

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 REPLY TO PETITIONER'S OPPOSITION TO
PATENT OWNER'S REVISED CONTINGENT MOTION TO AMEND**

IPR2025-00440

**Patent Owner’s Reply to Petitioner’s Opposition to Patent Owner’s Revised
Contingent Motion to Amend**

TABLE OF CONTENTS

	Page(s)
I. INTRODUCTION	1
II. REVISED CLAIM 22 MEETS THE REQUIREMENTS OF 35 U.S.C. § 316 AND 37 C.F.R. § 42.121	1
A. Revised Claim 22 Does Not Introduce New Matter	5
III. REVISED CLAIM 22 IS PATENTABLE	7
A. Revised Claim 22 Has Adequate Written Description Support.....	7
B. Revised Claim 22 is Enabled	11
C. Revised Claim 22 is Not Obvious Over the Prior Art.....	12
IV. CONCLUSION.....	12

**Patent Owner’s Reply to Petitioner’s Opposition to Patent Owner’s Revised
Contingent Motion to Amend**

TABLE OF AUTHORITIES

	Page(s)
 Cases	
<i>Alcon Rsch. Ltd. v. Barr Lab’ys, Inc.</i> , 745 F.3d 1180 (Fed. Cir. 2014)	11
<i>Bos. Sci. Corp. v. Johnson & Johnson</i> , 647 F.3d 1353 (Fed. Cir. 2011)	6
<i>Falko-Gunter Falkner v. Inglis</i> , 448 F.3d 1357 (Fed. Cir. 2006)	6, 7
<i>Inphi Corp. v. Netlist, Inc.</i> , 805 F.3d 1350 (Fed. Cir. 2015)	2
<i>Novozymes A/S v. DuPont Nutrition Bioscisc. APS</i> , 723 F.3d 1336 (Fed. Cir. 2013)	9
 Statutes	
35 U.S.C. § 316	1
 Other Authorities	
37 C.F.R. § 42.121	1

**Patent Owner's Reply to Petitioner's Opposition to Patent Owner's Revised
Contingent Motion to Amend**

TABLE OF EXHIBITS

<u>Exhibit No.</u>	<u>Description</u>
2001	Excerpt from U.S. Application No. 14/650,767 File History – Claims dated June 9, 2015
2002	Excerpt from U.S. Application No. 14/650,767 File History – Non-Final Rejection dated September 16, 2016
2003	FAQs for Interim Processes for PTAB Workload Management, <i>available at</i> https://www.uspto.gov/patents/ptab/faqs/interim-processes-workload-management
2004	Declaration of Michael A. Frohman, M.D., Ph.D. and exhibits from Opposition for European Patent No. 3530670
2005	Notice of Opposition to European Patent No. 3441466
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2007	Extract from the Register of European Patents for European Patent No. 4291648
2008	Ding, et al., “Molecular cloning and sequence analysis of Factor C cDNA from the Singapore horseshoe crab, <i>Carcinoscorpius rotundicauda</i> ,” Molecular Marine Biology and Biotechnology (1995) 4(1), 90-103, submitted in Opposition to European Patent No. 3441466
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**Patent Owner's Reply to Petitioner's Opposition to Patent Owner's Revised
Contingent Motion to Amend**

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**Patent Owner's Reply to Petitioner's Opposition to Patent Owner's Revised
Contingent Motion to Amend**

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**Patent Owner's Reply to Petitioner's Opposition to Patent Owner's Revised
Contingent Motion to Amend**

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**Patent Owner's Reply to Petitioner's Opposition to Patent Owner's Revised
Contingent Motion to Amend**

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**Patent Owner's Reply to Petitioner's Opposition to Patent Owner's Revised
Contingent Motion to Amend**

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**Patent Owner's Reply to Petitioner's Opposition to Patent Owner's Revised
Contingent Motion to Amend**

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**Patent Owner's Reply to Petitioner's Opposition to Patent Owner's Revised
Contingent Motion to Amend**

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**Patent Owner's Reply to Petitioner's Opposition to Patent Owner's Revised
Contingent Motion to Amend**

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**Patent Owner's Reply to Petitioner's Opposition to Patent Owner's Revised
Contingent Motion to Amend**

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**Patent Owner's Reply to Petitioner's Opposition to Patent Owner's Revised
Contingent Motion to Amend**

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2103	Graphical depiction of Clustal alignment of <i>Limulus polyphemus</i> , <i>Carcinoscorpius rotundicauda</i> , and <i>Tachypleus tridentatus</i> Factor C sequences
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**Patent Owner's Reply to Petitioner's Opposition to Patent Owner's Revised
Contingent Motion to Amend**

I. INTRODUCTION

Petitioner asserts that “Patent Owner’s (‘PO’s’) ‘revised’ amendment creates additional § 112 problems while simultaneously failing to address those rendering original claim 21 unpatentable.” Paper 42 (hereinafter, “Opp.”) at 1. Not so. PO’s revised claim 22 finds ample Section 112 support to be entitled its December 10, 2013 priority date, thus eliminating the references relied on by Petitioner as prior art for its unpatentability grounds.

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

Petitioner admits that PO’s revised claim 22 “resolve[s] the broadened scope” issue it raised in its Opposition to PO’s Original Motion to Amend. Opp. at 3. Despite this, Petitioner maintains its assertion that there is no support in the ’767 Application for the revised claim 22, asserting that “PO points to none.” *Id.* at 3-6. But revised claim 22 finds ample support in the ’767 Application. Paper 36 (hereinafter, “RMTA”) at 4-19.

First, Petitioner argues that the “’767 Application never discusses or describes the purported invention in terms of affirmatively **excluding** *Limulus polyphemus* recombinant Factor C proteins with residual activities ‘less than’ the now claimed

**Patent Owner's Reply to Petitioner's Opposition to Patent Owner's Revised
Contingent Motion to Amend**

upper ranges.” Opp. at 3 (emphasis in original).¹ But the law does not require the negative limitation be recited *in haec verba* in the specification. *Novartis Pharms. Corp. v. Accord Healthcare, Inc.*, 38 F.4th 1013, 1017 (Fed. Cir. 2022). Nor does the law require “a new and heightened standard for negative claim limitations.” *Inphi Corp. v. Netlist, Inc.*, 805 F.3d 1350, 1356 (Fed. Cir. 2015). Instead, “the hallmark of written description is disclosure.” *Novartis*, 38 F.4th at 1017 (internal citation omitted).

The '767 Application provides the necessary disclosure. It includes a section titled “***Modes for Carrying Out the Invention***” that states the “Factor C of the present invention is a ***Factor C derived from a horseshoe crab***” and specifically identifies ***L. polyphemus as a known species***. Ex. 1006 at 40². It includes a specific example titled “Expression of Factor C in mammalian cells (HEK293),” describing steps to produce Factor C in HEK293 cells. *Id.* at 87-88. It also states the “present invention encompasses the following modes” and then lists the following: (i)

¹ Petitioner’s assertion that “PO admitted that these lower bounds of the claimed residual activity ranges lacked written description support and an enabling disclosure when it did away with them in POs first failed attempt to cure claim 21,” Opp. at 4, is nothing more than unsupported conjecture.

² Emphasis added unless otherwise noted.

**Patent Owner's Reply to Petitioner's Opposition to Patent Owner's Revised
Contingent Motion to Amend**

residual activity in the presence of 21 mM sodium citrate at a minimum of 10%, *id.* at 17, and (ii) residual activity in the presence of 16 mM magnesium sulfate at a minimum of 15%. *Id.* at 18.

The '767 Application also explains that the “Factor C of the present invention may have low susceptibility to inhibition of activity by an ion,” noting 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, as compared with a control Factor C,**” identifying the control Factor C as including **recombinant Factor C expressed in insect cell Sf9 and a native Factor C.** Ex. 1006 at 50. It provides specific examples of the invention, including (i) higher residual activity in the presence of 21 mM sodium citrate **as compared with control Factor C;** (ii) higher residual activity in the presence of 16 mM magnesium sulfate **as compared with control Factor C;** (iii) residual activity of **10% or higher** or 20% or higher in the presence of 21 mM sodium citrate; and (iv) residual activity of **15% or higher** or 25% or higher in the presence of 16 mM magnesium sulfate. *Id.* at 41-42 [0035]. The '767 Application also 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 52 [0035]. Notably, the '767 Application provides a specific example, including data in Figure 7 showing residual activity of Factor C expressed from HEK293 cells. Ex.

**Patent Owner's Reply to Petitioner's Opposition to Patent Owner's Revised
Contingent Motion to Amend**

1006 at 96-99, 122. Thus, the '767 Application expressly describes the invention claimed in revised claim 22.

Second, Petitioner argues that “revised claim 22 covers the same unsupported and non-enabled range of Factor C protein residual activities as claim 21.” Opp. at 6. Petitioner’s argument, however, is premised on its incorrect assertion that revised claim 22 is **not** narrower than original claim 21. *Id.* at 4-6.³ As PO explained in its RMTA, revised claim 22 adds a further narrowing limitation to original claim 21 while maintaining the lower limits of the recited residual activity. RMTA at 3-4.

Petitioner’s argument that “there is nothing suggesting that the comparator proteins will have a residual activity **greater** than 10% in 21 mM sodium citrate or

³ Petitioner also seems to rely on PO’s citation to similar disclosures for Section 112 support for claim 21 as revised claim 22 as somehow indicating revised claim 22 is not narrower than claim 21. Opp. at 6-8. Petitioner’s argument finds no basis in the law and ignores the plain language of revised claim 22 that includes narrowing limitations. Petitioner also incorrectly asserts that PO “offers no explanation” as to why information from, for example, Figure 7 of the '767 Application supports or enables revised claim 22, Opp. at 7, despite PO addressing this at length in its RMTA. RMTA at 8-19.

**Patent Owner's Reply to Petitioner's Opposition to Patent Owner's Revised
Contingent Motion to Amend**

15% in 16 mM magnesium sulfate such that the scope of Factor C proteins encompassed by revised claim 22 would be **less than** original claim 21” ignores the disclosure in Figure 7 of the '767 Application. Opp. at 5. Figure 7 shows the Factor C expressed in HEK293 cells is not only “higher than” the comparator proteins, as required by revised claim 22, but it also is higher than the claimed residual activity floor. Ex. 1006 at 96-99, 122. Although Figure 7 shows residual activity for *T. Tridentatus* Factor C, as discussed below, a POSA would have understood that the residual activity would also be expected in *L. polyphemus* Factor C. Ex. 2108 ¶ 13.

A. Revised Claim 22 Does Not Introduce New Matter

As discussed in the RMTA, revised claim 22 does not introduce new subject matter. RMTA at 4-7. Petitioner asserts that the “higher than” limitations in revised claim 22 “introduce[] an entirely **different concept** into revised claim 22 relative to original claim 21—that the inventors somehow also possessed recombinant proteins from the *Limulus polyphemus* species of crab (whose underlying Factor C sequences had not yet been disclosed or elucidated) where such proteins would have residual activity values higher than **other** *Limulus polyphemus* Factor C proteins recombinantly expressed in Sf9 cells or those natively sourced from the crabs themselves,” and that Petitioner did not “describe such proteins or the claimed comparisons.” Opp. at 10-11 (emphasis in original).

**Patent Owner's Reply to Petitioner's Opposition to Patent Owner's Revised
Contingent Motion to Amend**

Petitioner's argument fails. As discussed above, these "higher than" limitations in revised claim 22 find ample support in the '767 Application. Moreover, as PO explained in its RMTA, while the '767 Application may not include a *specific* example of *L. polyphemus* Factor C, this "**does not** render the written description inadequate" as "actual reduction to practice is **not required** for written description." *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1366 (Fed. 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); *see also* RMTA at 8-19.

Factor C protein from *L. polyphemus* had been successfully isolated and characterized, as well as compared to Factor C from the *T. tridentatus* horseshoe crab as early as the 1990s. *See, e.g.*, Ex. 1022 at 150; Ex. 1025. And as PO's expert Dr. Schaefer explained, 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

**Patent Owner's Reply to Petitioner's Opposition to Patent Owner's Revised
Contingent Motion to Amend**

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 the functional domains are highly conserved between species of horseshoe crab such that the species exhibited a high degree of functional similarity. Ex. 2038 ¶¶ 85-102; Ex. 2108 ¶ 13. A POSA would have also understood that, despite the geographical and general physical or genetic differences across the species of horseshoe crabs, the coagulation cascade proteins (*e.g.*, Factor C) were structurally similar and functionally identical across species. Ex. 2038 ¶¶ 86-88, 98-102. A POSA would have therefore understood that even though the example in Figure 7 in the '767 Application depicts residual activity of *T. tridentatus* Factor C, because of the highly conserved nature of species, the claimed residual activity in revised claim 22 would also be expected in *L. polyphemus* Factor C. Ex. 2108 ¶ 13.

III. REVISED CLAIM 22 IS PATENTABLE

A. Revised Claim 22 Has Adequate Written Description Support

As discussed above, while the '767 Application does not include a specific example of *L. polyphemus* Factor C with the claimed residual activity values, this “**does not** render the written description inadequate” as “actual reduction to practice is **not required** for written description.” *Falko-Gunter*, 448 F.3d at 1366.

**Patent Owner's Reply to Petitioner's Opposition to Patent Owner's Revised
Contingent Motion to Amend**

Petitioner's repeated reliance on the lack of examples to *L. polyphemus* seeks to impose a higher burden than required to demonstrate written description support.

As PO's expert has stated, the functional domains are highly conserved between species of horseshoe crab such that the species exhibit a high degree of functional similarity. Ex. 2038 ¶¶ 85-102; Ex. 2108 ¶ 13. Thus, a POSA would have understood that, because of the highly conserved nature of species, even though the example in Figure 7 in the '767 Application depicts residual activity of *T. tridentatus* Factor C, the claimed residual activity in revised claim 22 would also be expected in *L. polyphemus* Factor C. Ex. 2108 ¶ 13.⁴

⁴ Petitioner's reliance on *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, is misplaced. Opp. at 14-16. In *Centocor*, no relationship between human TNF- α protein, the known mouse variable region satisfying the claim limitations, and potential human variable regions satisfying the claim limitations were disclosed. 636 F.3d 1341, 1350 (Fed. Cir. 2011). Here, in contrast, those skilled in the art understood a high sequence identity existed between *L. polyphemus* Factor C and *T. tridentatus* Factor C and that the functional domains are highly conserved between species such that a POSA would have expected that functional properties, such as maintaining residual activity in the claimed salt solutions, would be

**Patent Owner's Reply to Petitioner's Opposition to Patent Owner's Revised
Contingent Motion to Amend**

Petitioner's reliance on *Novozymes* is misplaced. Opp. at 17-20. In *Novozymes*, the claims required an alpha-amylase variant that had (i) at least 90% sequence identity to BSG alpha-amylase, (ii) an amino acid substitution at serine 239 and (iii) increased thermostability at certain conditions. *Novozymes A/S v. DuPont Nutrition Biosci. APS*, 723 F.3d 1336, 1348 (Fed. Cir. 2013). While the Court noted the specifically claimed species was not disclosed in the specification, this alone was not dispositive with the Court expressly stating that "in some cases, broad or generic disclosures can adequately describe particular constituent species." *Id.* at 1347. In *Novozymes*, the Court found no written description support because the specification mainly addressed BLA alpha-amylase, which only had 65.4% sequence identity with the claimed BSG, and the only disclosed substitution at position 239 **lacked** the claimed increased thermostability. *Id.* By contrast, here, it was known before 2013 that the individual amino acid compositions of *L. polyphemus* Factor C and *T. Tridentatuts* and their chain subunits are "indistinguishable," Ex. 1022 at 151, and the specification **discloses** a specific

highly conserved between each of the known horseshoe crab species. EX 2038

¶ 98.

**Patent Owner's Reply to Petitioner's Opposition to Patent Owner's Revised
Contingent Motion to Amend**

example of *T. Tridentatus* meeting the residual activity limitations required by revised claim 22. Ex. 1006 at 122 (Fig. 7).

Finally, Petitioner's repeated assertions for lack of written description support and its argument that "comparative conclusions between species could not be made," Opp. at 12, cannot be reconciled with its obviousness arguments in support of unpatentability of revised claim 22 (or even original claim 21). If, as Petitioner claims, a POSA could not make comparative conclusions between species, then this same logic would apply to Petitioner's obviousness analysis. While the patentability standards may be different between Section 112 and Section 103, Petitioner's obviousness analysis still relies on a POSA making comparative conclusions between species because the cited prior art only discloses residual activity data for ***T. tridentatus*, not the claimed *L. polyphemus*.**

Indeed, Petitioner's reasonable expectation of success argument expressly relies on the same comparative conclusions between species that it says are insufficient, as it assumes that if the claimed residual activity is achieved in *T. tridentatus*, it would reasonably be expected to be achieved in *L. polyphemus*. Opp. at 24 (arguing "a POSA reading Mizumura's reports on residual activity in *Tachypleus tridentatus* Factor C . . . would have found it obvious to try to generate an example of a HEK293-recombinantly produced *Limulus polyphemus* Factor C

**Patent Owner's Reply to Petitioner's Opposition to Patent Owner's Revised
Contingent Motion to Amend**

protein and would have *reasonably expected* that protein to fall within the claimed residual activity range, and higher than the comparators”).

Finally, as discussed above, incorporated here, ample written description support exists for revised claim 22's "higher than" residual activity limitations. The specification not only describes its invention as including Factor C proteins exhibiting higher residual activity than control Factor C (Sf9 or native) but also includes an express example and data in Figure 7 showing this relationship. Petitioner appears to imply that revised claim 22 requires possession of varying "degrees" of "higher" residual activity, but tellingly it cites no case law in support of this proposition. Opp. at 18-19. The specification provides ample written description support for the claimed comparison, which merely requires the inventive Factor C exhibit "higher" residual activity than the stated control Factor C in the claimed salt solutions and be above the minimum threshold values claimed.

B. Revised Claim 22 is Enabled

As explained in PO's RMTA, revised claim 22 does not require a broad range of residual activities and is enabled. RMTA at 13-19. Petitioner's attempt to distinguish revised claim 22 from those in *Alcon Rsch. Ltd. v. Barr Lab'ys, Inc.*, 745 F.3d 1180 (Fed. Cir. 2014), fails. Opp. at 22-23. Much like the claims in *Alcon*, revised claim 22 requires a comparative analysis such that the inventive Factor C's

**Patent Owner's Reply to Petitioner's Opposition to Patent Owner's Revised
Contingent Motion to Amend**

residual activity in HEK293 cells is *higher* than residual activity in control Factor C (*i.e.*, Factor C in Sf9 cells or native Factor C) while maintaining the lower residual activity limit presented in original claim 21. No particular magnitude of “higher” residual activity is required by revised claim 22, as the claim merely states that the inventive Factor C residual activity must be “higher.” The specification provides ample support teaching a POSA how to make and use the invention to practice the invention as claimed. *See generally* RMTA.

C. Revised Claim 22 is Not Obvious Over the Prior Art

Because revised claim 22 is entitled to its December 10, 2013 priority date, none of the references relied on by Petitioner qualify as prior art, and its unpatentability grounds fail. To the extent the Board determines that revised claim 22 is not entitled to the December 10, 2013 priority date, Petitioner's invalidity challenge still fails because Petitioner failed to meet its burden to demonstrate revised claim 22 is unpatentable, as its reasonable expectation of success theories cannot be reconciled with its arguments against Section 112 support. RMTA at 20-22; *see* Section III.A, *supra*.

IV. CONCLUSION

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

IPR2025-00440

**Patent Owner's Reply to Petitioner's Opposition to Patent Owner's Revised
Contingent Motion to Amend**

Respectfully Submitted,

Dated: May 20, 2026

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

IPR2025-00440

**Patent Owner's Reply to Petitioner's Opposition to Patent Owner's Revised
Contingent Motion to Amend**

CERTIFICATE OF PAGE LIMIT

I, the undersigned, certify that the foregoing PATENT OWNER'S REPLY TO PETITIONER'S OPPOSITION TO PATENT OWNER'S REVISED CONTINGENT MOTION TO AMEND complies with the page limits of 37 C.F.R. § 42.24(a) because it does not contain more than 12 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: May 20, 2026

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

IPR2025-00440

**Patent Owner's Reply to Petitioner's Opposition to Patent Owner's Revised
Contingent Motion to Amend**

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e)(4), lead counsel for Patent Owner hereby certifies that on May 20, 2026, a copy of this PATENT OWNER'S REPLY TO PETITIONER'S OPPOSITION TO PATENT OWNER'S REVISED CONTINGENT MOTION TO AMEND was served via the email correspondence address of record for Petitioner's counsel of record:

Scott A. McKeown (SMcKeown-PTAB@wolfgreenfield.com)

Flora Luo (FLuo-PTAB@wolfgreenfield.com)

Chelsea A. Loughran (CLoughran-PTAB@wolfgreenfield.com)

Respectfully Submitted,

Dated: May 20, 2026

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