

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CHARLES RIVER LABORATORIES, INC.,
Petitioner,

v.

SEIKAGAKU CORPORATION,
Patent Owner.

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

**PETITIONER'S SUR-REPLY IN SUPPORT OF OPPOSITION TO
PATENT OWNER'S REVISED CONTINGENT MOTION TO AMEND**

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I. INTRODUCTION

Patent Owner's (PO's) Motion and Reply fail to solve the problem PO has, which is that PO crafted a claim in August of 2021, reciting a genus of proteins with unpredictable functional features, that it did not possess and did not describe how to make by its Dec. 10, 2013 priority date (three years *before* it went ahead in 2016 and filed an unrelated patent on (and claimed to have then finally invented) the same proteins). PO inexplicably continues to rely upon *the same* disclosures in the specification and the same arguments regarding "functional conservation" of proteins across horseshoe crab species that it advanced in its POR and Sur-reply regarding claim 21. But to even reach the contingent patentability of substitute claim 22, those disclosures and arguments must have necessarily failed as to claim 21. Because claim 22 is not entitled to Dec. 10, 2013 priority date and overlaps in scope with claim 21, it too is obvious over the intervening prior art.

PO continues to rely on the argument that a POSA would have been able to predict the residual activity of the undisclosed genus of *Limulus polyphemus* Factor C proteins from evidence that the native Factor C proteins of such horseshoe crab shared structural and amino acid similarities with Factor C proteins of the claimed *L. polyphemus* Factor C protein. But the evidence of record demonstrates that such structural similarities *do not explain* the full scope of residual activities of the claimed recombinant proteins. Rather, Factor C proteins with identical protein

structure and amino acid sequence (i.e., from *the same species*) demonstrate widely varying residual activities depending on—as PO’s expert puts it: “multifactorial” variables. Because, as Dr. Jain explained, a POSA reading the ’767 Application “would have understood that relying on sequence homology (or, similarity) to assume the existence of functional identity would have been an oversimplified understanding of protein function and subject to error” (EX1003, ¶93) a POSA *would not* have made the functional extrapolation across the full scope of claimed proteins that PO argues for. PO’s motion to substitute an unsupported claim with another of the same defect should be denied.

A. Revised Claim 22 Lacks Written Description Support

1. Claim 22 Recites The Same Residual Activity Thresholds as Claim 21 and PO Relies on the Same Disclosures

PO does not dispute that there is no difference between claim 21’s limitation:

(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

and the inverted negative of this limitation:

wherein the horseshoe crab Factor C protein is not a horseshoe crab Factor C protein having less than 10% residual activity in the presence of 21 mM sodium citrate; and...having less than 15% residual activity in the presence of 16 mM magnesium sulfate.

Petitioner does not demand “*in haec verba*” recitation or any “heightened” amount of support for this claim but rather argues that there is not *any*

demonstration that the inventors were in possession of the full scope of claimed *L. polyphemus* recombinant Factor C proteins defined by this claim. And PO cites no different or additional evidence supporting claim 22 and these open ended ranges than it cited as purportedly supporting claim 21.

Specifically, the “Modes for Carrying out the Invention” passage was cited in the POR (at 13) and merely identifies *L. polyphemus* as a known species of horseshoe crab—not one which the inventors understood to have had the functional requirements of claim 22 when recombinantly expressed via HEK-293 cells. The example regarding production of recombinant Factor C in HEK-293 cells was also cited in the POR in support of claim 21 (at 13-14) but related to a different species of horseshoe crab—not *L. polyphemus*. The recitation of the particular lower endpoints (now upper exclusionary endpoints) was cited in the POR in support of claim 21 (at 20, 26) and are mentioned in a laundry list of values unlinked to any particular recombinant Factor C protein. EX1006, 18. The concept that a particular Factor C would exhibit a “higher” residual activity in the presence of a particular ion concentration “as compared with the control Factor C” ***is the definition*** of residual activity and is listed at page 51 of the ’767 Application as a recitation of isolated features, untethered to any particular recombinant Factor C expressed in any particular system, or from any particular species of horseshoe crab. ***Nowhere*** described is an example of the “integrated whole” of claim 22 as

opposed to “a collection of independent limitations.” *Novozymes, A/S v. Dupont Nutrition Biosciences APS*, 723 F.3d 1336, 1349 (Fed. Cir. 2013)¹. Likewise, Figure 7 neither evidences residual activity for the claimed *L. polyphemus* recombinant Factor C proteins nor evidences that the inventors were in possession of the entire genus of Factor C proteins defined by the claimed residual activity ranges. Instead, Figure 7 merely shows variable (wide error bars) residual activity measurements for a **single example** of the **unclaimed** HEK293-produced *T. tridentatus* Factor C proteins with values (lanes 2 and 5) only slightly above the claimed lower ranges. To the extent the data in Figure 7 shows one example of a residual activity value for recombinant *T. tridentatus* Factor C in each ionic

¹ PO attempts to distinguish *Novozymes* by relying on the fact that “it was known before 2013 that the individual amino acid compositions of *L. polyphemus* Factor C and *T. Tridentatus* and their chain subunits are ‘indistinguishable.’” Reply, 9. But, as discussed in section I.A.3., *infra*, such structural similarity between native *L. polyphemus* and *T. tridentatus* **does not** explain the variability in residual activity. The ’767 Application provides no more explanation for the residual activity values of the undisclosed recombinant *L. polyphemus* Factor C proteins than the *Novozymes* specification provided explanation for which substitutions would increase thermostability. *Novozymes* is on point.

solution, such is not within the claimed genus and does not demonstrate possession of residual activity values across the full scope of claim 22. Instead, because the inventors ***abandoned*** the one structural feature thought to distinguish the claimed recombinant Factor C proteins from those in the prior art (EX1004, 85-86), the '767 Application merely invites POSAs to complete the invention.

2. PO Did Not Add “Narrowing” Limitations, But In Any Case, Such Limitations are Not Described.

The '767 Application suggests that the residual activity for comparator Sf9-expressed and native Factor C proteins are ***very low***. See EX1006, FIG. 7. Thus, the purported “limitation” that the claimed Factor C proteins have a “higher than” residual activity than the control proteins, while simultaneously excluding those with values than 10% or 15% in the claimed ionic solutions captures ***the same universe of Factor C proteins*** that would be captured without the “higher than” limitation at all (*i.e.*, claim 21). PO does not refute this understanding of the scope of claim 22, nor explain how the “higher than” limitations are actually narrowing. PO states only that “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.” Reply, 4-5. But again, because the comparator proteins are ***lower*** than the residual activity “floor”, what proteins are covered by claim 21 that are ***not*** covered by claim 22? None. Claim 22 is not narrower than claim 21.

Regardless of its precise scope, claim 22 embraces the same (or nearly the same) genus of recombinant *L. polyphemus* Factor C proteins as claim 21 without disclosing a representative species or common structural feature. Claim 22 does not find support in the '767 Application where claim 21 did not.

3. PO's Argument Regarding "Functional Conservation" Does Not Create Written Description Where There is None.

On pages 6-7 of its Reply, PO restates the same argument it made in the POR (at 17-24) regarding why claim 21 should be found to have an adequate written description in the '767 Application even though that priority disclosure does not describe any species of the genus of claim 21. PO again points to the post-priority date understanding of the amino acid similarity between the *T. tridentatus* and the *L. polyphemus* Factor C proteins and reasons that a POSA could have uncovered this information by Dec. 10, 2013 and from it "understood that...the claimed residual activity in revised claim 22 would also be expected in *L. polyphemus* Factor C." Reply 7. There are three fundamental errors in PO's logic that demonstrate why claim 22 lacks an adequate written description.

First, this argument is identical to the one PO made in its POR in support of the patentability of claim 21 (POR, 17-24) but again, if claim 22 is being considered, it is because that argument was deemed insufficient (or rejected).

Second, PO's argument regarding "functional conservation," does not provide a POSA with an understanding or expectation regarding the comparability

of the full scope of residual activity values across species, and in fact, the weight of the evidence points the other way. For example, as the data shows in Figure 7 in the '767 Application, Factor C proteins with the *exact same functional motifs and amino acid sequences* have very different residual activity values. These highly variable residual activity values seen *within the same species* demonstrate that residual activity *is not tied* to the underlying amino acid sequence similarity or protein motifs. In addition, the inventors themselves characterized the post-filing residual activity values they had gathered for recombinant *T. tridentatus* and *L. polyphemus* Factor C proteins as “unexpected.” EX1004, 82-86, 150-153. Such unexpected variability in residual activity was seen in samples of the *same species of protein*. See e.g., EX1004, 85, FIG. 1. Contrary to PO’s assertion, the structural similarity of the protein itself in terms of amino acid sequence similarity or protein motif similarity *would not* have provided a POSA with an expectation that the full scope of claimed residual activity values for Factor C across different species of horseshoe crab would be predictably comparable. Dr. Jain emphasized this. EX1002, ¶¶82-84, 89-110. And, many of the references PO cited regarding the percent homology that had been hypothesized to exist between Factor C amino acid sequences for *T. tridentatus* and *L. polyphemus* also reported *differences* between horseshoe species of Factor C in various specific assays measuring Factor C activity. EX2035, 21, FIGS. 1, 6; EX2049, 4, 5, FIG.3; EX2036, Abstract, 4;

see also Paper No. 32, 13-19. Even PO's expert explained that the concept of ion inhibition involves "multiple mechanisms," is "multifactorial," and is "much more complicated than the terminal sialic acids." EX1069, 56:9-59:6. PO's theory about the functional conservation of protein domains between species of horseshoe crab does not fill in the gaping absence of disclosure in the '767 Application as to whether the undisclosed recombinant *L. polyphemus* Factor C proteins would have residual activity values across the full scope of the claimed range.

In addition, because similarities in protein functional domains and amino acid sequences do not explain variable residual activities, there ***is no identified relationship*** between recombinant Factor C protein and residual activity value—much like there was no relationship "between the human TNF- α protein, the known mouse variable region that satisfies the critical claim limitations, and potential human variable regions that will satisfy the claim limitations." *Centocor Ortho Biotech, Inc. v. Abbott Lab'ys.*, 636 F.3d 1341 (Fed. Cir. 2011). Despite PO's attempt to distinguish it (Reply, 8-9, n.4), *Centocor* is on point.

Third, PO's argument that a POSA ***could have*** obtained the undisclosed *L. polyphemus* Factor C sequences, and then made comparisons, and then drawn a conclusion about the function across species of horseshoe crab should be rejected as improper gap-filling—"the written description requirement is not satisfied by what could have been disclosed, but was not." *Enzo Biochem, Inc. v. Gen-Probe*

Inc., 285 F.3d 1013, 1022 (Fed. Cir. 2002); *Goeddel v. Sugano*, 617 F.3d 1350, 1356 (Fed. Cir. 2010) (no written description even where it was undisputed that a skilled person “could” identify undisclosed sequence information, because “the question is not whether...[a POSA] might have been able to produce the [claimed protein] by building upon the teachings of the [priority document].”). PO’s argument requires an extraordinary amount of extraneous information to be imported into the ’767 Application for a PO to draw a conclusion about the purported residual activity similarity expected “across species.” Reply, 7. Such importation of information is improper and does not save a claim otherwise lacking an adequate written description. *Rivera v. International Trade Commission*, 857 F.3d 1315, 1321 (Fed. Cir. 2017) (“The knowledge of ordinary artisans may...[not be used] to teach limitations that are not in the specification.”). PO’s reliance on *Falkner v. Inglis*, 448 F.3d 1357, 1367–68 (Fed. Cir. 2006) is unavailing and distinguishable. In *Falkner*, while an example was not required, the missing sequence disclosure was considered “well known” in the art in view of “undisputed testimony that as of the time of filing of the [priority application] publications in professional journals ***had disclosed the DNA sequence of the poxvirus genome*** along with the locations of the ‘essential regions.’” *Id.* at 1365. In this case, by contrast, PO’s expert ***admits*** that no publication “disclosed the DNA sequence” of the *L. polyphemus* Factor C protein by Dec. 10, 2013. EX2038, ¶36; EX1067,

32:2-6. And the inventors claimed the recombinant expression of such “unknown” sequences as a new invention three years later. EX1005, ¶¶01-17, 25, 36, 46, 67-68, 122, 180, 183; EX1043, ¶¶55-57. PO’s urged multi-step uncovering of missing information by the POSA cannot later supplement what *should have* been disclosed in the ’767 Application, but was not. Finally, PO’s cited *Boston Scientific Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1366 (Fed. Cir. 2011) supports Petitioner. There the Court affirmed that no reasonable jury could conclude that the patent in question contained sufficient written description support because, while patentee’s expert alleged a correlation between the structure and function of the functionally claimed genus, the specification indicated that such correlation was not well-known. *Id.* at 1366-67. Here, Dr. Schaefer alleges that the similar structural features of native Factor C proteins across species would allow a POSA to make a prediction about the full scope of residual activities of the claimed recombinant genus. But that alleged correlation does not explain the claimed unexpected function and so a POSA would not make such prediction.

B. Revised Claim 22 Lacks an Enabling Disclosure

Claim 22 now suffers from *two* enablement deficiencies. The ’767 Application does not teach a POSA how to make and use such proteins that meet the claimed *open ended numerical* ranges across the full scope of such claimed range, nor does it teach a POSA how to make and use all such proteins having a

residual activity *exceeding the comparator* protein values. At best, the '767 Application teaches a POSA to use the protocol for making recombinant proteins from a different species of horseshoe crab but with *L. polyphemus* sequence information (that the POSA has to separately obtain) and then *hope* that such protein satisfies the claimed requirement. But as discussed above (§I.A.3. *infra*), such hope is not anchored to any structural relationship and the '767 Application provides no other explanation or guiding disclosure for a POSA on how to make and use such proteins *across the full scope of claimed functional requirements* (i.e., at 50%, 80%, 100% residual activity). PO's foisting of the burden of undue trial and error experimentation on the POSA is the hallmark of lack of full scope enablement. *In re Fisher*, 427 F.2d 833, 835, 839 (C.C.P.A. 1970) (claims reciting a potency of "at least 1 International Unit of ACTH per milligram" were not enabled when the specification disclosed compounds with a maximum potency of 1.11 and 2.3 International Units per milligram, which was insufficient to "allow an inventor to dominate all compositions with potencies far in excess of those obtainable from the specification plus ordinary skill"); *Gevo, Inc. v. Butamax Advanced Biofuels LLC*, 2013 Markman 3914467, 2013 WL 3914467 (D. Del. 2013) (no enablement—"Claim 1 broadly claims that the recombinant yeast produce isobutanol at a yield of 'at least 10% of theoretical yield.' However, the patent's examples teach a maximum theoretical yield of 12.8%...***There is no***

direction or guidance disclosed in the patent to instruct a [POSA] on how to optimize or change the process to achieve the higher yields.”); *Magsil Corp. v. Hitachi Global Storage Techs., Inc.*, 687 F.3d 1377, 1379–80 (Fed. Cir. 2012).

C. Claim 22 Is Obvious Over the Prior Art

The *full scope* of claim 22 were neither described nor enabled by the ’767 Application as of Dec. 10, 2013. However by April 30, 2019, a POSA would have reasonably expected that the combination of teachings provided in Mizumura and either the ’498 PCT or McClymont would have yielded *an example* of the claimed Factor C proteins meeting the residual activity range defined by claim 22. Such is based on the inventor’s own 2018 testimony, and the ’498 PCT’s report of the *L. polyphemus* sequence information, successful recombinant production, and comparable activity level with *T. tridentatus*. EX1005, ¶¶155-185, 191; EX1009, ¶¶205-206, 282-290; EX1002, ¶¶179-187. PO offered no response in its Reply, but this Board has *rejected* the “inconsistent argument” allegation PO lodges. *Arkema Inc. v. Honeywell Int’l Inc.*, PGR2016-00012, 2016 WL 5404194 (P.T.A.B. Sept. 2, 2016). “A reasonable expectation of success of achieving one composition within the scope of the claim...differs from reasonably enabling the full scope of the claim.” *Id.*

II. CONCLUSION

For the foregoing reasons, entry of revised claim 22 should be denied.

Respectfully submitted,

Date: June 3, 2026

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

I certify that on June 3, 2026, a copy of the foregoing document, including any exhibits filed therewith, is being served via electronic mail, as previously consented to by Patent Owner, upon the following:

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