claim 1 except that its preamble recites, "A method for measuring endotoxin in a test specimen, the method comprising," (as opposed to "[a] method for producing an endotoxin assay agent") and claim 10 additionally includes the limitation, "mixing the endotoxin assay agent and a test specimen, and measuring progress of a cascade reaction."

EX1001, cls. 1, 10. The minor differences between claims 1 and 10 do not remedy the enablement deficiencies identified above. Jain, ¶123.

Like claim 1, claim 10 requires recombinant Factor C expressed and secreted from either the *Tachypleus tridentatus* or *Limulus polyphemus* species via the CHO or HEK mammalian expression systems. Like claim 1, claim 10 requires recombinant Factor B and Pro-clotting enzyme produced from any species of crab via any mammalian host system. Like claim 1, claim 10 allows for the three zymogen proteins to be produced via the same or different host cell systems and mixed-and-matched at will. And like claim 1, claim 10 requires the combination of proteins to be useful for “measuring endotoxin in a test specimen.” EX1001, cl. 10. Thus, for all of the reasons explained in Section IX.A, above, regarding the scope, breadth, and lack of teaching on how to make and use the invention of claim 1, apply equally to claim 10. For at least this reason, the ’767 Application fails to enable a POSA to make or use the full scope of the method of claim 10. Jain, ¶¶124-26.

C. None of Challenged Claims 2-9 Are Enabled by the Disclosure of the ’767 Application.

Dependent claims 2-9 narrow claim 1 in certain respects, none of which serve to limit those claims to a scope that is enabled by the disclosure found in the ’767 Application. Jain, ¶127.

1. Claims 2 and 3

Claims 2 and 3 recite that the Factor B and Pro-clotting enzyme components of the claimed assays, respectively, are expressed via “a Chinese Hamster Ovary cell or a Human Embryonic Kidney cell” however as discussed in Section IX.A.2.d, above, the ’767 Application provides no disclosure of how to produce these proteins recombinantly in *any* mammalian expression system at all, let alone in CHO or HEK cells. The only system that the ’767 Application describes as having been used for production of recombinant Factor B and Pro-clotting enzyme is the insect cell (Sf9) system and the ’767 Application disparages this Sf9 insect expression systems as generating inferior recombinant proteins with respect to endotoxin detection activity. Ex. 1017, 98(¶0137) (“Particularly, recombinant Factor C (CHO) exhibited the highest residual activity in many cases. In contrast, recombinant Factor C (Sf9) was most susceptible to reaction inhibition in many injections.”). The ’767 Application disparages other insect expression systems as failing to express functional proteins at all. Ex. 1017, 95-96(¶0132) (“[T]he recombinant Factor C derived from *Carcinoscorpius rotundicauda* and produced in insect cell S2 (132 kDa) is reported to exhibit no protease activity in response to endotoxin.”); Jain, ¶128.

Moreover as discussed in Section VIII.C, above, the genus defined by claims 2 and 3 is as broad as the conservatively estimated genus of claim 1. Jain, ¶129.

The '767 Application's disclosure of expressing Factor B and Pro-clotting enzyme from a single species (*Tachypleus tridentatus*) via the Sf9 insect cell system would not have enabled a POSA to make and use the full scope of claim 2 wherein the recombinant Factor B proteins and Pro-clotting enzymes of the claimed assay are to be derived from any species of horseshoe crab, are expressed in CHO or HEK cells, and must work in an assay with other zymogen proteins produced from the same or different species, via the same or different expression systems, to detect endotoxin.

Instead, a POSA would have had to engage in significant and undue experimentation and trial-and-error to arrive at Factor B proteins (claim 2) and Pro-clotting enzymes (claim 3) suitable for use in the endotoxin detection assays of such claims. Jain, ¶130.

2. Claim 4

Claim 4 limits the species of Factor B and Pro-clotting enzymes to *Tachypleus tridentatus* and *Limulus polyphemus*. Again, while this narrowing of species options reduces the genus of endotoxin detection assays to at least 864 members, the '767 Application still fails to enable a POSA how to make and use such assay because, again, claim 4 requires that Factor B and Pro-clotting enzyme are recombinantly expressed in a mammalian cell as a host cell and the '767 Application only provides guidance regarding the recombinant expression of these

zymogen proteins in insect expression systems. Ex. 1017, 89-90(¶¶0118-120). Jain, ¶¶131-32.

Claim 4 also is broad enough to encompass production of the endotoxin assay wherein the three zymogen proteins are expressed in the same or different host cells, but as discussed in Section IX.A.2.d.iii, above, the '767 Application provides no examples or guidance on how to make or use an assay encompassing either of these combination scenarios. And claim 4 recites production of *Tachypleus tridentatus* and *Limulus polyphemus* zymogen proteins, but again, the gene and amino acid sequences for such proteins from the *Limulus polyphemus* species of horseshoe crab was not yet known or disclosed. See § VIII.B.2, *supra*. For the same reasons that the '767 Application does not enable the genus of challenged claim 1, it also does not enable the slightly narrower genus of claim 4. Jain, ¶¶133-34.

3. Claims 5-9

Challenged claims 5-9 depend from claim 1 but recite additional details about the claimed assay. Claims 5-6 recite features of Factor C (having sialic acid of a particular amount (5) or having particular molecular weight (6)). The '767 Application posits that expression of Factor C in mammalian cells generates Factor C with greater (α -2,3)-linked terminal sialic acid in a greater amount compared with Factor C expressed using Sf9 (insect cells). Ex. 1017, 98-99(¶¶0137-38).

However, such theory does not serve to limit the genus of possible combinations set forth in challenged claim 1, nor does it provide a POSA with sufficient information to make or use all of the thousands of possible combinations of recombinant proteins for making the claimed endotoxin assay agent. Jain, ¶¶135-36.

Challenged claim 9 requires that the three zymogen proteins are “separately expressed in individually established host cells” however there is no indication in the ’767 Application regarding how to ensure that factors that are separately expressed can be then combined to produce a functioning endotoxin assay agent particularly where it is unclear from the ’767 Application what concentration of each protein should be used in order to generate the claimed endotoxin detection agent across all of the thousands of possible combinations of proteins encompassed by claim 1, to generate a functional endotoxin detection agent. Jain, ¶137.

Finally, challenged claims 7-8 recited filtering the culture supernatant comprising the horseshoe crab Factor C (claim 7) and formulating the assay as a solid, liquid, or gel (claim 8). Any disclosure provided by the ’767 Application as to these additional details (of claims 7 and 8) does not remedy the lack of enablement of claim 1 as demonstrated in Section IX.A, above, and so for the same reasons discussed above, claims 5-9 are not enabled by the ’767 Application. Jain, ¶¶138-39.

For at least these reasons, the '767 Application does not enable a POSA to make and use the full scope of the invention recited in challenged claims 1-10.

X. GROUND 3: THE '629 PUBLICATION ANTICIPATES CLAIMS 1-10 OF THE '109 PATENT.

Grounds 1 and 2 above demonstrate that challenged claims 1-10 are unpatentable as failing to find adequate written description support or an enabling disclosure in the '767 Application (identical to the '109 patent specification itself and all applications in the priority chain of the '109 patent). To the extent Patent Owner pivots from the priority claim of the '109 patent and argues that its specification as filed on July 3, 2023, in view of the advancement of the art over the preceding decade, adequately describes and enables such claims, those claims are anticipated by (or at the very least would have been obvious over) intervening prior art such as U.S. Pat. Publication No. 2019/0241629 ("the '629 Publication") published on August 8, 2019. To the extent Patent Owner seeks to establish entitlement to any other effective filing date, such would be the burden of Patent Owner and would raise factually intensive issues warranting institution and a trial for adequate determination.

A. The '629 Publication Is Prior Art To The Challenged Claims As Those Claims Are Not Entitled To An Effective Filing Date Earlier Than The Actual Filing Date of the '109 Patent (July 3, 2023).

The '629 Publication (EX1015) is the August 8, 2019 United States Publication of PCT/JP2017/037629 (Published as WO 2018/074498). It is titled, “Recombinant Proteins Derived From Genus *Limulus*, and DNA Molecules Encoding Same,” and lists Hikaru Mizumura, Yuki Kobayashi, and Toshio Oda as inventors. If Patent Owner argues—or this Board determines—that the challenged claims 1-10 are entitled to an effective filing date of no earlier than the July 3, 2023 actual filing date of the '109 patent, the '629 Publication is prior art to the '109 patent under 35 U.S.C. § 102(a)(1). None of the exceptions of 35 U.S.C. § 102(b) apply because the '629 Publication was published more than one year prior to the actual filing date of the '109 patent. Jain, ¶¶141-45

B. The '629 Publication Anticipates Challenged Claim 1.

1. [1PRE.A] “A method for producing an endotoxin assay agent”

The '629 Publication describes the detection of endotoxin via what it refers to as “an assay system” and describes the assembly of such assay system to measure the “activation of the three types of recombinant proteins depending on an endotoxin.” EX1015, ¶¶0353-358 (“In the presence of 50 mM Tris buffer solution (pH 8.0) and a synthetic substrate (Boc-LGR-pNA), with respect to various combinations of the three types of recombinant proteins obtained in the above (6),

activation of the three types of recombinant proteins depending on an endotoxin was examined....[T]he cascade reaction is caused by contact with an endotoxin. Further, it was shown for the first time that by utilizing these recombinant proteins, an endotoxin can be detected.”); *see also id.*, ¶¶0268-0277, cl. 1-4; Jain, ¶146.

2. [1PRE.B] “comprising a horseshoe crab Factor C, a horseshoe crab Factor B, and a horseshoe crab Pro-clotting enzyme, the method comprising”

The '629 Publication discloses the expression of horseshoe crab Factor C, Factor B, and Pro-clotting enzyme. EX1015, ¶¶0350-352 (“(6) Expression of Recombinant Protein...By doing this, the expression and acquisition of the protein (SEQ ID NO: 2) that may have the factor C activity of *Limulus polyphemus*, the protein (SEQ ID NO: 6) that may have the factor B activity thereof, and the protein (SEQ ID NO: 14) that may have the proclotting enzyme activity thereof were achieved for the first time. The analysis of the activity of these proteins will be described below.”); *see also id.*, cls. 1-4, ¶¶0135-137, 0169-171, 0182-184; Jain, ¶147.

3. [1A] “expressing the horseshoe crab Factor C in a Chinese Hamster Ovary cell or a Human Embryonic Kidney cell as a host cell,”

The '629 Publication discloses expression of Factor C in a CHO cell. EX1015, ¶¶0341-345 (“[T]he elucidation of the full-length sequences (SEQ ID NO: 1 and SEQ ID NO: 3) of cDNAs encoding a protein that may have the factor

C activity of *Limulus polyphemus*, and the full-length sequences (SEQ ID NO: 2 and SEQ ID NO: 4) of amino acids of the protein was achieved for the first time.”), 0350 (“The cDNA (SEQ ID NO: 13) obtained in the above (5) was ligated to a vector pCA7 for protein expression in mammalian cells, whereby an expression plasmid was obtained. The cDNA (SEQ ID NO: 5) obtained in the above (4) was ligated to the vector pCA7 for protein expression according to a literature (Kobayashi et al., 2015, J Biol Chem, 290: 19379-19386)⁸, whereby an expression plasmid was obtained. By using these expression plasmids and the expression plasmid (in which the cDNA of SEQ ID NO: 1 was integrated) obtained in the above (3-7), and ExpiCHO™ Expression System (Thermo Fisher Scientific), recombinant proteins thereof were obtained as culture supernatant fractions.”), 0351-352; *see also id.*, ¶0161; Jain, ¶148.

4. [1B] “secreting the horseshoe crab Factor C into an extracellular culture supernatant,”

The '629 Publication discloses secreting the horseshoe crab Factor C into an extracellular culture supernatant. EX1015, ¶0350 (“(6) Expression of Recombinant Protein [0350] The cDNA (SEQ ID NO: 13) obtained in the above (5) was ligated

⁸ Kobayashi et al., (Ex. 1007, 19385) incorporated by reference into the '629 Publication, reported on the production of functional recombinant Factor B in the HEK cell line.

to a vector pCA7 for protein expression in mammalian cells, whereby an expression plasmid was obtained. The cDNA (SEQ ID NO: 5) obtained in the above (4) was ligated to the vector pCA7 for protein expression according to a literature (Kobayashi et al., 2015, J Biol Chem, 290: 19379-19386), whereby an expression plasmid was obtained. By using these expression plasmids and the expression plasmid (*in which the cDNA of SEQ ID NO: 1 was integrated*) *obtained in the above (3-7), and ExpiCHO™ Expression System (Thermo Fisher Scientific), recombinant proteins thereof were obtained as culture supernatant fractions.*"); Jain, ¶149.

5. [1C] “and recovering the horseshoe crab Factor C in the culture supernatant,”

The '629 Publication discloses recovering the Factor C in the culture supernatant. EX1015, ¶¶0350-352 (“By using these expression plasmids and the expression plasmid (in which the cDNA of SEQ ID NO: 1 was integrated) obtained in the above (3-7), and ExpiCHO™ Expression System (Thermo Fisher Scientific), recombinant proteins thereof were *obtained as culture supernatant fractions*. The transfection of the expression plasmids into cells and *collection of the recombinant proteins* were carried out according to the accompanying instructions. By doing this, the expression and *acquisition of the protein (SEQ ID NO: 2) that may have the factor C activity* of *Limulus polyphemus*, the protein (SEQ ID NO: 6) that may have the factor B activity thereof, and the protein (SEQ

ID NO: 14) that may have the proclotting enzyme activity thereof were achieved for the first time. The analysis of the activity of these proteins will be described below.”); Jain, ¶150.

6. [1D] “wherein the recovered horseshoe Factor C has activity of Factor C, and”

The '629 Publication discloses that the recovered Factor C claimed has “activity of Factor C.” EX1015, ¶¶0352-355 (“By doing this, the expression and acquisition of the protein (SEQ ID NO: 2) that may have the factor C activity of *Limulus polyphemus*...[was] achieved for the first time....[A]ctivation of the three types of recombinant proteins depending on an endotoxin was examined using a United States Pharmacopeia reference standard endotoxin (USP-RSE, Seikagaku Corporation) (0 EU/mL and 0.05 EU/ml, EU is the endotoxin unit) as a specimen. This reaction was carried out at 37° C. for 30 minutes. If a cascade reaction proceeds in this assay system, the protein having factor C activity is activated by the endotoxin, the protein having factor B activity is activated by this activated protein having factor C activity, the protein having proclotting enzyme activity is activated by this activated protein having factor B activity, and the synthetic substrate Boc-LGR-pNA is cleaved by this activated protein having proclotting enzyme activity, whereby pNA is released. The release of pNA was detected by measuring a change in the absorbance (A405 nm). As a result, when all the three types of recombinant proteins were included, cleavage of the synthetic substrate

was observed (FIG. 3)....[I]t was shown for the first time that the expressed protein that may have the factor C activity, the expressed protein that may have the factor B activity, and the expressed protein that may have the proclotting enzyme activity ***have the factor C activity, the factor B activity, and the proclotting enzyme activity, respectively***, and the cascade reaction is caused by contact with an endotoxin. Further, it was shown for the first time that by utilizing these recombinant proteins, an endotoxin can be detected.”); Jain, ¶151.

7. [1E] “**wherein the horseshoe crab Factor C is a *Tachypleus tridentatus* Factor C or a *Limulus polyphemus* Factor C,**”

The '629 Publication discloses recombinant Factor C from the horseshoe crab species, *Limulus polyphemus*. EX1015, ¶¶0350-352 “(6) Expression of Recombinant Protein...By doing this, the expression and acquisition of the protein (SEQ ID NO: 2) that may have the factor C activity of *Limulus polyphemus*...[was] achieved for the first time. The analysis of the activity of these proteins will be described below.”), 0353-355 (“(7) Measurement of Activity...From this, it was shown for the first time that ***the expressed protein that may have the factor C activity***, the expressed protein that may have the factor B activity, and the expressed protein that may have the proclotting enzyme activity ***have the factor C activity***, the factor B activity, and the proclotting enzyme activity, respectively, and the cascade reaction is caused by contact with an

endotoxin. Further, it was shown for the first time that by utilizing these recombinant proteins, an endotoxin can be detected.”); Jain, ¶¶152-53.

8. [1F] “expressing the horseshoe crab Factor B having activity of Factor B in a mammalian cell as a host cell”

The '629 Publication discloses expressing horseshoe crab Factor B having the activity of Factor B. EX1015, ¶¶0346-347 (“(4) *Acquisition of cDNA (Second cDNA) of Protein Having Factor B Activity of Limulus polyphemus*...By doing this, the full-length sequences (SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, and SEQ ID NO: 11) of cDNAs encoding a protein that may have the factor B activity of *Limulus polyphemus*...were elucidated”), 0350-355 (“The cDNA (SEQ ID NO: 5) obtained in the above (4) was ligated to the vector pCA7 for protein expression according to a literature (Kobayashi et al., 2015, J Biol Chem, 290: 19379-19386), whereby an expression plasmid was obtained. By using these expression plasmids and the expression plasmid (in which the cDNA of SEQ ID NO: 1 was integrated) obtained in the above (3-7), *and ExpiCHO™ Expression System (Thermo Fisher Scientific)*, recombinant proteins thereof were obtained as culture supernatant fractions....[A]ctivation of the three types of recombinant proteins depending on an endotoxin was examined....As a result, when all the three types of recombinant proteins were included, cleavage of the synthetic substrate was observed (FIG. 3)....FB denotes the protein expressed from the cDNA obtained in the above

(4)....*From this, it was shown for the first time that the expressed protein that may have...the factor B activity, [had] the factor B activity.*”); Jain, ¶154.

9. [1G] “expressing the horseshoe crab Pro-clotting enzyme having activity of Pro-clotting enzyme in a mammalian cell as a host cell, and”

The '629 Publication discloses expressing horseshoe crab Pro-clotting enzyme having the activity of Pro-clotting enzyme. EX1015, ¶¶0348-349 (“(5) *Acquisition of cDNA (Third cDNA) of Protein Having Pro-clotting Enzyme Activity of Limulus polyphemus*...By doing this, the full-length sequences (SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, and SEQ ID NO: 19) of cDNAs encoding a protein that may have the proclotting enzyme activity of Limulus polyphemus...were elucidated”), 0350-355 (“*The cDNA (SEQ ID NO: 13) obtained in the above (5) was ligated to a vector pCA7 for protein expression in mammalian cells* whereby an expression plasmid was obtained....By using these expression plasmids and the expression plasmid (in which the cDNA of SEQ ID NO: 1 was integrated) obtained in the above (3-7), *and ExpiCHO™ Expression System* (Thermo Fisher Scientific), recombinant proteins thereof were obtained as culture supernatant fractions....[A]ctivation of the three types of recombinant proteins depending on an endotoxin was examined....As a result, when all the three types of recombinant proteins were included, cleavage of the synthetic substrate was observed (FIG. 3)....PCE denotes the protein expressed from the

cDNA obtained in the above (5)...*From this, it was shown for the first time that the expressed protein that may have the proclotting enzyme activity...[has] the proclotting enzyme activity.*"); Jain, ¶155.

10. [1H] “producing an endotoxin assay agent comprising the horseshoe crab Factor C, the horseshoe crab Factor B, and the horseshoe crab Pro-clotting enzyme,”

The '629 Publication discloses the production of an assay agent comprising all three Factors (Factor C, Factor B and pro-clotting enzyme), including steps to detect endotoxin using the recombinant horseshoe crab three-factor composition. EX1015, ¶¶0354-355 (“If a cascade reaction proceeds *in this assay system*, the protein having factor C activity is activated by the endotoxin, the protein having factor B activity is activated by this activated protein having factor C activity, the protein having proclotting enzyme activity is activated by this activated protein having factor B activity, and the synthetic substrate Boc-LGR-pNA is cleaved by this activated protein having proclotting enzyme activity, whereby pNA is released...(7) Measurement of Activity From this, it was shown for the first time that the expressed protein that may have the factor C activity, the expressed protein that may have the factor B activity, and the expressed protein that may have the proclotting enzyme activity *have the factor C activity, the factor B activity, and the proclotting enzyme activity, respectively, and the cascade reaction is caused by contact with an endotoxin. Further, it was shown for the first time that by*

utilizing these recombinant proteins, an endotoxin can be detected.”); *see also id.*, ¶¶0268-277, cls. 1-4; Jain, ¶156.

11. [1I] **“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.”**

The '629 Publication discloses the production of an endotoxin assay agent wherein the host cells for expressing Factor B, Factor C, and Pro-clotting enzyme are the same. EX1015, ¶0350 (“(6) Expression of Recombinant Protein [0350] The cDNA (SEQ ID NO: 13) obtained in the above (5) was ligated to a vector pCA7 for protein expression in mammalian cells, whereby an expression plasmid was obtained. The cDNA (SEQ ID NO: 5) obtained in the above (4) was ligated to the vector pCA7 for protein expression according to a literature (Kobayashi et al., 2015, J Biol Chem, 290: 19379-19386), whereby an expression plasmid was obtained. By using these expression plasmids and the expression plasmid (in which the cDNA of SEQ ID NO: 1 was integrated) obtained in the above (3-7), and ExpicHO™ Expression System (Thermo Fisher Scientific), recombinant proteins thereof were obtained as culture supernatant fractions.”); *see also id.*, ¶0161; Jain, ¶157.

For at least the aforementioned reasons, the '629 Publication anticipates challenged claim 1. Jain, ¶158,

C. The '629 Publication Discloses Every Limitation of Independent Claim 10.

Independent claim 10 differs only minimally from claim 1. For the same reasons why the '629 Publication discloses each of the limitations of claim 1, that prior art reference discloses each of the overlapping limitations of claim 10. Jain, ¶159. The '629 Publication also discloses the additional non-overlapping limitation of challenged claim 10.

1. [10PRE] “A method for measuring endotoxin in a test specimen”

The '109 patent utilizes the term “specimen” broadly, in accordance with what a POSA would understand “specimen” to mean. EX1001, 29:7-23 (“The test specimen which can be subjected to endotoxin assay is not particularly limited. Examples of the specimen include water for medical use...The test specimen may be, for example, an injection.”). The '629 Publication discloses a method for measuring endotoxin in a test specimen. EX1015, ¶¶0064-75 (“A method for detecting an endotoxin in a specimen, including a step of bringing the recombinant first protein into contact with the specimen.”), 0258-267 (“The method for detecting an endotoxin of the present invention is a method for detecting an endotoxin in a specimen including a step of bringing the recombinant first protein into contact with the specimen.”), 0353-355 (“In the presence of 50 mM Tris buffer solution (pH 8.0) and a synthetic substrate (Boc-LGR-pNA), with respect to

various combinations of the three types of recombinant proteins obtained in the above (6), *activation of the three types of recombinant proteins depending on an endotoxin was examined using a United States Pharmacopeia reference standard endotoxin (USP-RSE, Seikagaku Corporation) (0 EU/mL and 0.05 EU/ml, EU is the endotoxin unit) as a specimen*. This reaction was carried out at 37° C. for 30 minutes....[T]he cascade reaction is caused by contact with an endotoxin. Further, it was shown for the first time that by utilizing these recombinant proteins, an endotoxin can be detected.”); *see also id.* cls. 1-4; Jain, ¶¶160-61.

2. The '629 Publication Discloses Limitations [10A]-[10H] and [10K] For The Same Reasons Discussed Above Regarding Limitations [1A]-[1I].

All but one of the remaining limitations of claim 10 is identical to those discussed above regarding claim 1. Jain, ¶162. The following table relates the limitations of claim 10 with the discussion of the same limitation above in the context of claim 1. Consequently, the '629 Publication discloses these limitations of claim 10 for the same reasons it discloses them for claim 1. Jain, ¶163.

[10A] expressing the horseshoe crab Factor C in a Chinese Hamster Ovary cell or a Human Embryonic Kidney cell as a host cell,	<i>See discussion of [1A] above.</i>
[10B] secreting the horseshoe crab Factor C into an extracellular culture supernatant,	<i>See discussion of [1B] above.</i>
[10C] and recovering the horseshoe crab Factor C having activity of Factor C secreted in the culture supernatant,	<i>See discussion of [1C] above.</i>

[10D] wherein the recovered horseshoe Factor C has activity of Factor C, and	See discussion of [1D] above.
[10E] wherein the horseshoe crab Factor C is a <i>Tachypleus tridentatus</i> Factor C or a <i>Limulus polyphemus</i> Factor C,	See discussion of [1E] above.
[10F] expressing the horseshoe crab Factor B having activity of Factor B in a mammalian cell as a host cell,	See discussion of [1F] above.
[10G] expressing the horseshoe crab Pro-clotting enzyme in a mammalian cell as a host cell,	See discussion of [1G] above.
[10H] producing an endotoxin assay agent comprising the horseshoe crab Factor C, the horseshoe crab Factor B, and the horseshoe crab Pro-clotting enzyme,	See discussion of [1H] above.
[10K] 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.	See discussion of [1I] above.

3. The '629 Publication Discloses Limitations [10I] and [10J]

a. [10I] “mixing the endotoxin assay agent and a test specimen, and”

The '109 Patent uses the term “mixing” broadly and in accordance with how a POSA would understand that term. EX1001, 26:24-32 (“For example, the step of mixing the endotoxin assay agent of the present invention with the test specimen may comprise the following steps (A) to (C): (A) a step of adding the Factor C of the present invention to the reaction system; (B) a step of adding the Factor B of

the present invention to the reaction system; and (C) a step of adding the Pro-clotting enzyme to the reaction system.”). Jain, ¶164.

The '629 Publication discloses this additional limitation of challenged claim 10. EX1015, ¶¶0353-354 (“(7) Measurement of Activity *In the presence of 50 mM Tris buffer solution (pH 8.0) and a synthetic substrate (Boc-LGR-pNA), with respect to various combinations of the three types of recombinant proteins obtained in the above (6), activation of the three types of recombinant proteins depending on an endotoxin was examined using a United States Pharmacopeia reference standard endotoxin* (USP-RSE, Seikagaku Corporation) (0 EU/mL and 0.05 EU/ml, EU is the endotoxin unit) as a specimen. This reaction was carried out at 37° C. for 30 minutes....The final concentrations of the proteins in the reaction solution (100 µL) *in a state of being mixed with the endotoxin specimen* were as follows: FC: 22.8 µg/mL; FB: 20.0 µg/mL; and PCE: 23.5 µg/mL.”); *see also id.*, ¶¶0266, 0272; *see also* Jain, ¶165.

b. [10J] “measuring progress of a cascade reaction,”

The '629 Publication discloses the measuring of progress of a cascade reaction as a method for measuring endotoxin. EX1015, ¶0354 (“If a cascade reaction proceeds in this assay system, the protein having factor C activity is activated by the endotoxin, the protein having factor B activity is activated by this activated protein having factor C activity, the protein having proclotting enzyme

activity is activated by this activated protein having factor B activity, and the synthetic substrate Boc-LGR-pNA is cleaved by this activated protein having proclotting enzyme activity, whereby pNA is released. *The release of pNA was detected by measuring a change in the absorbance (A405 nm). As a result, when all the three types of recombinant proteins were included, cleavage of the synthetic substrate was observed (FIG. 3).*”). For at least the aforementioned reasons, the ’629 Publication anticipates challenged claim 10. Jain, ¶¶166-67.

D. The ’629 Publication Discloses Every Limitation of Challenged Claims 2-10.

1. Claim 2

Claim 2 depends from claim 1 but further requires that “the mammalian cell expressing the Factor B is a Chinese Hamster Ovary cell or a Human Embryonic Kidney cell.” The ’629 Publication discloses this additional limitation on the expression of Factor B. EX1015, ¶¶0346-347 (“(4) Acquisition of cDNA (Second cDNA) of Protein Having Factor B Activity of *Limulus polyphemus*...By doing this, the full-length sequences (SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, and SEQ ID NO: 11) of cDNAs encoding a protein that may have the factor B activity of *Limulus polyphemus*...were elucidated.”), 0350 (“The cDNA (SEQ ID NO: 5) obtained in the above (4) was ligated to the vector pCA7 for protein expression according to a literature (Kobayashi et al., 2015, J Biol Chem, 290: 19379-19386), whereby an expression plasmid was obtained. By using these expression plasmids

and the expression plasmid (in which the cDNA of SEQ ID NO: 1 was integrated) obtained in the above (3-7), and ExpiCHO™ Expression System (Thermo Fisher Scientific), recombinant proteins thereof were obtained as culture supernatant fractions.”); Jain, ¶¶168-69.

2. Claim 3

Claim 3 depends from claim 1 but further requires that “the mammalian cell expressing the Pro-clotting enzyme is a Chinese Hamster Ovary cell or a Human Embryonic Kidney cell.” The ’629 Publication discloses this additional limitation on the expression of Pro-clotting enzyme. EX1015, ¶¶0348-349 (“4) Acquisition of cDNA (Third cDNA) of Protein Having Proclotting Activity of Limulus polyphemus...By doing this, the full-length sequences (SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 19, and SEQ ID NO: 21) of cDNAs encoding a protein that may have the proclotting enzyme activity of Limulus polyphemus...were elucidated.”), 0350 (“The cDNA (SEQ ID NO: 13) obtained in the above (5) was ligated to the vector pCA7 for protein expression in mammalian cells, whereby an expression plasmid was obtained...By using these expression plasmids and the expression plasmid (in which the cDNA of SEQ ID NO: 1 was integrated) obtained in the above (3-7), and ExpiCHO™ Expression System (Thermo Fisher Scientific), recombinant proteins thereof were obtained as culture supernatant fractions.”); Jain, ¶¶170-71.

3. Claim 4

Claim 4 depends from claim 1 but further requires that “the horseshoe crab for the Factor B and/or the horseshoe crab for the Pro-clotting enzyme is selected from the group consisting of *Tachypleus tridentatus* and *Limulus polyphemus*.” The ’629 Publication discloses this additional limitation on the Factor B and Pro-clotting enzyme of the claimed assay. EX1015, ¶¶0346-349 (describing “Acquisition of cDNA (Second cDNA) of Protein Having Factor B Activity of *Limulus polyphemus*” and sequence reference for same (“By doing this, the full-length sequences (SEQ ID NO: 5...) of cDNAs encoding a protein that may have the factor B activity of *Limulus polyphemus*, and the full-length sequences”) and describing “Acquisition of cDNA (Third cDNA) of Protein Having Proclotting Enzyme Activity of *Limulus polyphemus*” and sequence reference for same (i.e., “By doing this, the full-length sequences (SEQ ID NO: 13...) of cDNAs encoding a protein that may have the proclotting enzyme activity of *Limulus polyphemus*”)); Jain, ¶¶172-74.

4. Claim 5

Claim 5 depends from claim 1 but further requires that the claimed Factor C contains “(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.” While the ’629 Publication does not explicitly state that the recombinant

Factor C protein described therein contains (α -2,3)-linked terminal sialic acid in a greater amount than that of recombinantly produced Factor C from insect cells, a POSA would understand this to be inherently disclosed by the teachings of the '629 Publication as to be the natural result of production of *Limulus polyphemus* recombinant Factor C expressed in CHO (mammalian) cells. The '629 Publication discloses the recombinant expression of Factor C via CHO cells. *See* EX1015, ¶¶0341-345, 0350. The prior art (including the 2015 publication of the '109 patent specification) explains that post-translational addition of (α -2,3)-linked terminal sialic acid is the result of recombinant production using mammalian expression system and is a result that does not occur with non-mammalian systems such as insect cells (Sf9). EX1016, ¶0325 ("In N-type sugar chain modification of a protein *in mammalian cells*, sugar molecules are stepwise added to an asparagine residue of the protein, and eventually, a sugar chain containing terminal sialic acid (i.e., complex-type) is formed."); *see also id.*, ¶0328 ("The above analysis indicates that the N-type sugar chain of recombinant Factor C expressed in mammalian cells (CHO and HEK) contains (α -2,3)-linked terminal sialic acid, and that the N-type sugar chain of recombinant Factor C expressed in insect cells (Sf9) contains no (α -2,3)-linked terminal sialic acid."); EX1019, 2 ("While native mammalian glycoproteins often have *complex* type N-glycans with terminal sialic acids, insect cell-derived recombinant glycoproteins usually have much simpler side chains,

known as *paucimannosidic* N-glycans, at sites normally occupied by complex, terminally sialylated structures.”). Jain, ¶¶175-77.

Because the '629 Publication reports production of *Limulus polyphemus* Factor C recombinantly via CHO mammalian cells and does not otherwise indicate or describe any mutations to such cells, a POSA would understand such Factor C to inherently containing (α -2,3)-linked terminal sialic acid in a greater amount compared with the same protein recombinantly expressed using the Sf9 insect cell system. Jain, ¶178; *see SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343-44 (Fed. Cir. 2005) (ruling that claim directed to PHC hemihydrate, was inherently anticipated by patentee's prior-art patent describing and claiming PHC anhydrate even though that prior-art patent did not describe the hemihydrate form of PHC where “[t]he '196 patent discloses a method of manufacturing PHC anhydrate that naturally results in the production of PHC hemihydrate”); *see also Wedeco UV Techs., Inc. v. Calgon Carbon Corp.*, No. 01-924 (JAG), 2006 WL 1867201, at *8-14 (D.N.J. 2006), *aff'd*, 223 F. App'x 982 (Fed. Cir. 2007) (granting summary judgment that claims directed to a process of killing a naturally occurring bacteria, Crypto, were inherently anticipated where each of the process steps was disclosed in the prior art and it was admitted that if the prior art process was applied to water containing the bacteria Crypto, the prior art process would disinfect the bacteria as claimed); *Schering Corp. v. Geneva Pharms.*, 339 F.3d

1373, 1379 (Fed. Cir. 2003) (affirming summary judgment that patentee’s own prior-art patent disclosing a drug inherently anticipated a later claimed metabolite of that drug even though the prior-art patent did not disclose anything about the metabolite because the record evidence showed that the metabolite naturally formed upon the ingestion of the prior-art drug when taken in a manner disclosed in the prior-art patent).

5. Claim 6

Claim 6 depends from claim 1 but further requires that the claimed Factor C “has a molecular weight of 115 kDa to 130 kDa, as measured through SDS-PAGE under a nonreducing condition.” While the ’629 Publication does not explicitly measure the recombinantly produced Factor C protein as part of its experimental disclosure and therefore does not explicitly report on the weight of Factor C as measured by SDS-PAGE under a nonreducing condition, a POSA in 2023 would have reasonably expected and immediately understood from the disclosure of the ’629 Publication that the recombinant Factor C protein described therein would have this weight. Jain, ¶179.

As early as 1991, the field had measured and characterized the weight of *native* Factor C from the *Limulus polyphemus* species of horseshoe crabs as 123 kDa. EX1025, 151 (“Characterization of L. polyphemus Factor C—The purity of

the final preparation of *L.*-factor C was examined by SDS-PAGE. The purified zymogen factor C gave a single band of 123 kDa under nonreduced conditions.”).

While recombinant expression of this protein in mammalian cells could generate a version with a slightly higher weight in view of post-translational modifications adding, for example, (α -2,3)-linked terminal sialic acid, a POSA would understand such weight to increase by only a few kilodaltons. Table 1 of the '109 patent itself (publicly available at least as early as October 29, 2015 in the United States publication of the '767 Application (EX1016, ¶0320), US 2015/0307864), demonstrates that *natural* lysate *Tachypleus tridentatus* Factor C was measured to have a weight of 124 kDa, but when produced by CHO DG22 and HEK293 mammalian cells, a weight of 128 and 124 kDa, respectively.

Based on the disclosure of recombinant production of Factor C in mammalian cells in the '629 Publication and based on a POSA's general knowledge about such proteins, such POSA would reasonably expect that the 123 kDa Factor C from native *Limulus polyphemus* (measured by SDS PAGE under nonreducing conditions) would weigh between 115 and 130 kDa when produced recombinantly pursuant to the protocol disclosed in the '629 Publication and measured under the same conditions (SDS PAGE under nonreducing conditions). Jain, ¶180.

6. Claim 7

Claim 7 depends from claim 1 but further recites that the claimed method requires “filtering the culture supernatant comprising the horseshoe crab Factor C.” The ’629 Publication discloses this additional limitation of challenged claim 7. EX1015, ¶0350 (“By using these expression plasmids and the expression plasmid (in which the cDNA of SEQ ID NO: 1 was integrated) obtained in the above (3-7), and ExpiCHO™ Expression System (Thermo Fisher Scientific), recombinant proteins thereof were obtained as culture supernatant fractions. The transfection of the expression plasmids into cells and collection of the recombinant proteins were carried out according to the accompanying instructions.”). The User Guide for the ExpiCHO™ Expression System (last updated in 2018) instructs—under the subheading “CLARIFICATION OF CELL CULTURE SUPERNATANT”—a user to “Filter supernatant through a 0.22-µm filter.” EX1041, 17. In view of the clear directive of the ’629 Publication to reference the “accompanying instructions” for the CHO expression system a POSA would have understood the ’629 Publication to be disclosing the filtering of the obtained culture supernatant fractions. Jain, ¶¶181-82.

7. Claim 8

Claim 8 depends from claim 1 but further requires that “the endotoxin assay agent is formulated as a solid, a liquid, or a gel.” The ’629 Publication discloses

that the recombinant Factor C, recombinant Factor B, and recombinant Pro-clotting enzyme are mixed in a solution (i.e., a liquid). EX1015, ¶0354 (“The final concentrations of the proteins in the reaction solution (100 L) in a state of being mixed with the endotoxin specimen were as follows: FC: 22.8 µg/mL; FB: 20.0 µg/mL; and PCE: 23.5 µg/mL. Each assay was carried out by setting N=3, and a standard deviation was also shown in the drawing as an error bar.”) A POSA would understand a “solution” to be a liquid. Jain, ¶¶183-84; *see also* EX1015, ¶0274 (“Further, the form of this detecting agent is also not particularly limited, and the agent can be formulated into an arbitrary form such as a solid form (for example, a lyophilized form) or a liquid form.”).

8. Claim 9

Claim 9 depends from claim 1 but further requires that the “horseshoe crab Factor C, the horseshoe crab Factor B, and the horseshoe crab Pro-clotting enzyme are separately expressed in individually established host cells.” The ’629 Application describes the separate expression of each zymogen protein in individual host cells. EX1015, ¶0350 (“The cDNA (SEQ ID NO: 13) obtained in the above (5) was ligated to a vector pCA7 for protein expression in mammalian cells, whereby an expression plasmid was obtained. The cDNA (SEQ ID NO: 5) obtained in the above (4) was ligated to the vector pCA7 for protein expression according to a literature (Kobayashi et al., 2015, J Biol Chem, 290: 19379-19386),

whereby an expression plasmid was obtained. By using these expression plasmids and the expression plasmid (in which the cDNA of SEQ ID NO: 1 was integrated) obtained in the above (3-7), and ExpiCHO™ Expression System (Thermo Fisher Scientific), recombinant proteins thereof were obtained as culture supernatant fractions.”); Jain, ¶¶185-86.

For at least the above reasons, the ’629 Publication anticipates challenged claims 1-10 of the ’109 patent. Jain, ¶187.

E. The ’629 Publication Is Enabled

The ’629 Publication is presumed to be enabled. *See e.g., Samsung Elecs. Co. v. Queen’s Univ. at Kingston*, IPR2015-00584, Paper 53, at 22 (PTAB July 27, 2016)) (“[P]rior art printed publications are presumptively enabling.”) (*citing In re Antor Media Corp.*, 689 F.3d 1282, 1287-88 (Fed. Cir. 2012)). In view of this presumption, Petitioner has satisfied its initial burden of production with respect to its anticipation challenge to claims 1-10. *E.g., Samsung*, IPR2015-00584, Paper 53, at 22-23 (*citing Impax Labs., Inc. v. Aventis Pharms., Inc.*, 545 F.3d 1312, 1316 (Fed. Cir. 2008); *see also Pfizer, Inc. v. Genentech, Inc.*, IPR2017-02019, Paper 16, at 18-19 (PTAB Feb. 12, 2018) (finding petitioner satisfied the burden of production when petitioner relied on a reference disclosing each limitation of the challenged claim and on expert testimony). Jain, ¶188.

Patent Owner thus carries the burden to argue or produce evidence that the '629 Publication is not prior art because it is not enabled. *E.g., Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1379-80 (Fed. Cir. 2015); *see also Samsung*, IPR2015-00584, Paper 53, at 22-23. But Patent Owner cannot meet this burden at least because POSAs would have been able to carry out the claimed methods and such POSAs ***did carry out*** the experiments described in the disclosure and examples of the '629 Publication without undue experimentation, and more is not required. *Jain* ¶¶189-90; *In re Gleave*, 560 F.3d 1331, 1335 (Fed. Cir. 2009) (observing that art anticipating a method claim need only show that a POSA “would know how to use—in other words, to practice or to carry out—the method in light of the reference,” but need not demonstrate utility).

The '629 Publication is enabling in any case. To be enabling, an anticipating reference must provide a description from which a POSA in the field of the invention can practice the subject matter alleged to anticipate the claimed invention, without undue experimentation. *Antor*, 689 F.3d at 1290-91. The '629 Publication provides not only general and background disclosure of the subject matter of the challenged claims, but experimental examples of recombinantly producing the three-factor assay claimed, using a mammalian expression system (CHO), to generate Factor C having the activity of Factor C, Factor B having the activity of Factor B, and Pro-clotting enzyme having the activity of Pro-clotting

enzyme for one of the two claimed horseshoe species (*Limulus polyphemus*), to successfully detect endotoxin. Jain, ¶¶191-92. A POSA would have been able to follow the detailed directives of the '629 Publication to assemble an endotoxin detection assay or to test for endotoxin within the scope of the options set forth in the challenged claims. Jain, ¶193.

For at least the foregoing reasons, if Patent Owner pivots away from priority claim and argues that the challenged claims are described and enabled by the disclosure of the '109 patent specification as-filed in view of the state of the art at that time (July 3, 2023), those claims are anticipated by the '629 Publication.

XI. CONCLUSION

Petitioner respectfully requests that the Board institute review and cancel claims 1-10 of the '109 patent.

Dated: January 15, 2025

Respectfully submitted,
Charles River Laboratories, Inc.

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

APPENDIX A: CLAIM LISTING

The following claim listing assigns element labels (e.g., [1A], [1B], etc.) to certain claims for clarity.

Claim 1
[1PRE.A] A method for producing an endotoxin assay agent
[1PRE.B] comprising a horseshoe crab Factor C, a horseshoe crab Factor B, and a horseshoe crab Pro-clotting enzyme, the method comprising:
[1A] expressing the horseshoe crab Factor C in a Chinese Hamster Ovary cell or a Human Embryonic Kidney cell as a host cell,
[1B] secreting the horseshoe crab Factor C into an extracellular culture supernatant,
[1C] and recovering the horseshoe crab Factor C in the culture supernatant,
[1D] wherein the recovered horseshoe Factor C has activity of Factor C, and
[1E] wherein the horseshoe crab Factor C is a <i>Tachypleus tridentatus</i> Factor C or a <i>Limulus polyphemus</i> Factor C,
[1F] expressing the horseshoe crab Factor B having activity of Factor B in a mammalian cell as a host cell,
[1G] expressing the horseshoe crab Pro-clotting enzyme having activity of Pro-clotting enzyme in a mammalian cell as a host cell, and
[1H] producing an endotoxin assay agent comprising the horseshoe crab Factor C, the horseshoe crab Factor B, and the horseshoe crab Pro-clotting enzyme,
[1I] 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.
Claim 2
The method according to claim 1, wherein the mammalian cell expressing the Factor B is a Chinese Hamster Ovary cell or a Human Embryonic Kidney cell.
Claim 3
The method according to claim 1, wherein the mammalian cell expressing the Pro-clotting enzyme is a Chinese Hamster Ovary cell or a Human Embryonic Kidney cell.
Claim 4
The method according to claim 1, wherein the horseshoe crab for the Factor B and/or the horseshoe crab for the Pro-clotting enzyme is selected from the group consisting of <i>Tachypleus tridentatus</i> and <i>Limulus polyphemus</i> .
Claim 5

The method according to claim 1, wherein the horseshoe crab Factor C contains (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
The method according to claim 1, wherein the horseshoe crab Factor C has a molecular weight of 115 kDa to 130 kDa, as measured through SDS-PAGE under a nonreducing condition.
Claim 7
The method according to claim 1, further comprising filtering the culture supernatant comprising the horseshoe crab Factor C.
Claim 8
The method according to claim 1, wherein the endotoxin assay agent is formulated as a solid, a liquid, or a gel.
Claim 9
The method according to claim 1, wherein the horseshoe crab Factor C, the horseshoe crab Factor B, and the horseshoe crab Pro-clotting enzyme are separately expressed in individually established host cells.
Claim 10
[10PRE] A method for measuring endotoxin in a test specimen, the method comprising
[10A] expressing a horseshoe crab Factor C in a Chinese Hamster Ovary cell or a Human Embryonic Kidney cell as a host cell,
[10B] secreting the horseshoe crab Factor C into an extracellular culture supernatant,
[10C] and recovering the horseshoe crab Factor C in the culture supernatant,
[10D] wherein the recovered horseshoe Factor C has activity of Factor C, and
[10E] wherein the horseshoe crab Factor C is a <i>Tachypleus tridentatus</i> Factor C or a <i>Limulus polyphemus</i> Factor C,
[10F] expressing a horseshoe crab Factor B having activity of Factor B in a mammalian cell as a host cell,
[10G] expressing a horseshoe crab Pro-clotting enzyme having activity of Pro-clotting enzyme in a mammalian cell as a host cell,
[10H] producing an endotoxin assay agent comprising the horseshoe crab Factor C, the horseshoe crab Factor B, and the horseshoe crab Pro-clotting enzyme,
[10I] mixing the endotoxin assay agent and a test specimen, and
[10J] measuring progress of a cascade reaction,
[10J] 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.

CERTIFICATE OF SERVICE UNDER 37 C.F.R. § 42.6 (E)(4)

I certify that on January 15, 2025, I will cause a copy of the foregoing document, including any exhibits or appendices filed therewith, to be served via Priority Express Mail at the following correspondence address of record for the patent:

SUGHRUE MION, PLLC
2000 PENNSYLVANIA AVENUE, N.W.
SUITE 9000
WASHINGTON, DC 20006

Date: January 15, 2025

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

CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24, the undersigned certifies that the foregoing Petition for *Inter Partes* Review contains 18,676 words excluding a table of contents, a table of authorities, Mandatory Notices under § 42.8, a certificate of service or word count, or appendix of exhibits or claim listing. Petitioner has relied on the word count feature of the word processing system used to create this paper in making this certification.

Date: January 15, 2025

/MacAulay Rush/

MacAulay Rush

Paralegal

WOLF, GREENFIELD & SACKS, P.C.