

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CHARLES RIVER LABORATORIES, INC.,

Petitioner,

v.

SEIKAGAKU CORPORATION,

Patent Owner.

Case No. IPR2025-00440

Patent No. 11,236,318

PATENT OWNER'S CONTINGENT MOTION TO AMEND

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<u>Exhibit No.</u>	<u>Description</u>
2001	Excerpt from U.S. Application No. 14/650,767 File History – Claims dated June 9, 2015
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2003	FAQs for Interim Processes for PTAB Workload Management, available at https://www.uspto.gov/patents/ptab/faqs/interim-processes-workload-management
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I. INTRODUCTION

Patent Owner Seikagaku Corporation (“Seikagaku” or “PO”) respectfully submits this contingent motion to amend to substitute claim 21 of U.S. Patent No. 11,236,318 (“the ’318 Patent”) for proposed claim 22, contingent on the outcome of this trial. If claim 21 is determined to be unpatentable by the Board, PO requests that the Board grant this Motion and issue the corresponding substitute claim 22 presented herein.

PO’s proposed substitute claim 22 meets all of the requirements of 35 U.S.C. § 316(d) and 37 C.F.R. § 42.21. While PO must demonstrate these requirements are met, it does not bear the burden of persuasion with respect to the patentability of the substitute claim. *Aqua Products Inc. v. Matal*, 872 F.3d 1290, 1306 (Fed. Cir. 2017) (en banc). As explained below, however, narrowed substitute claim 22 finds Section 112 support to be afforded a December 10, 2013 priority date, thus eliminating the references relied upon by Petitioner in its unpatentability grounds as prior art.

II. STATEMENT OF REQUESTED RELIEF

First, PO requests preliminary guidance pursuant to 37 C.F.R. § 42.121(a)(1)(ii) and the Scheduling Order (Paper 15 at 5). *Second*, should the Board find claim 21 unpatentable, PO requests that the Board consider substitute claim 22 (Appendix A).

III. SUBSTITUTE CLAIM 22 MEETS THE REQUIREMENTS OF 35 U.S.C. § 316 AND 37 C.F.R. § 42.121

A motion to amend must (i) propose a reasonable number of substitute claims; (ii) that respond to a ground of unpatentability involved in the trial; (iii) that do not enlarge the scope of the claims or introduce new matter; and (iv) are not shown by a preponderance of the evidence to be unpatentable. *See* Memorandum re: Guidance on Motions to Amend in view of *Aqua Products* (Nov. 21, 2017) at 2; 35 U.S.C. § 316(d); 37 C.F.R. § 42.121. Petitioner bears the burden of showing that the substitute claims are unpatentable. *Lectrosonics, Inc. v. Zaxcom, Inc.*, IPR2018-01129, Paper 15 at 4 (P.T.A.B. Feb. 25, 2019) (precedential) (“Lectrosonics”).

A. Proposed Substitute Claim 22 Listing

As required by 37 C.F.R. § 42.121(b), PO submits Appendix A listing substitute claim 22.

B. PO Proposes a Reasonable Number of Substitute Claims

“There is a rebuttable presumption that a reasonable number of substitute claims per challenged claim is one (1) substitute claim.” *Lectrosonics* at 4. PO proposes a one-for-one substitution, which is reasonable and thus satisfies 35 U.S.C. § 316(d)(1)(B) and 37 C.F.R. § 42.121(a)(3). *See Intuitive Surgical, Inc. v. Ethicon LLC*, IPR2018-00933, Paper 31 at 9 (P.T.A.B. Dec. 3, 2019); *see also Lectrosonics* at 45-46.

C. The Substitute Claim Responds to Patentability Grounds Involved in this Trial

Substitute claim 22 responds to Petitioner's arguments that claim 21 of the '318 Patent is not entitled to its December 10, 2013 priority date because the '767 Application does not provide adequate written description support or enable the full scope of the claim. Petitioner's Section 112 arguments include its assertion that the inventors did not possess the full scope of the claimed residual activity range or enable this full range without undue experimentation. *See, e.g.*, Pet. at 5.

This amendment directly responds to those priority date arguments by narrowing the residual activity limitations to overcome the priority date challenge, thus rendering Petitioner's unpatentability Grounds 1 and 2 moot because the relied-upon references are not prior art.

D. Substitute Claim 22 Does Not Broaden the Claim Scope or Introduce New Subject Matter

"A motion to amend may not present substitute claims that enlarge the scope of the claims of the challenged patent or introduce new subject matter." *Lectrosonics* at 6-8. PO's substitute claim complies with each of these requirements.

1. The Substitute Claim Does Not Broaden the Claim Scope

First, substitute claim 22 narrows the scope of the claim. As seen in Appendix A, substitute claim 22 narrows the scope of the claim by requiring the Factor C protein exhibit a "higher" residual activity in the presence of *both* 21 mM sodium

citrate and 16 mM magnesium sulfate, as opposed to the original claim 21 that only required a certain residual activity in one of these salt solutions. Moreover, substitute claim 22 further narrows the scope of the claim by incorporating a specific comparator for the residual activity (*i.e.*, requiring the residual activity of the recombinantly produced Factor C expressed in HEK293 cells to be “higher” as compared to the residual activity of Factor C expressed in a Sf9 cell or native *Limulus polyphemus* Factor C protein) as compared to original claim 21 that required a residual activity over a claimed minimum threshold.

2. The Substitute Claim Does Not Introduce New Matter

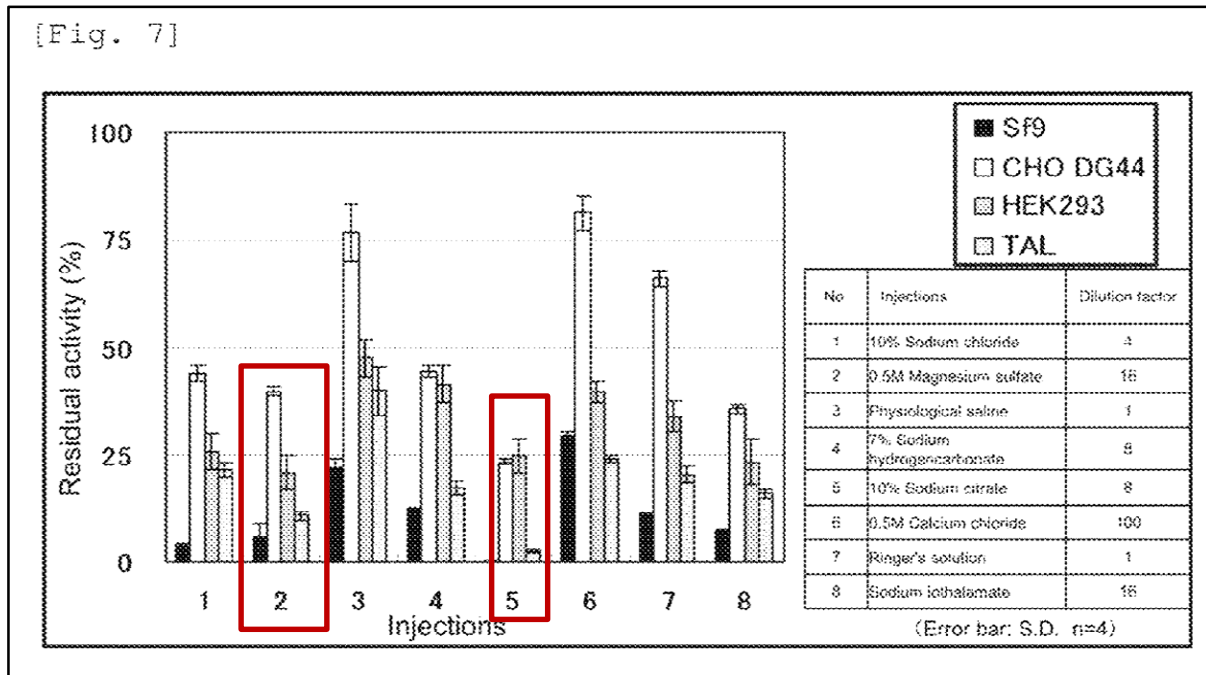
Second, substitute claim 22 does not introduce new subject matter but is instead supported by, not only the '318 Patent specification but also the priority '767 Application.¹ The specification explains that the “Factor C of the present invention may have low susceptibility to inhibition of activity by an ion” and that this “refers to the state that the Factor C of the present invention exhibits a high residual activity in the presence of an ion.” Ex. 1001 at 17:20-24. The specification expressly identifies recombinant Factor C expressed in insect cell Sf9 and native Factor C,

¹ As Petitioner concedes, the '318 Patent specification and the '767 Application specification are identical. Pet. at 21-22. Citations to the '318 Patent should thus be understood to also be present in the '767 Application.

which are the two comparators added to substitute claim 22, as examples of this control Factor C. *Id.* at 4:5-9, 4:21-25.

The specification further identifies salt solutions to measure the residual activity, including the claimed 21 mM sodium citrate and 16 mM magnesium sulfate, and it further states the “Factor C of the present invention may have any one of the above properties singly or *two or more of the above properties in combination.*” *Id.* at 17:31-18:38.² As evidenced in, for example, Figure 7, the specification further demonstrates that recombinantly produced Factor C in HEK293 cells exhibited higher residual activity in each of 21 mM sodium citrate and 16 mM magnesium sulfate as compared to a control factor C of native Factor C (TAL) or Factor C recombinantly produced in Sf9 cells. Ex. 1001 at 35:25-43; Fig. 7.

² Emphasis added unless otherwise noted.



Ex. 1001 at Figs. 4, 7 (annotated).

As such, the substitute claim 22 does not introduce new matter or enlarge the claim scope.

IV. PERSON OF ORDINARY SKILL IN THE ART (“POSA”)

In this motion and in the concurrently-filed PO Response, PO proposes the following definition of a POSA: a POSA would have a Ph.D. in molecular biology, biochemistry, or enzymology and at least two years of experience with cloning genes, expressing cloned genes as proteins, and characterizing them. Ex. 2038 ¶ 49. The POSA may also collaborate with others, including those with specific experience in conducting structure-function analyses of enzyme function, evaluating the activity of horseshoe crab zymogen proteins individually, or in a cascade reaction for endotoxin detection and quantitation. *Id.*

V. CLAIM CONSTRUCTION

In this Motion, Patent Owner agrees that the terms in substitute claim 22 can be afforded their plain and ordinary meaning.

VI. PROPOSED SUBSTITUTE CLAIM 22 IS PATENTABLE

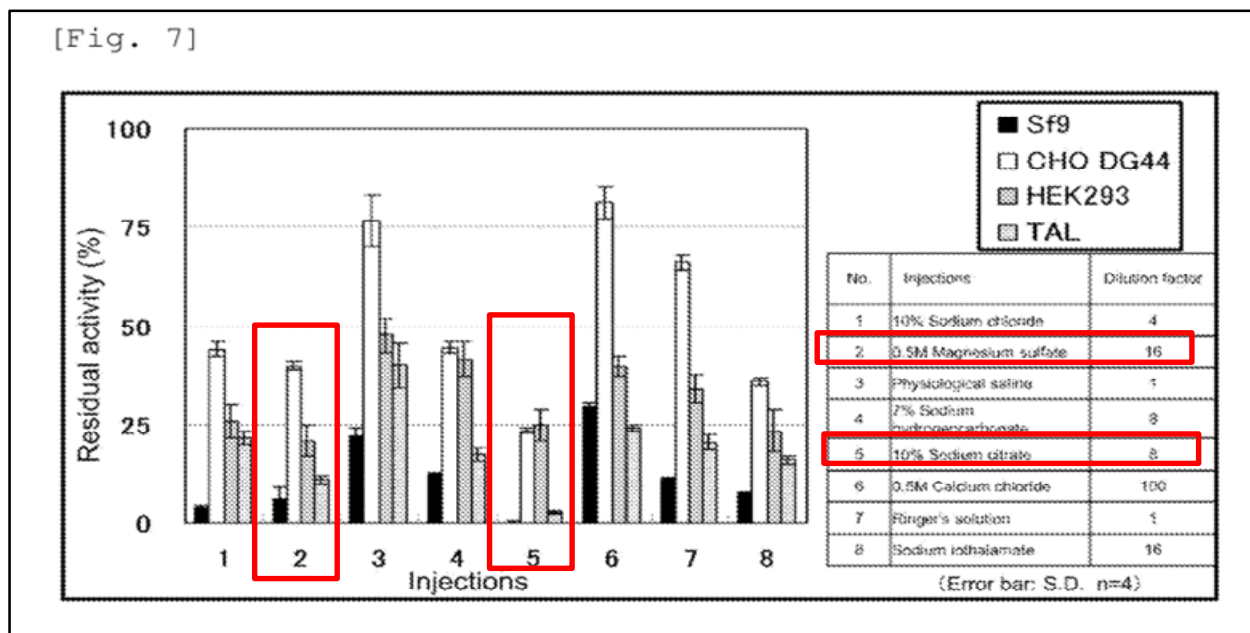
PO does not bear the burden of persuasion with respect to the patentability of the substitute claim 22. *Aqua Products*, 872 F.3d at 1306. Nonetheless, PO asserts that the contingent substitute claim 22 is patentable over the cited prior art because the substitute claim 22 is entitled to a December 10, 2013 priority date, thus rendering the references relied upon by Petitioner non-prior art. Contingent claim 22 narrows the residual activity limitation to recite “wherein the Factor C protein exhibits a higher residual activity in the presence of 21 mM sodium citrate and 16 mM magnesium sulfate, as compared with the corresponding *Limulus polyphemus* Factor C protein expressed in a Sf9 cell or a native *Limulus polyphemus* Factor C protein.” This residual activity limitation finds ample written description support and is enabled in the '767 Application.

A. Substitute Claim 22 Has Ample Written Description Support in the '767 Application

The '767 Application includes an example titled “Inhibition of activity by injection” that details measuring the residual activity of Factor C recombinantly expressed in HEK293 cells in the claimed salt solutions of 21 mM sodium citrate and 16 mM magnesium sulfate. Ex. 1006 at 96-99. The '767 Application not only

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discloses the procedure used for this measurement in Figure 4, but it also provides results in Figure 7, demonstrating that expression of Factor C in HEK293 cells resulted in a **higher** residual activity in the presence of 21 mM sodium citrate and in the presence of 16 mM magnesium sulfate as compared to corresponding *Tachypleus tridentatus* Factor C protein expressed in a Sf9 cell or a native *Tachypleus tridentatus* Factor C protein. Ex. 1006 at 96-99, 119.



Ex. 1006 at 122 (annotated).

Any argument by Petitioner that this data reflects only residual activity values for *Tachypleus tridentatus* and not the claimed *Limulus polyphemus* misses the mark. As the Federal Circuit has made clear, “the absence of examples . . . **does not** render the written description inadequate” and “actual reduction to practice is **not required** for written description.” *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1366 (Fed.

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Cir. 2006). Moreover, “a patentee may rely on information that is ‘well-known in the art’ for purposes of meeting the written description requirement,” because “the specification is viewed from the perspective of one of skill” in the relevant art. *Bos. Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1366 (Fed. Cir. 2011).

Factor C protein from *Limulus polyphemus* had been successfully isolated and characterized, as well as compared to Factor C from the *Tachypleus tridentatus* horseshoe crab as early as the 1990s. *See, e.g.*, Ex. 1022 at 150; Ex. 1025. Moreover, by October 31, 2012, researchers at the University of Connecticut had sequenced and deposited (i) a 188 Mb *Limulus polyphemus* cDNA amoebocyte transcriptome under BioProject accession number PRJNA178588; and (ii) a 4 Gb shotgun sequence of the *Limulus polyphemus* genome under BioProject accession number PRJNA178587. Ex. 2038 ¶¶ 36, 61. This sequence information was publicly available by at least **October 31, 2013**. *Id.* ¶ 37; Ex. 2052; Ex. 2053; Ex. 2054; Ex. 2057.

As PO's expert Dr. Schaefer explains, a POSA would have been capable of assembling **97.2% of the full Factor C coding sequence** based on the known similarities between *Tachypleus tridentatus* and *Limulus polyphemus*, as well as based on the publicly available University of Connecticut sequence information. Ex. 2038 ¶¶ 61-64. As Dr. Schaefer further explains, as of December 10, 2013, a POSA could have easily recovered the remaining sequence by applying standard methods

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well within the skill of a POSA. *Id.* ¶¶ 65-81. That the '767 Application did not expressly recite this sequence information is irrelevant to the written description analysis. *See, e.g., Falko-Gunter*, 448 F.3d at 1367-68.

As Patent Owner's expert Dr. Schaefer further explains, a POSA would have expected as of December 10, 2013 that key regions encoding functional units of Factor C and motifs for its interaction with partner proteins would be **highly conserved** across species of horseshoe crabs. Ex. 2038 ¶ 85; *see also id.* ¶ 20 (noting horseshoe crabs evolved slowly earning a "living fossils" moniker); *id.* ¶¶ 86-91. Indeed, as Dr. Schaefer notes, out of 1,020 amino acids, there are only **11 non-conservative substitutions** in either *C. rotundicauda* or *T. tridentatus* Factor C, with only **5 within identified conserved domains**. *Id.* ¶¶ 90-97; Ex. 2081.

Thus, a POSA would have understood that (i) the functional domains are highly conserved between species of horseshoe crab, and (ii) the '767 Application data in Figure 7 showing the claimed residual activity of *Tachypleus tridentatus* Factor C in HEK293 cells would translate to *Limulus polyphemus* Factor C in HEK293 cells maintaining the claimed residual activity properties. *Id.* ¶ 94.

Moreover, any argument by Petitioner that the substitute claim 22 language requires possession of a wide range of residual activities likewise fails. As written, substitute claim 22 merely requires the residual activity of the recombinantly produced Factor C in HEK293 cells be **higher** than the residual activity of the control

Factor C (*i.e.*, Factor C expressed in Sf9 cells or native Factor C). Figure 7, as discussed above, clearly demonstrates that the inventors had possession of this invention, and nothing more is required. While PO disagrees that claim 21 as originally written requires possession of a full range of residual activities, as explained in the Response filed concurrently herewith, if the Board should disagree, the proposed substitute claim 22 remedies that requirement by merely requiring the residual activity of the inventive Factor C be higher than specifically articulated control Factor C, which finds ample written description support for reasons discussed above. *See, e.g., Alcon Rsch. Ltd. v. Barr Lab'ys, Inc.*, 745 F.3d 1180, 1189 (Fed. Cir. 2014).

Thus, the knowledge of a POSA at the time of the '767 Application and the disclosures in the application itself, provide adequate written description support for substitute claim 22.

B. The '767 Application Enables the Full Scope of Substitute Claim 22 of the '318 Patent

Any assertion that the full scope of substitute claim 22 is not enabled by the '767 Application also fails. To the extent the Board agrees with Petitioner that claim 21 as originally written requires residual activity values across a wide claimed range, as discussed above, substitute claim 22 removes that requirement by merely requiring a comparative analysis that the inventive Factor C's residual activity be

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higher than the residual activity in control Factor C. With this narrowing in mind, undue experimentation would not have been required to make the full scope of substitute claim 22 based on the disclosure in the '767 Application.

To assess whether undue experimentation is required, courts examine a number of factual considerations referred to as the *Wands* factors, which include (i) the quantity of experimentation necessary, (ii) the amount of direction or guidance presented, (iii) presence or absence of working examples, (iv) nature of the invention, (v) state of the prior art, (vi) relative skill of those in the art, (vii) predictability or unpredictability of the art, and (viii) breadth of the claims. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). A proper analysis of the *Wands* factors demonstrates that undue experimentation would **not** have been required, and the '767 Application enables the full scope of substitute claim 22.

1. Substitute claim 22 is Not Broad (*Wands* Factor 8)

Substitute claim 22 is *narrowly* confined to a specific species of horseshoe crab (*Limulus polyphemus*) recombinantly expressed from a specific host cell (HEK293) with a higher residual activity in specifically claimed concentrations of specific salt solutions as compared to specifically identified control Factor C. It does not encompass a broad genus.

2. Quantity of Experimentation Necessary; Amount of Direction or Guidance Presented; Presence or Absence of Working Examples (*Wands* Factors 1-3)

The law does not require working examples to find enablement, *Alcon Rsch. Ltd. v. Barr Lab'ys, Inc.*, 745 F.3d 1180, 1189-1190 (Fed. Cir. 2014), and the '767 Application provides examples that a skilled artisan would have used as a roadmap to practice the full scope of the claimed invention without undue experimentation. The '767 Application describes producing Factor C in mammalian cells, including HEK293 cells, and discusses a specific example detailing the production of recombinant Factor C in HEK293 cells. Ex. 1006 at 53-54, 87-88. It also provides a specific procedure in Figure 4 for measuring Factor C activity and discloses a specific example where the residual activity of recombinantly produced Factor C, including Factor C expressed in HEK293 cells, was measured in the claimed salt solution concentrations and determined to be higher than the residual activity of the control Factor C. Ex. 1006 at 96-99, Figs. 4, 7.

With the specification's guidance, a skilled artisan would have known how to use HEK293 cells to recombinantly express Factor C and how to measure the residual activity of the Factor C in the claimed salt solution concentrations to achieve the claimed higher residual activity as compared to control Factor C. Ex. 2038 ¶¶ 114-118. The lack of the examples using *Limulus polyphemus* Factor C does not change the conclusion. Given what was well known in the prior art and the admitted

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high level of skill, a skilled artisan could have implemented the specification's teachings to make and use the claimed Factor C from *Limulus polyphemus* without undue experimentation. Ex. 2038 ¶ 116.

In sum, the specification would have enabled a skilled artisan to make and use Claim 22 because (i) undue experimentation had not been required to practice the invention, and (ii) the specification provides direction and examples regarding expression of Factor C in HEK293 cells and measuring residual activity in the claimed salt solutions.

**3. Nature of the Invention; State of the Prior Art; and
Predictability of the Art (*Wands* Factors 4, 5, 7)**

Wands factors 4, 5, and 7 further support that substitute claim 22 is enabled. Ex. 2038 ¶¶ 111-112.

**a. Undue Experimentation Would Not Have been
Required to Characterize the Sequence of *Limulus
Polyphemus* and Recombinantly Express it in
HEK293 Cells Before 2013**

As discussed, the '767 Application describes examples of recombinantly expressing Factor C in HEK293 cells. *See, e.g.*, Ex. 1006 at 53-54, 87-88. Additionally, as discussed, more than *two decades* before the 2013 filing date of the '767 Application, Dr. Tokunaga and his group had already isolated Factor C from *Limulus polyphemus* and compared its properties and amino acid compositions with those of *Tachypleus tridentatus*—the same species of horseshoe crab used in the

examples in the '767 Application. Ex. 1022 at 150-151, 155. As Dr. Tokunaga reported, the “immunological and biochemical properties” of the purified Factor C from *Limulus polyphemus* are “*indistinguishable*” from those of Factor C isolated from *Tachypleus tridentatus*, and “the individual amino acid compositions of the two proteins and of their chain subunits were *indistinguishable*.” Ex. 1022 at 150-151, 153.

Moreover, in 2003, researchers had successfully isolated Factor C from *Limulus polyphemus* and determined that “the Limulus factor C sequence closely matched the *Asian species, with >90% sequence identity*.” Ex. 2035 at [0134]. Additionally, by December 10, 2013, the information available from public sources would have allowed a POSA to arrive at the cDNA sequence of *Limulus polyphemus* Factor C through routine experimentation. Ex. 2038 ¶¶ 58-60.

Given the state of the prior art and the nature of the invention, a POSA would have had a ready, working knowledge of the sequence and the immunological and biochemical properties of *Limulus polyphemus* to practice the full scope of substitute claim 22 without undue experimentation. Ex. 2038 ¶¶ 111-112.

**b. Undue Experimentation Would Not Have Been
Required to Practice the Claimed Residual Activity in
Substitute Claim 22 Before 2013**

As discussed, the '767 Application details how to measure residual activity of Factor C recombinantly expressed in HEK293 cells, including in the salt solution

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concentrations of substitute claim 22. Ex. 1006 at 96-99, Figs. 4, 7. It also discloses that Factor C produced in HEK293 cells exhibited higher residual activity than control Factor C. Ex. 1006 at Fig. 7. It further identifies *Limulus polyphemus* in the “Modes for Carrying Out the Invention” section. Ex. 1006 at 40. Given this and the skilled artisan’s knowledge, undue experimentation would not have been required to practice the full scope of contingent claim 22. *See, e.g., Rimfrost AS v. Aker BioMarine Antarctic AS*, No. PGR2018-00033, Paper 9 at 10-14 (P.T.A.B. Aug. 29, 2018) (Petitioner failed to establish that the limitation “8% to 15% w/w ether phospholipid” was not enabled despite specification including only an example having 7.4%); *see also Alcon*, 745 F.3d at 1189.

4. Wands Factor 6 Supports a Finding that Substitute Claim 22 is Enabled

As even Petitioner’s expert admits, recombinant technology was well known in 2013. *See, e.g.,* Ex. 1002 ¶ 5 (describing his work in 2006-2008 “evaluat[ing] the recombinant Factor C endotoxin kit”). Moreover, as discussed, the ’767 Application describes the process for making recombinant Factor C using HEK293 cells and provides a procedure for assessing whether the recombinantly produced Factor C in HEK293 cells demonstrates higher residual activity than control Factor C in the claimed salt solution concentrations. Given the admitted high skill of a POSA, she would not have had to unduly experiment to design, express, and test recombinant

Factor C proteins, particularly in view of the roadmap provided by the '767 Application.

As such, under the *Wands* factors, the '767 Application teaches how to make and use the full scope of substitute claim 22 without undue experimentation and thus enables the claim.

Accordingly, the '767 Application provides written description support and enables the full scope of substitute claim 22 of the '318 Patent such that it should be afforded its December 10, 2013 priority date. With this proper priority date applied, none of the art relied upon by Petitioner in its two invalidity grounds qualifies as prior art and both grounds fail.

VII. SECONDARY CONSIDERATIONS OF NON-OBVIOUSNESS

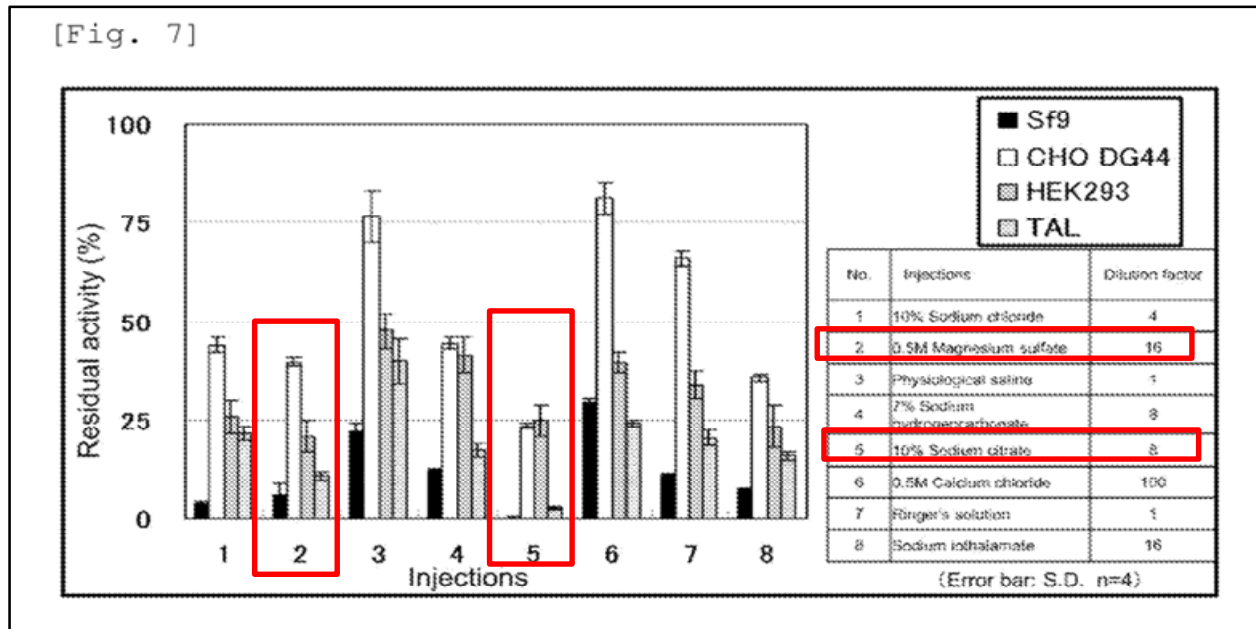
Assuming even the substitute claim 22 is not entitled to its December 10, 2013 priority date, the existence of secondary considerations of non-obviousness, specifically unexpected results, support a finding that substitute claim 22 of the '318 is not unpatentable. *See, e.g., Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573 (Fed. Cir. 1996) (“It is the secondary considerations that are often most probative and determinative of the ultimate conclusion of obviousness or nonobviousness.”).

“In considering unexpected results, courts ask whether the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the

relevant art would have found surprising or unexpected” compared to the prior art as of the priority date. *Forest Labs., LLC v. Sigmapharm Labs., LLC*, 918 F.3d 928, 937 (Fed. Cir. 2019) (cleaned up). The starting reference point for evaluating unexpectedness is the closest prior art. *See Bristol-Myers*, 752 F.3d at 977; *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006).

The closest prior art in this instance is Mizumura, which describes residual activity for *Tachypleus tridentatus* Factor C recombinantly produced in different cells, including in HEK293 cells. Ex. 1009 at Fig. 7. Substitute claim 22, however, requires the recombinantly produced Factor C be from *Limulus polyphemus*, not *Tachypleus tridentatus*. As evidenced by data presented during prosecution of the '318 Patent, as well as post-priority date evidence, Factor C from *Limulus polyphemus* exhibits unexpectedly superior residual activity values in the claimed 21 mM sodium citrate and 16 mM magnesium sulfate solutions as compared to the residual activity observed for Factor C from *Tachypleus tridentatus*.

In Mizumura, residual activity data for *Tachypleus tridentatus* Factor C recombinantly produced in CHO cells is provided in Figure 7 (reproduced below). Column 2 shows the residual activity in the claimed 16 mM magnesium sulfate while column 5 shows the residual activity in the claimed 21 mM sodium citrate.



Ex. 1009 at Fig. 7 (annotated).

From the data in Figure 7, the residual activity in the claimed 16 mM magnesium sulfate for Factor C recombinantly produced in CHO DG44 cells is approximately 40% and is approximately 20-25% for Factor C recombinantly produced in HEK293 cells. The residual activity in the claimed 21 mM sodium citrate for Factor C recombinantly produced in CHO DG44 cells is approximately 25% and is approximately 20-30% for Factor C recombinantly produced in HEK293 cells.

During prosecution of the '318 Patent, Patent Owner submitted a declaration from inventor Dr. Mizumura showing residual activity for recombinantly produced *Limulus polyphemus* Factor C in CHO cells (white boxes below). Column 2 illustrates the residual activity in the claimed 16 mM magnesium sulfate, and column

5 illustrates the residual activity in the claimed 21 mM sodium citrate. The residual activity in 16 mM magnesium sulfate for *Limulus polyphemus* Factor C recombinantly produced in CHO DG44 cells is approximately 50-55%. “Evidence of unexpected results ‘may be [considered] even if that evidence was obtained after the patent's filing or issue date.’” *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 923 F. Supp. 2d 602, 684 (D. Del. 2013), *aff'd*, 752 F.3d 967 (Fed. Cir. 2014). Column 2 illustrates the residual activity in the claimed 16 mM magnesium sulfate, and column 5 illustrates the residual activity in the claimed 21 mM sodium citrate. The residual activity in 16 mM magnesium sulfate for *Limulus polyphemus* Factor C recombinantly produced in CHO DG44 cells is approximately 50-55%.

When comparing the residual activity for recombinantly produced *Limulus polyphemus* Factor C in CHO DG44 cells as compared to recombinantly produced *Tachypleus tridentatus* Factor C in CHO DG44 cells, the *Limulus polyphemus* Factor C exhibits unexpectedly superior residual activity to *Tachypleus tridentatus*. Ex. 2042 ¶¶ 43-48.

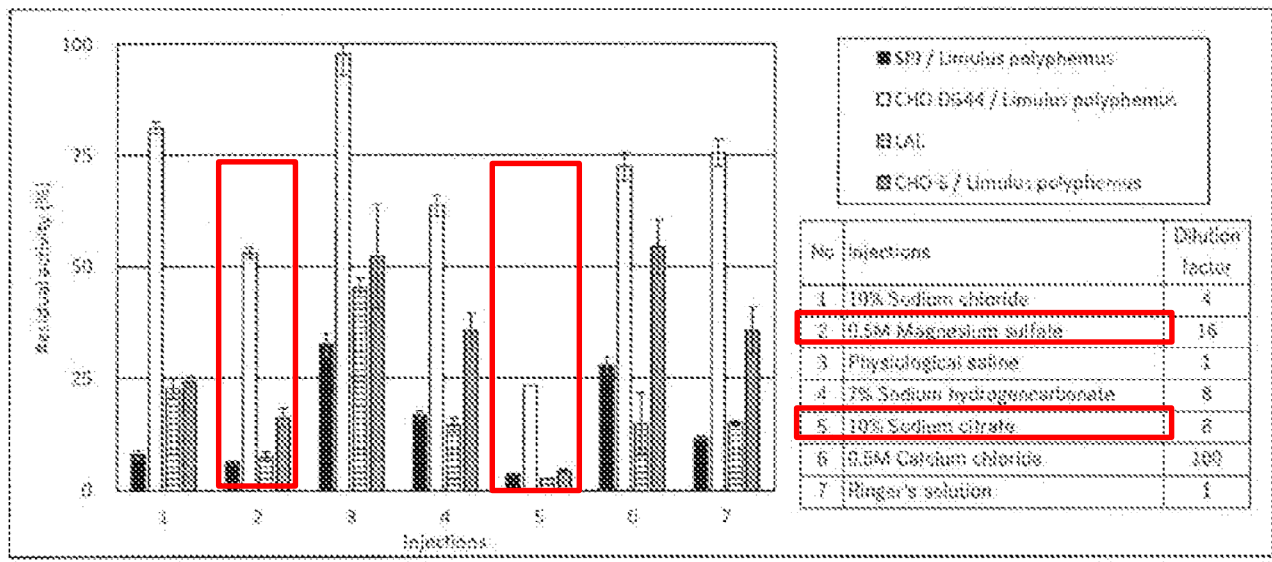


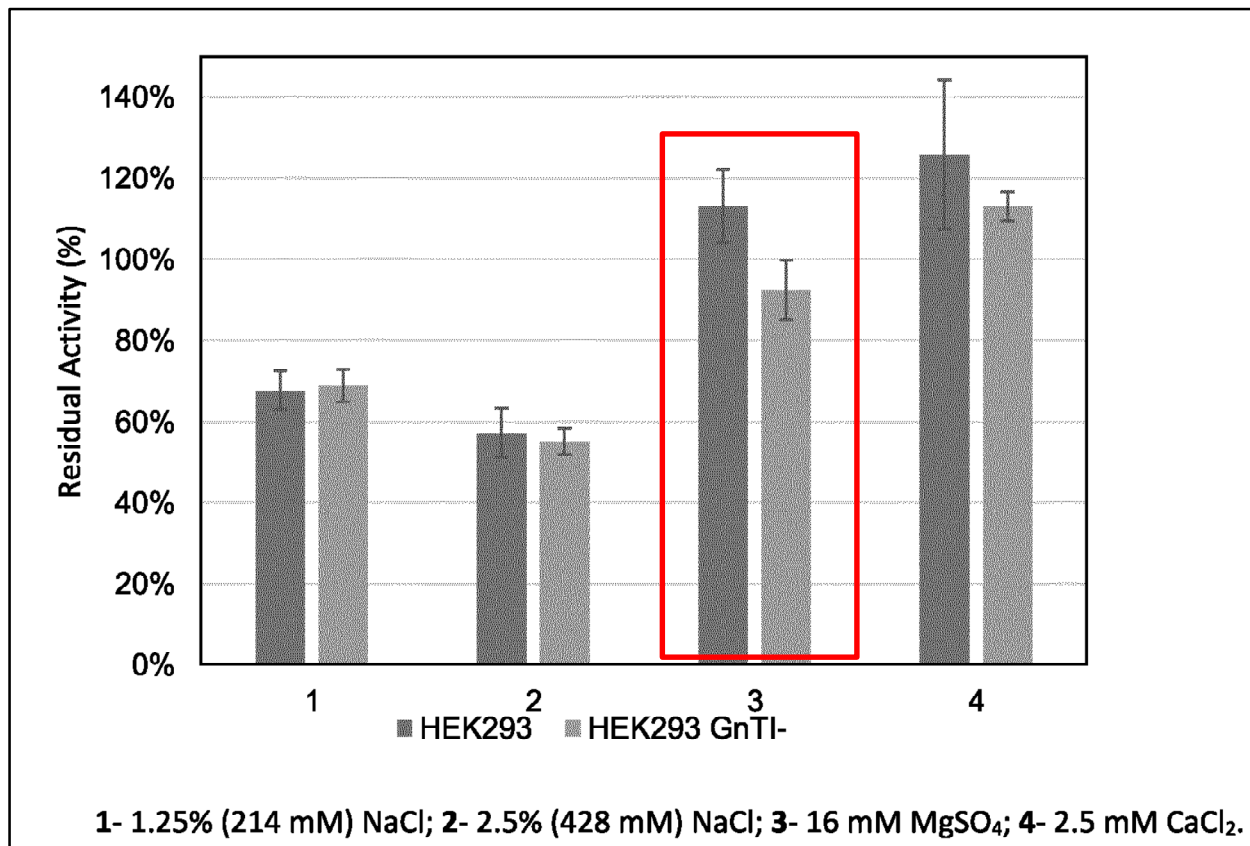
Fig. 1. Residual Activity of *L. polyphemus* Factor Cs in the Presence of Salt

Ex. 1004 at 85 (annotated).

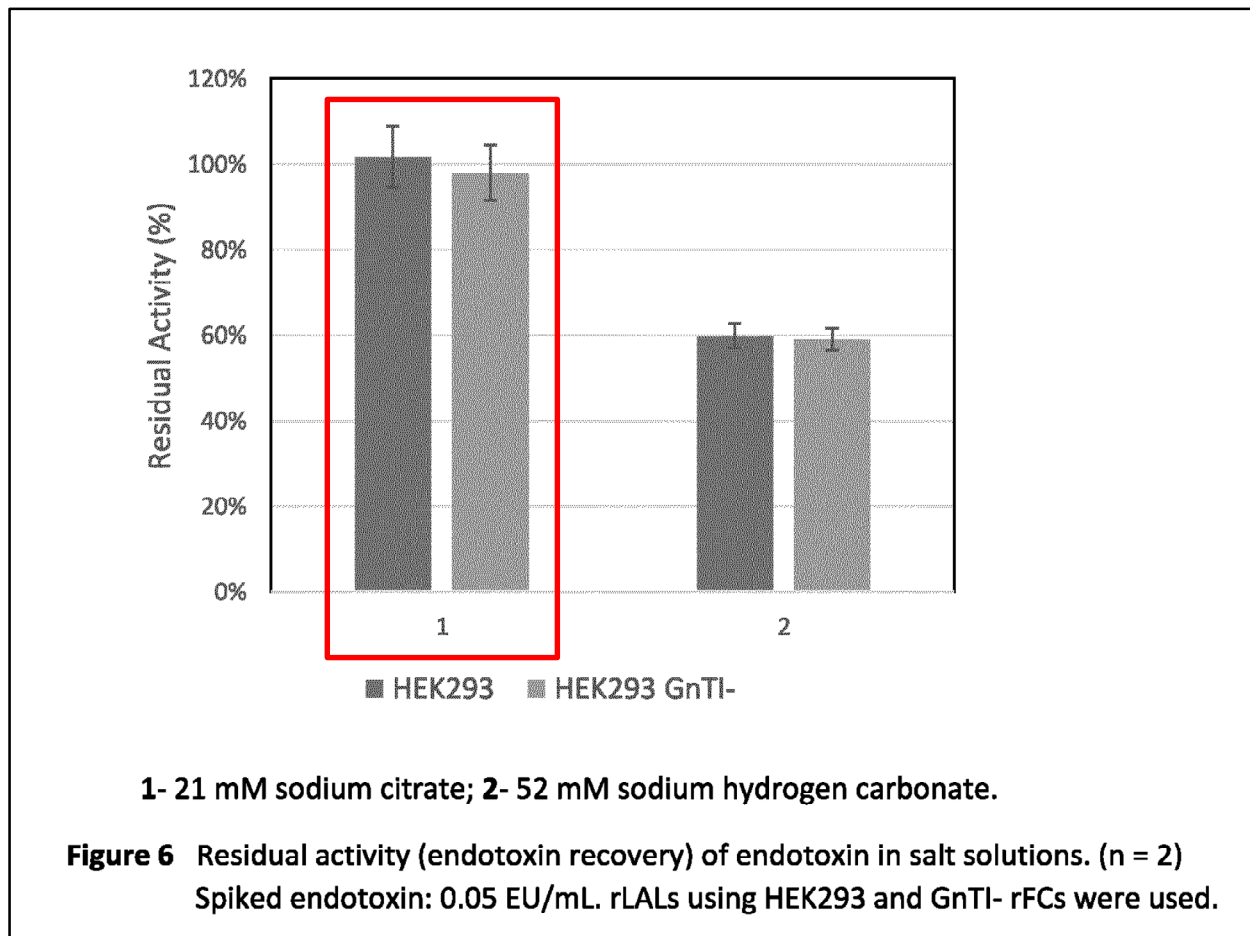
Based on this data, a POSA would have recognized that recombinantly producing Factor C in *Limulus polyphemus* exhibits unexpected results as compared to the closest prior art that recombinantly produces *Tachypleus tridentatus*. Ex. 2042 ¶¶ 48, 51. Data submitted as part of a European Opposition proceeding for EP Patent No. EP3441466 further confirms the unexpected and superior properties of *Limulus polyphemus* Factor C.

During the Opposition proceeding, data showing residual activity of *Limulus polyphemus* Factor C recombinantly produced in the claimed HEK293 cells was submitted. Ex. 2033. As seen in the below data, when the recombinant Factor C from *Limulus polyphemus* was tested in the claimed 16 mM magnesium sulfate solution, it exhibited residual activity between 90-120% (inclusive of error bars) in

HEK293 cells, and it exhibited residual activity approximately between 90-110% (inclusive of error bars) in the claimed 21 mM sodium citrate solution.



Ex. 2033 at Fig. 4.



Ex. 2033 at Fig. 6 (annotated).

Comparing this for *Limulus polyphemus* Factor C to the data observed in Figure 7 of Mizumura further demonstrates that the claimed invention provides superior residual activity and thus demonstrates unexpected results. Ex. 2042 ¶ 54. *Limulus polyphemus* recombinantly produced in HEK293 cells exhibited residual activity between 90-120% (inclusive of error bars) in 16 mM magnesium sulfate (Fig. 4) and residual activity approximately between 90-110% (inclusive of error bars) in 21 mM sodium citrate (Fig. 6). This is far superior to the residual activity observed

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for *Tachypleus tridentatus* Factor C recombinantly produced in HEK293 cells, which demonstrated approximately 20-25% residual activity in 16 mM magnesium sulfate (Mizumura Fig. 7, column 2) and about 20-30% residual activity in 21 mM sodium (Mizumura Fig. 7, column 5). The *Limulus polyphemus* Factor C expressed in HEK293 cells also presents a much greater residual activity relative to that expressed in Sf9 cells and native *Limulus polyphemus* Factor C as compared to the difference observed between *Tachypleus tridentatus* Factor C in HEK293 cells relative to expression in Sf9 cells or native *Tachypleus tridentatus*. See Ex. 1009 at Fig. 7; Ex. 1004 at 85.

As such, the claimed invention of Factor C from *Limulus polyphemus* recombinantly produced in HEK293 cells exhibits unexpectedly superior salt tolerance in the claimed salt solutions as compared to the closest prior art of Mizumura. Ex. 2042 ¶ 55. As Patent Owner's expert Dr. Morris explains, a POSA would not have expected this magnitude of difference in residual activities between the two strains of Factor C but would have instead expected functional equivalence in terms of activity between the species. Ex. 2040 ¶¶ 49-50. This evidence weighs in favor of finding substitute claim 22 of the '318 Patent not unpatentable.

VIII. CONCLUSION

For reasons discussed above, if the Board should find claim 21 of the '318 Patent unpatentable, the Board should issue substitute claim 22 and maintain its patentability.

Respectfully Submitted,

Dated: December 1, 2025

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

CERTIFICATE OF PAGE LIMIT

I, the undersigned, certify that the foregoing Patent Owner's Contingent Motion to Amend complies with the page limits of 37 C.F.R. § 42.24(a) because it does not contain more than 25 pages. This paper also complies with the typeface requirements of 37 C.F.R. § 42.6(a)(2)(ii) and the type style requirements of 37 C.F.R. § 42.6(a)(2)(iii) and (iv).

Respectfully Submitted,

Dated: December 1, 2025

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

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e)(4), lead counsel for Patent Owner hereby certifies that on December 1, 2025, a copy of this PATENT OWNER'S CONTINGENT MOTION TO AMEND was served via the email correspondence address of record for Petitioner's counsel of record:

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Respectfully Submitted,

Dated: December 1, 2025

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APPENDIX A – SUBSTITUTE CLAIM

The proposed substitute for claim 21 is shown in marked-up form below. Underlining indicates proposed additions to the original claim 21 and double brackets indicate proposed deletions from the original claim 21.

Claim 22. [Proposed substitute for claim 21] A horseshoe crab Factor C protein having activity of Factor C,

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

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

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

[[(2) 15% or higher in the presence of 16 mM magnesium sulfate]] in the presence of 21 mM sodium citrate and 16 mM magnesium sulfate, as compared with the corresponding *Limulus polyphemus* Factor C protein expressed in a Sf9 cell or a native *Limulus polyphemus* Factor C protein.