

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 RESPONSE

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<u>Exhibit No.</u>	<u>Description</u>
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I. INTRODUCTION

Patent Owner Seikagaku Corporation (“Seikagaku” or “PO”) respectfully submits this Response to the Board’s decision to institute trial (Paper 14, the “Decision”) and to the Petition for *Inter Partes* Review (“Petition” or “Pet.”) of claim 21 of U.S. Patent No. 11,236,318 (“’318 Patent”) filed by Petitioner Charles River Laboratories, Inc. (“Petitioner” or “CRL”).

As the Board notes in its Decision, a “foundational issue for Petitioner’s asserted grounds of unpatentability is whether [the art it relies on] qualify as prior art, which in turn depends on the priority date to which claim 21 is entitled.” Decision at 15. Petitioner asserts that claim 21 should only be afforded an effective filing date of April 30, 2019—the filing date of the ’318 Patent—because the priority application U.S. 14/650,767 (“the ’767 Application”) fails to enable and provide written description support for claim 21. But Petitioner’s priority date arguments fail on numerous fronts.

Not only does Petitioner fail to account for what was known in the art and must be considered when analyzing whether the ’767 Application provides written description support and enables the full scope of the claim, but more troubling, its priority-date arguments contradict its obviousness assertions. Specifically, while Petitioner argues a lack of Section 112 support for claim 21 because the residual activity of one species of horseshoe crab cannot be understood to translate to the

same residual activity in a different species, it asserts the opposite when arguing reasonable expectation of success under Section 103.

Petitioner's arguments cannot be reconciled, and, as such, the patentability of claim 21 of the '318 Patent should be upheld.

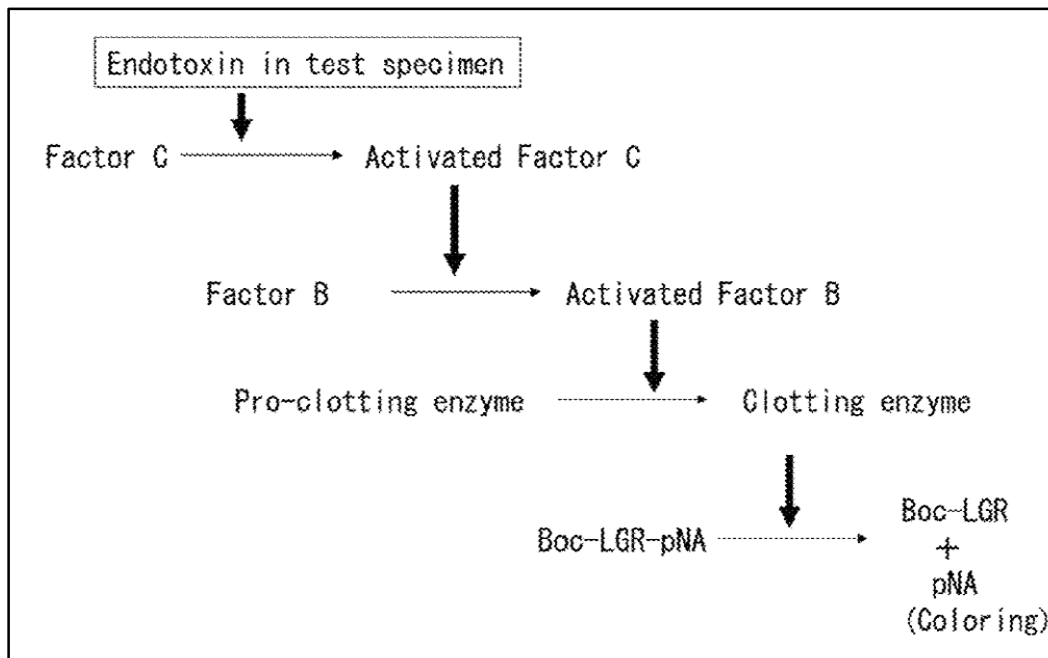
II. TECHNICAL BACKGROUND

Four living species of horseshoe crab exist: (i) *Carcinoscorpius rotundicauda*, (ii) *Limulus polyphemus*, (iii) *Tachypleus gigas*, and (iv) *Tachypleus tridentatus*. Ex. 2038 ¶ 20; Ex. 2068 at 1-2. *Carcinoscorpius rotundicauda* and *Tachypleus tridentatus* are found in Asia while *Limulus polyphemus* is primarily found along the east coast of North America. *Id.*

At least as early as the 1960s, researchers discovered that *Limulus polyphemus* underwent blood clotting when infected with bacterial endotoxin. Ex. 1023 at 265; Ex. 1001 at 1:41-45; Ex. 2038 ¶ 21. Because of the ubiquitousness of bacterial endotoxins, and the potential for harm to patients if these endotoxins end up in pharmaceutical and medical products, researchers began exploring this clotting phenomenon in horseshoe crabs to detect the presence of endotoxins. Ex. 1028 at 277; Ex. 1001 at 1:27-31.

This research led to the development of a limulus amoebocyte lysate ("LAL"), which has "been used widely in the detection of endotoxin in pharmaceuticals, surgical implants, water and food." Ex. 1028 at 277. LAL relies on various proteins

in the blood of horseshoe crabs that undergoes a coagulation cascade in the presence of an endotoxin. *Id.*; Ex. 1001 at 1:46-54; Ex. 2038 ¶ 22. Figure 1 from the '318 Patent (reproduced below) illustrates this cascade.



Notably, each of the four species of horseshoe crab utilizes the same coagulation cascade in response to endotoxin exposure. Ex. 2038 ¶ 23.

As seen above, Factor C is the first serine protease zymogen in the coagulation cascade, and the sequence and biochemical properties for native Factor C in *Tachypleus tridentatus*, *Limulus polyphemus*, and *Carcinoscorpius rotundicauda* have been studied extensively. Ex. 2038 ¶ 24. Indeed, as Petitioner's expert Dr. Jain admits, the "gene and amino acid sequences for Factor C and related proteins for *Tachypleus tridentatus* and *Carcinoscorpius rotundicauda* species of horseshoe

crab were known prior to the earliest claimed priority date of the '318 patent.” Ex. 1002 ¶ 40 (citing Ex. 1012, Ex. 1007); *see also* Ex. 2038 ¶¶ 32-33.

For example, in 1991, Dr. Muta and his group published the *Tachypleus tridentatus* Factor C cDNA sequence and amino acid sequence and characterized its domains. Ex. 1007 at 6554; Ex. 2038 ¶¶ 26-27. Also in 1991, Dr. F. Tokunaga and his colleagues at Kyushu University successfully isolated and characterized Factor C protein from the *Limulus polyphemus* species of horseshoe crab and compared its properties to Factor C from the *Tachypleus tridentatus* horseshoe crab. Ex. 1022 at 150; Ex. 2038 ¶¶ 28-31. Tokunaga compared the amino acid compositions of the intact *Limulus polyphemus* Factor C with *Tachypleus tridentatus* Factor C and determined that “the individual amino acid compositions of the two proteins and of their chain subunits were *indistinguishable*.” Ex. 1022 at 151.

In the new Millennium, the scientific literature reported additional discoveries. In 2003, US 2003/0054432 (“the '432 Publication”) disclosed that the applicants had successfully “isolated the factor C from *Limulus*” and that “[t]ryptic peptide sequencing revealed that the *Limulus* factor C sequence closely matched the Asian species, *with >90% sequence identity*.” Ex. 2035 at [0134]; Ex. 2038 ¶ 34. In 2006, Drs. Alwis and Milton reported that “the Factor C of *Carcinoscorpius rotundicauda* has 89.3% homology with that of *Limulus polyphemus*, North American horse shoe [*sic*] crab Factor C.” Ex. 2036 at 4. In 2009, Dr. Loverock

and his group reported that the “rFC protein derived from *C. rotundicauda* shares a 90.5% identical amino acid sequence with the native Factor C protein derived from *L. polyphemus*.” Ex. 2049 at 2. And in 2010, the literature reported that peptides obtained from *Limulus polyphemus* hemolymph were homologous to proteins from other crab species, including “Limulus clotting Factor C” from *Tachypleus tridentatus*. Ex. 2037 at 7; *see also* Ex. 2038 ¶¶ 34-35.

On October 31, 2012, researchers at the University of Connecticut sequenced and **deposited** (i) a 188 Mb *Limulus polyphemus* cDNA amoebocyte transcriptome under BioProject accession number PRJNA178588; and (ii) a 4 Gb whole genome shotgun sequence of the *Limulus polyphemus* under BioProject accession number PRJNA178587. Ex. 2050; Ex. 2051; Ex. 2038 ¶ 36. This data was published by October 31, 2013 and thus available to a POSA as of December 10, 2013. *Id.* ¶¶ 37-38, 59, 66, 105.

In addition to understanding the sequence and similarities between the various horseshoe crab species, those skilled in the art also had successfully produced Factor C using recombinant technology well before 2013. By the 1990s, researchers had recombinantly expressed Factor C in *Escherichia coli*, yeast and mammalian cells. Ex. 1028 at 277; *see also* Ex. 1002 ¶ 39; Ex. 1001 at 2:32-41.

III. THE '318 PATENT

Filed on April 30, 2019, the application that led to the '318 Patent is a continuation of Application No. 15/983,725, filed on May 18, 2018, now Pat. No. 10,982,202, which is a continuation of application No. 14/650,767, filed as application No. PCT/JP2013/083082 on **December 10, 2013**, now Pat. No. 10,144,923. The '318 Patent also claims foreign priority to JP 2012-269840, filed December 10, 2012.

A. Claim 21

Claim 21 recites:

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 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.

Ex. 1001 at cl. 21.

This claim captures a focal point of the inventors' contribution to the field:
successful recombinant production of Factor C in a mammalian cell (*i.e.*, a HEK293

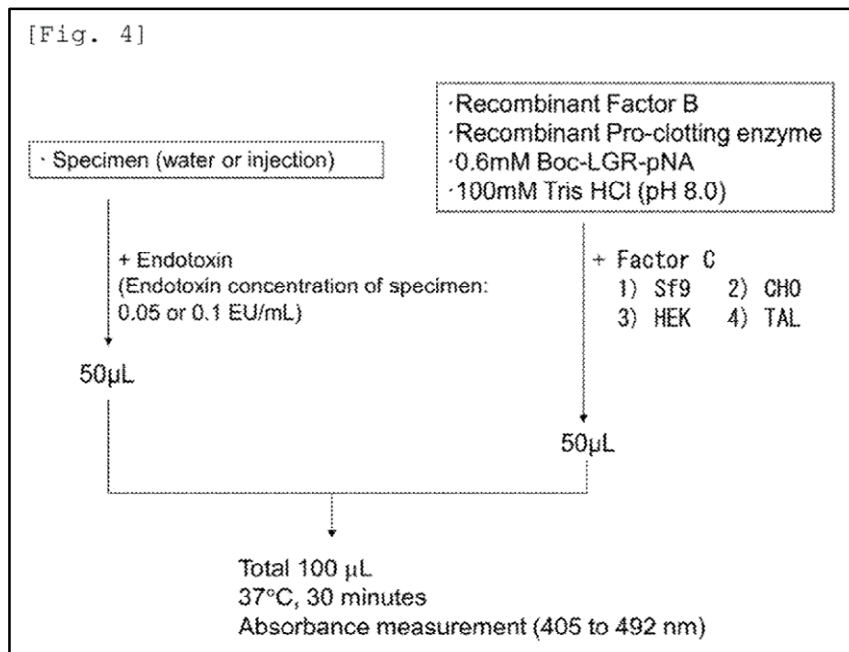
cell) that exhibits less susceptibility to inhibition in the presence of ions (*i.e.*, high residual activity).

B. Specification of the '318 Patent

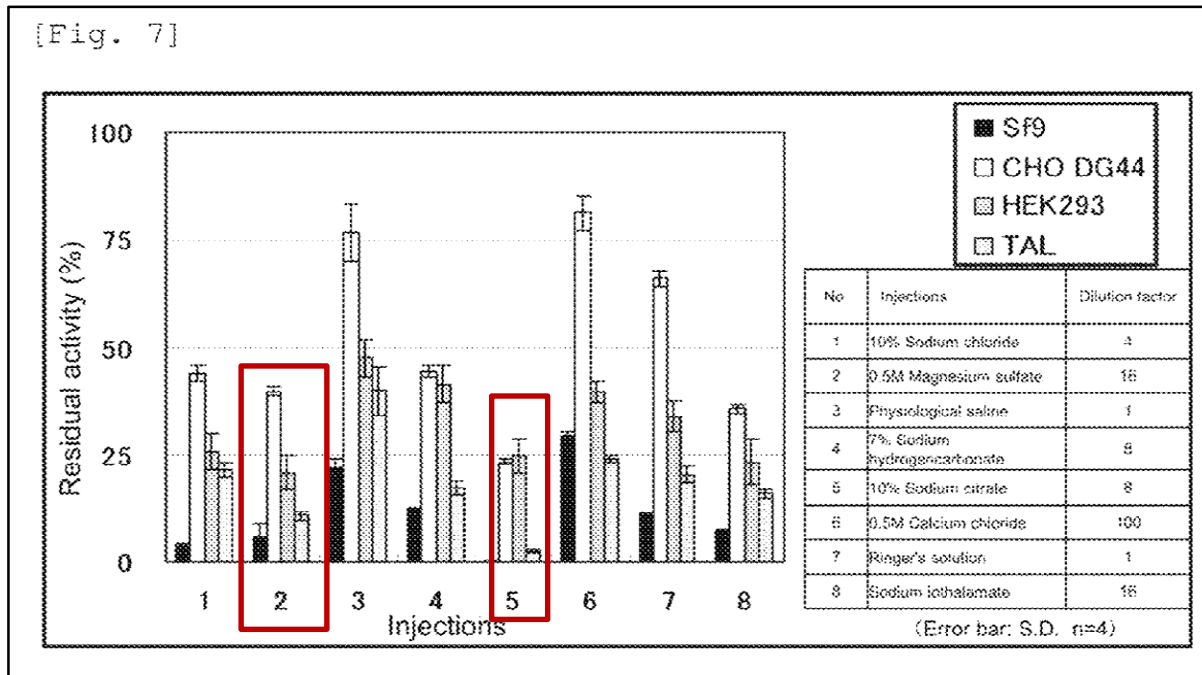
The specification of the '318 Patent describes the “Factor C of the present invention” as having “low susceptibility to inhibition of activity by an ion,” which refers to “the state that the Factor C of the present invention *exhibits a high residual activity in the presence of an ion, as compared with a control Factor C.*” Ex. 1001 at 17:20-25. The specification provides *specific means* to quantify whether the recombinant Factor C demonstrates this inventive “low susceptibility to inhibition of activity by an ion” by (i) explaining how to determine the residual activity and (ii) providing minimum threshold values in specific salt concentrations for the residual activity. Ex. 1001 at 3:49-51, 4:6-8, 34:39-35:43, Fig. 7.

The specification also describes the preparation of Factor C using HEK293 cells as host cells and measuring the inhibition of activity of the Factor C in the presence of salt ions. Ex. 1001 at 31:14-43, 34:39-35:43. Figure 4 shows the procedure by which activity of Factor C was measured, and Figure 7 shows that expressing Factor C in mammalian cells (CHO DG44 and HEK293) generates higher residual activity in the presence of the claimed salt solutions (*i.e.*, 21 mM

sodium citrate and 16 mM magnesium sulfate)¹ compared to residual activity observed in native *Tachypleus tridentatus* (TAL) or Factor C recombinantly produced in Sf9 cells. Ex. 1001 at 35:20-21, 35:26-43, Figs. 4, 7.



¹ As the specification explains, an 8-fold dilute of 10 w/v% sodium citrate injection yields a final sodium concentration of about 21 mM, and a 16-fold dilute of 0.5 M magnesium sulfate injection yields a final magnesium sulfate concentration of about 16 mM. Ex. 1001 at 35:4-7, 15-17.



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

C. Prosecution History of the '318 Patent

Following back-and-forth rejections and amendments between the Patent Office (“PTO”) and Applicant, in June 2021, Applicant submitted an agenda for a phone interview with the PTO, which included new claim 24 that ultimately issued as claim 21. Ex. 1004 at 96-98. Applicant subsequently amended its claims to include claim 24 and presented an affidavit from inventor Dr. Hikaru Mizumura as part of its arguments responding to the PTO’s latest rejection. *Id.* at 82-87. In the affidavit, Dr. Mizumura presented experimental data showing the residual activity of *Limulus polyphemus* Factor C recombinantly produced in various cells, including in the claimed salt solutions of 16 mM magnesium sulfate and 21 mM sodium citrate. *Id.* at 85. Dr. Mizumura also directed the PTO to a document cited on the February

3, 2021 IDS (Ex. 2033) that demonstrated unexpectedly high residual activity for recombinant *Limulus polyphemus* Factor C expressed in HEK293 cells, including in the presence of the claimed salt solutions. Ex. 1004 at 85-86 (describing Ex. 2033 at Figs. 4, 6). The PTO subsequently allowed the claims, noting that unexpected results existed to rebut the *prima facie* case of obviousness. Ex. 1004 at 21.

IV. PERSON OF ORDINARY SKILL IN THE ART

Petitioner proposes the following definition of a person of ordinary skill in the art (“POSA”):

A POSA in the technical field relating to the '318 patent would have a Ph.D. degree in biological, chemical or biochemical engineering, molecular biology, or biochemistry and at least two years of experience utilizing or assessing horseshoe crab Factor C (lysate, purified native and/or recombinantly produced) for endotoxin detection and quantitation. More education could substitute for experience, and vice versa.

Pet. at 19.

Patent Owner disagrees with Petitioner's definition of a POSA. Claim 21 does not require knowledge of biological, chemical or biochemical engineering. Patent Owner proposes that 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

The Petition does not assert that any terms require construction. Pet. at 19-20. Patent Owner agrees that the terms in claim 21 can be afforded their plain and ordinary meaning for purposes of this proceeding.

VI. CLAIM 21 IS ENTITLED TO ITS DECEMBER 10, 2013 EFFECTIVE FILING DATE

Petitioner erroneously asserts that the '767 Application in the priority chain “fails to describe and enable” claim 21. Pet. at 22-42. As described below, the '767 Application provides ample written description support and enables the full scope of claim 21.

A. The '767 Application Provides Written Description Support for Claim 21

Petitioner's written description argument hinges on its assertion that claim 21 “encompasses a *genus* of recombinantly produced *Limulus polyphemus* Factor C proteins satisfying either one of these exceedingly wide ranges for the functional characteristic of ‘residual activity.’” Pet. at 23. In support, Petitioner argues (i) no examples using *Limulus polyphemus* exist in the '767 Application; (ii) differences

in species would yield differences in protein function; (iii) no structural feature common to the claimed genus correlates with function; and (iv) Applicants' statements in a later application confirm the lack of written description support. Pet. at 23-31. Each argument fails.

1. The Law of Written Description Does Not Require Specific Examples

Petitioner's reliance on the lack of specific examples in the '767 Application related to *Limulus polyphemus* ignores the law. "There is *no rigid requirement that the disclosure contain 'either examples or an actual reduction to practice'*"; the proper inquiry is whether the patentee has provided an adequate description that 'in a definite way identifies the claimed invention' in sufficient detail such that a person of ordinary skill would understand that the inventor had made the invention at the time of filing." *Regeneron Pharms., Inc. v. Mylan Pharms. Inc.*, 127 F.4th 896, 916 (Fed. Cir. 2025). Moreover, "a patentee may rely on information that is well-known in the art' to the extent it informs how a relevant artisan would reasonably understand what is actually described in the specification." *BASF Plant Sci., LP v. Commonwealth Sci. and Indus. Rsch. Org.*, 28 F.4th 1247, 1264 (Fed. Cir. 2022).

The '767 Application provides the requisite description such that a POSA would have understood the inventors had possession of the invention of claim 21 as of at least the 2013 filing date for the '767 Application.² Ex. 2038 ¶¶ 52-60.

First, in a section titled “***Modes for Carrying Out the Invention***,” the '767 Application states that the “Factor C of the present invention is a ***Factor C derived from a horseshoe crab***” and specifically identifies *Limulus polyphemus* as a known species. Ex. 1006 at 40.³ Thus, the '767 Application identifies the specifically claimed *Limulus polyphemus* species as part of its invention.

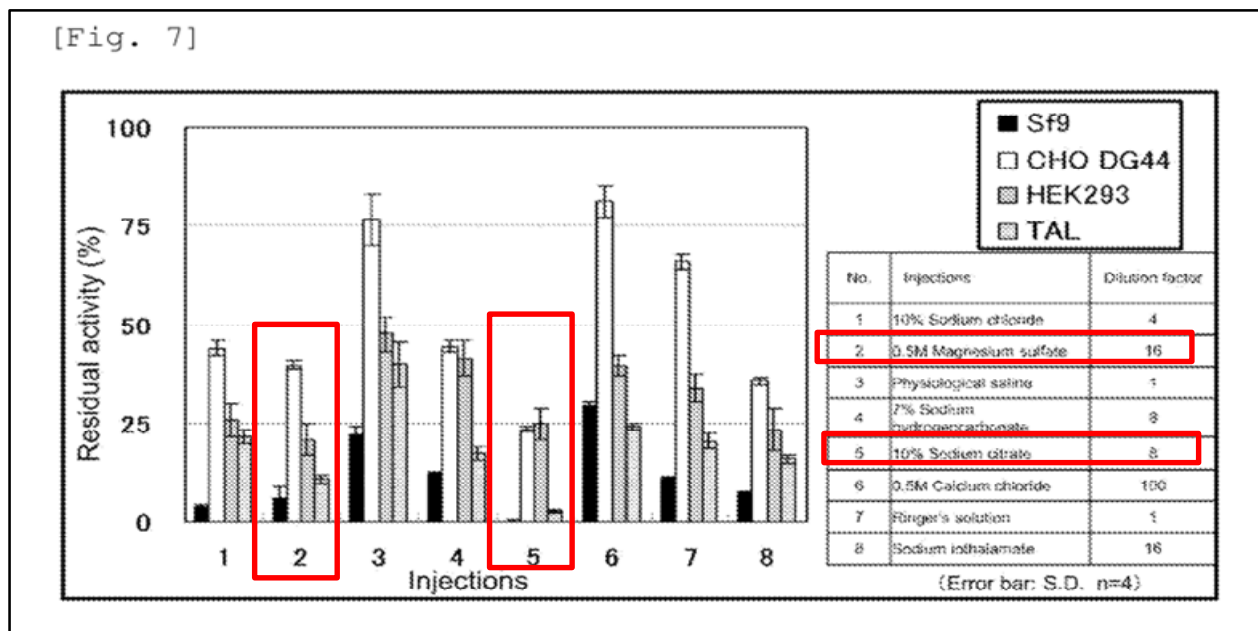
Second, the specification includes a specific example titled “Expression of Factor C in mammalian cells (HEK 293),” which describes steps to produce Factor

² The '318 Patent also claims foreign priority to JP App. No. 2012-269840, filed December 10, 2012. Petitioner does not separately assert that the '318 Patent is not entitled to that priority date but instead states that it analyzed the '767 Application “as representative of each disclosure (including the '840 JP Priority Application and the '082 PCT (Ex. 1035)) in the priority chain extending back to December 10, 2012.” Pet. at 22.

³ For all citations to Ex. 1006, PO cites to the page numbers reflected in the footnote exhibit stamp applied by Petitioner.

C using HEK293 cells as the host cell—the same host cell claim 21 recites. Ex. 1006 at 87.

Third, 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 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 the claimed residual activity of 10% or higher in the presence of 21 mM sodium citrate (column 5) and 15% or higher in the presence of 16 mM magnesium sulfate (column 2). Ex. 1006 at 96-99, 119.



Ex. 1006 at 122 (annotated).

Despite these express disclosures, Petitioner argues the inventors did not have possession of the claimed invention because the specification does not include a specific example of a recombinant Factor C protein derived from *Limulus polyphemus* with the claimed residual activity. Pet. at 25. Petitioner's argument misses the mark.

As discussed, “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. Cir. 2006); *see also Regeneron*, 127 F.4th at 916. 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).

As the Board acknowledged, as of December 10, 2013, a POSA would have understood that “*Limulus polyphemus* and *Tachypleus tridentatus* are similar in certain aspects,” including (i) “that ‘immunological and biochemical properties of the purified Factor C [isolated from *L. polyphemus*] are **indistinguishable** from those of factor C isolated from *Tachypleus* hemocytes” and (ii) that “‘the *Limulus* factor C sequence closely matched the Asian species, with >90% sequence identity.’”

Paper 14 at 20-21 (citing Ex. 1022 at 150-152 and Ex. 2035 ¶ 134); *see also* Section II, *supra*.

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. 2050; Ex. 2051; 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 as of December 10, 2013 would have been able to assemble **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 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 ("When the prior art includes the nucleotide information" or accessible sources provide the necessary sequence information "satisfaction of the written description requirement

does not require either the recitation or incorporation by reference... of such genes and sequences.”).

Although the Board noted the then-unrebutted opinion of Petitioner's expert Dr. Jain “that ‘certain sequence differences between [*Limulus polyphemus*] and *Tachypleus tridentatus* were **non-conservative** (i.e., potentially giving rise to changes in function in terms of enzymatic activity of Factor C),” Paper 14 at 21 (citing Ex. 1002 ¶ 94 (emphasis in original)), Dr. Jain's opinion that non-conservative substitutions could **potentially** give rise to functional changes is not only speculative but also based only on **partial** sequences he compared from Tokunuga. Ex. 1002 ¶¶ 95-99.

Critically, Dr. Jain's statements as to lack of Section 112 support contradict his later opinion that claim 21 would have been obvious because “given similarities overall, [a POSA would] expect the [*Limulus polyphemus* and *Tachypleus tridentatus*] to be **comparable in terms of residual activity**.” Ex. 1002 ¶ 182; see also Pet. at 52. On the one hand, Petitioner cannot argue residual activity data for *Tachypleus tridentatus* fails to provide Section 112 support for claims directed to *Limulus polyphemus* while, on the other, argue that **the same data** demonstrates a reasonable expectation of success for purposes of its obviousness analysis.

As Patent Owner's expert Dr. Schaefer explains, and contrary to Dr. Jain's and Petitioner's priority date-based attacks, 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.

As of December 10, 2013, a POSA also would have known how to compare the amino acid sequences of Factor C from various horseshoe crab species to assess which residues in *Limulus polyphemus* Factor C are non-conserved compared to other horseshoe crab species. Ex. 2038 ¶ 92. Out of 1,020 amino acids, Patent Owner's expert Dr. Schaefer found 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. Dr. Schaefer further provided a Clustal alignment of Factor C proteins from *Limulus polyphemus*, *Tachypleus tridentatus*, and *Carcinoscorpius rotundicuada* (Ex. 2103), concluding a POSA would have expected that functional properties, such as residual activity in the claimed salt solutions, would be highly conserved among the three species of horseshoe crabs. Ex. 2038 ¶¶ 97-98; *see also id.* ¶¶ 99-102.

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.

Petitioner erroneously argues that claim 21 lacks written description support because it requires a “wide range” of residual activities. Pet. at 23-34. Petitioner ignores the meaning of “residual activity” within the context of the invention and thus improperly assumes that the inventors must show support for a “wide range” of residual activities.

As the '318 Patent explains, “it has been known that the American horseshoe crab (*Limulus polyphemus*) undergoes a blood clotting when it is infected with a Gram-negative bacterium,” and that its coagulation cascade has been “conventionally employed for the detection of endotoxins” such as in pharmaceutical injections administered *in vivo*. Ex. 1001 at 1:41-45; *see also id.* at 1:46-54. As the '318 Patent further explains, because pharmaceutical injections frequently contain a variety of salts (ions), a “[p]roblem to be [s]olved by the [i]nvention” is to ensure that the cascade reaction, including Factor C, is not susceptible to reaction inhibition in the presence of these salts. Ex. 1001 at 2:63-3:8.

According to the '318 Patent, the desired “low susceptibility to inhibition of activity by an ion,” “refers to the state that the Factor C of the present invention exhibits a ***high residual activity*** in the presence of an ion.” Ex. 1006 at 50-52.

Critically, the “residual activity” is “*defined* as a *relative reactivity (%)* observed for a measurement specimen (endotoxin concentration: 0.05 EU/mL) prepared by adding endotoxin to an ion-containing test specimen, with respect to the reactivity observed for another measurement specimen (endotoxin concentration: 0.05 EU/mL) prepared by adding endotoxin to injection water as 100%, in the assay system shown in FIG. 4.” Ex. 1001 at 18:8-15; Ex. 1006 at 52.

Based on these disclosures, a POSA would have understood the residual activities in claim 21 recite the minimum threshold of relative reactivity in different salt solutions (*i.e.*, sodium citrate and magnesium sulfate) that must be present for the recombinantly produced Factor C to exhibit the inventive concept: low susceptibility to inhibition of activity by an ion. The '767 Application expressly identified these minimum threshold values, noting that “low susceptibility to inhibition of activity by an ion” can refer to residual activity values of “10% or higher” in the presence of 21 mM sodium citrate and “15% or higher” in the presence of 16 mM magnesium sulfate. Ex. 1006 at 50-52.

Petitioner's attempt to impose a requirement that the inventors had to show a disclosure of residual activities across a wide range ignores that “[t]he specification does not need to describe ‘every conceivable and possible future embodiment of [the] invention.’” *Regeneron*, 127 F.4th at 916. Instead, “the proper inquiry is whether the patentee has provided an adequate description that ‘in a definite way

identifies the *claimed invention*’ in sufficient detail such that a person of ordinary skill would understand that the inventor had made the invention at the time of filing.” *Allergan v. Sandoz*, 796 F.3d at 1308 (quoting *Ariad*, 598 F.3d at 1352). The ’767 Application amply meets this requirement.

Even if written description requires possession of a wide range of residual activities, which PO disagrees is the proper lens to view the claim, the residual activity of *Limulus polyphemus* Factor C recombinantly produced in HEK293 cells when tested in the claimed salt solutions demonstrates residual activity nearing and exceeding 100%. Ex. 2033 at Figs. 4, 6. This demonstrates that the inventors possessed the full scope of the claimed invention. *See, e.g., Allergan, Inc.*, 796 F.3d at 1309 (“A claim that recites a property that is necessarily inherent in a formulation that is adequately described is not invalid as lacking written description merely because the property itself is not explicitly described.”).

Coupled with a POSA’s knowledge of the art, the ’767 Application provides more than sufficient written description, including test data, to support the inventors had possession of the full scope of the invention by December 2013.

2. High Degrees of Similarity Exist Between the Species of Horseshoe Crabs

Petitioner also asserts that differences in species would yield differences in protein function such that “the failure to provide any experimental example or

verified structural link between species giving rise to such similar function only confirms lack of possession.” Pet. at 26-27. Specifically, Petitioner asserts that “[w]ithout the full gene and amino acid sequence information for *Limulus polyphemus* Factor C in 2013 from which **any comparison** could even be made to any other species, any view about the resulting functional characteristics . . . would have been mere speculation.” Pet. at 27 (emphasis in original).

Yet Petitioner ignores three critical facts, each fatal to its argument. *First*, by December 10, 2013, the deposits made in October 2012 by the University of Connecticut would have allowed a POSA to arrive at the cDNA sequence of *Limulus polyphemus* Factor C through routine experimentation. *See* Section II, VI.A.1, *supra*. *Second*, researchers had not only successfully characterized Factor C protein from the *Limulus polyphemus* amoebocytes well before 2013 but also had compared it to Factor C from the *Tachypleus tridentatus* horseshoe crab—the species used in Figure 7 of the ’767 Application. Ex. 2038 ¶ 91. *Third*, despite the geographical and general physical or genetic differences across the species of horseshoe crabs, a POSA would have understood that the coagulation cascade proteins (*e.g.*, Factor C) were structurally similar and functionally identical across species. *Id.* ¶ 86; *see also id.* ¶¶ 87-88, 98-102.

For example, by December 10, 2013, the U.S. Pharmacopeia chapter on bacterial endotoxin testing described amoebocyte lysate as “a lyophilized product

obtained from the lysate of amoebocytes... from the horseshoe crab (*Limulus polyphemus* or *Tachypleus tridentatus*).” Ex. 2104 at 1. The corresponding chapters in the European Pharmacopoeia and Japanese Pharmacopoeia were harmonized with the USP in 2012. Ex. 2105 at 1; Ex. 2106 at 4; Ex. 2038 ¶ 100. These compendia reflect the understanding in the art that the coagulation cascade and its constituent proteins are functionally identical between *Limulus polyphemus* and *Tachypleus tridentatus*.

Moreover, by at least 1991, Dr. Tokunaga and his colleagues at Kyushu University had isolated and characterized Factor C protein from the *Limulus polyphemus* species of horseshoe crab and compared its properties to Factor C from the *Tachypleus tridentatus* horseshoe crab. Ex. 1022 at 150, 155. Dr. Tokunaga determined that “the ***immunological and biochemical properties*** of the purified factor C [in *Limulus polyphemus*] are ***indistinguishable*** from those of factor C isolated from *Tachypleus* hemocytes.” *Id.* at 150-151. He also compared the amino acid compositions of the intact *Limulus polyphemus* Factor C with *Tachypleus tridentatus* Factor C and determined that “the individual amino acid compositions of the two proteins and of their chain subunits were ***indistinguishable***.” *Id.* at 151.

Further, the '432 Publication in 2003 described recombinant Factor C and noted that “[m]ethods of producing proteins recombinantly are well known in the art.” Ex. 2035 at Abstract, [0030], [0032]. As the '432 Publication explained,

researchers had successfully “isolated the Factor C from *Limulus*” and determined that “the *Limulus* factor C sequence *closely matched the Asian species, with >90% sequence identity.*” *Id.* at [0134]. And in 2006, Drs. Alwis and Milton reported that “the Factor C of *Carcinoscorpius rotundicauda* has 89.3% homology with that of *Limulus polyphemus*, North American horse shoe [*sic*] crab Factor C.” Ex. 2036 at 4. Additionally, in 2009, it was reported that “[t]he rFC protein derived from *C. rotundicauda* shares a 90.5% identical amino acid sequence with the native Factor C protein derived from *L. polyphemus.*” Ex. 2049 at 2.

As explained above, a POSA in December 2013 would have understood that Factor C proteins from *Tachypleus tridentatus* and *Limulus polyphemus* were highly conserved across the species. Ex. 2038 ¶¶ 85-102. Given this, a POSA would have understood that the functional activity, such as meeting the claimed residual activity, would be maintained across the species. *Id.*

Since “a patentee can rely on information that is ‘well-known in the art’ to satisfy written description,” this knowledge and the disclosures in the ’767 Application demonstrate claim 21 has ample written description support. *Streck, Inc. v. Rsch. & Diagnostic Sys., Inc.*, 665 F.3d 1269, 1285 (Fed. Cir. 2012); *see also Zoltek Corp. v. U.S.*, 815 F.3d 1302, 1308 (Fed. Cir. 2016) (“The written description ‘need not include information that is already known and available to the experienced public.’”).

3. Petitioner Improperly Asserts that a Structural Feature Common to the Claims is Required for Written Description Support

Petitioner also argues that claim 21 lacks written description support because the inventors failed to provide a structural feature common to the claimed genus that correlates with function. Pet. at 29-31. But, as discussed in Sections VI.A.1-2, *supra*, the '767 Application provides sufficient written description support for the claimed invention when viewed from a POSA's perspective.

Petitioner's argument incorrectly analyzes claim 21 as a broad genus claim that requires either a disclosure of representative species or structural features common to the members of the genus such that a POSA could visualize or recognize the members of the genus. Pet. at 30-31. But claim 21 does *not* recite a broad genus. To the contrary, it *narrowly* claims (i) Factor C from a specific horseshoe crab species—*Limulus polyphemus*—(ii) that is recombinantly expressed from a specific host cell—HEK 293—and (iii) that meets a minimum residual activity threshold in specifically claimed salt solution concentrations. Ex. 1001 at cl. 21.

According to the Federal Circuit, where, as here, the claim is narrow and the specification discloses its subject matter in terms of a broad genus, the specification must “*provide sufficient ‘blaze marks’ to guide a reader through the forest of*

disclosed possibilities' toward the claimed invention." *Pharmacyclics LLC v. Alvogen, Inc.*, No. 2021-2270, 2022 WL 16943006, at *7 (Fed. Cir. Nov. 15, 2022).⁴

That is precisely what the '767 Application provides. As discussed, it explains that the "Factor C of the present invention may have *low susceptibility to inhibition of activity by an ion*" and identifies the claimed residual activity values of 10% or higher in the presence of 21 mM sodium citrate and 15% or higher in the presence of 16 mM magnesium sulfate as "*[s]pecific examples* of 'low susceptibility to inhibition of activity by an ion.'" Ex. 1006 at 50-52. It also includes examples (i) utilizing HEK293 cells as the host cells to recombinantly produce Factor C and (ii)

⁴ The '767 Application, repeatedly notes the various attributes and characteristics of "*Factor C of the present invention*." See, e.g., Ex. 1006 at 50-52 (describing that "Factor C of the present invention" exhibits the claimed residual activities in the claimed salt solutions); *id.* at 53-54 (describing that "Factor C of the present invention" can be expressed in HEK293 cells). While the '767 Application also provides specific examples that rely on the *Tachypleus tridentatus* species of horseshoe crab, those examples do not mean that the inventors *only* possessed Factor C from that particular species. Indeed, the inventors specifically cited *Limulus polyphemus* in its "Modes for Carrying Out the Invention" section. Ex. 1006 at 40.

demonstrating that Factor C expressed in these cells meets the minimum threshold of the claimed residual activity. Ex. 1006 at 53-54, 87-88, 96-99, Fig. 4, Fig. 7. And it identifies *Limulus polyphemus* as one of **four** existing species of horseshoe crab in the “Modes for Carrying Out the Invention” section. Ex. 1006 at 40. Thus, a POSA would have understood that the ‘767 Application provides sufficient blaze marks towards the narrowly claimed invention of claim 21.

As discussed above, researchers reported before December 2013 that “[t]he rFC protein derived from *C. rotundicauda* shares a 90.5% identical amino acid sequence with the native Factor C protein derived from *L. polyphemus*.” See, e.g., Ex. 2049 at 2. As Patent Owner’s expert Dr. Schaefer explains, a POSA would have understood as of December 2013 that the Factor C genes and proteins from *Tachypleus tridentatus* and *Limulus polyphemus* would have high sequence identity and similarity. Ex. 2038 ¶ 91. A POSA also would have understood as of December 2013 how to generate sequence similarity and structure comparisons between the Factor C protein of *Limulus polyphemus* and both *Tachypleus tridentatus* and *Carcinoscorpius rotundicauda*, which Patent Owner’s expert Dr. Schaefer did, and would have understood that functional properties, such as residual activity, would be highly conserved among the various species of horseshoe crab. Ex. 2038 ¶¶ 92-98.

**4. PO's Statements in the '498 PCT Do Not Support
Petitioner's Lack of Written Description Argument**

Petitioner further points to statements in the '498 PCT (Ex. 1005), which has two overlapping inventors with the '318 Patent, as supporting its lack of written description argument. Pet. at 31-32. Specifically, Petitioner asserts the statement that “in *Limulus polyphemus*, the proteins and their genes involved in the mechanism of coagulation caused by endotoxin **have not been completely identified structurally or functionally**” is “fatal” to the question of written description support for claim 21. Pet. at 32 (emphasis in original).

Not so. Ex. 2038 ¶¶ 103-105. Although the inventors of the '498 PCT may have been the first to identify the **full-length** cDNA sequence for *Limulus polyphemus* Factor C (Ex. 1005 at [0017]), other skilled artisans had the knowledge and means to do so as well.⁵ As discussed, by 2006 the literature disclosed that researchers had (i) isolated Factor C from *Limulus polyphemus*; (ii) sufficiently identified its sequence to run a homology comparison with other species of horseshoe crabs; and (iii) documented the substantial homology among Factor C proteins from various horseshoe crabs, including that *Limulus polyphemus* are “**indistinguishable**” from those of Factor C isolated from *Tachypleus tridentatus*. See, e.g., Ex. 2036 at 4; Ex. 1022 at 152; Ex. 2035 at [0134]. Skilled artisans also

⁵ The '498 PCT did not issue as a patent in the United States.

would have known that only eleven out of 1,020 amino acid substitutions in *Limulus polyphemus* are non-conservative substitutions and that functional properties would be highly conserved among the horseshoe crab species. Ex. 2038 ¶¶ 90-98. What's more, skilled artisans would have had access to the University of Connecticut's sequence deposits for *Limulus polyphemus*, which would have allowed them to assemble a full-length cDNA sequence using conventional techniques. Ex. 2038 ¶¶ 61-81 (as of December 10, 2013, a POSA would have been able to assemble 97.2% of the full Factor C coding sequence based on the known similarities between *Tachypleus tridentatus* and *Limulus polyphemus*, as well as the publicly available University of Connecticut sequence information).

Thus, the discussion in the '498 PCT fails to support Petitioner's lack of written description assertion.

**a. Statements in the Opposition to EP Patent No.
3530670 Undercut Petitioner's Arguments about the
'498 PCT**

In an Opposition proceeding filed against PO's European Patent No. 3530670 ("EP '670") ("the Opposition"), the challenger not only submitted arguments against the patentability of EP '670 but also submitted a declaration from Michael A. Frohman, M.D., Ph.D.—an expert in "biochemistry, immunology, developmental and molecular biology, with 38 years of experience in molecular cloning." Ex. 2004 ¶ 2.

As detailed in Patent Owner's Preliminary Response, the evidence strongly suggests that Petitioner submitted the Opposition and commissioned Professor Frohman's declaration. *See* Paper 7 at Section VI.B.5. Further evidencing Petitioner's role in the Opposition, in response to Patent Owner's Motion to Compel Routine Discovery (Paper 12), Petitioner argued that it "cannot comply with PO's unjustified discovery request [to confirm Petitioner filed the Opposition] without violating at least the attorney-client privilege and the work product doctrine." Paper 13 at 6. This argument necessarily implicates Petitioner as the party that filed the Opposition. As Patent Owner explained in its Motion, if "CRL is *not* the party behind the Opposition, then there is no attorney-client relationship involving CRL and, thus, no privilege." Paper 12 at 1 (emphasis in original). CRL's adamantness that privilege exists all but confirms it is the party behind the Opposition and Dr. Frohman's declaration.

Given the likelihood that Petitioner submitted the Opposition, its arguments in its Petition that directly contravene arguments made in the Opposition should be disregarded if not viewed with extreme skepticism. For example, the Opposition discusses EP 2939241 (D1), which is a European patent having the same specification as the '767 Application. Ex. 1048 ¶¶ 4, 51. In the Opposition, the Opponent argued that "*D1 already discloses 'a recombinant Factor C protein derived from Limulus polyphemus (LFC).'*" *Id.* ¶155. This directly contradicts

Petitioner's assertions in this proceeding that the '767 Application does not mention or describe a single example of the claimed recombinant *Limulus polyphemus* Factor C proteins. Pet. at 25 (section heading a.).

Notably, the Opponent also *criticized* statements within the '498 PCT. For example, the Opposition states that “the mere statement in par. [0012] . . . which alleges that the determination of this [*Limulus polyphemus*] sequence ‘*could not be achieved by general techniques*’ *is entirely unsupported*.” Ex. 1048 ¶ 75; *see also id.* ¶ 35 (stating paragraph [0012] “is very generic and entirely unsupported”). The Opponent also pointed to the 2006 reference from Alwis & Milton discussing sequence homology (Ex. 2036) as “support[ing] [the Opponent’s] position that the patent’s claim that the sequence could not be previously determined is factually incorrect.”). *Id.* at 9, n.2.

Assuming Petitioner commissioned the Opposition, the Board should give Petitioner's contradictory assertions little, if any, weight and determine that the '767 Application provides adequate written description for claim 21.

B. The '767 Application Enables the Full Scope of Challenged Claim 21 of the '318 Patent

Petitioner also asserts that the '767 Application does not enable the full scope of claim 21. Pet. at 35. Specifically, Petitioner contends that “the '767 Application does not teach a POSA how to make or use recombinant *Limulus polyphemus* Factor

C proteins with any particular residual activity value” and “[t]o do so a POSA would have needed to engage in significant experimentation to make proteins exhibiting a residual activity across such a wide claimed range.” Pet. at 37.

But the relevant inquiry is whether *undue* experimentation is required, as “a specification may call for a *reasonable amount* of experimentation to make and use a patented invention.” *U.S. Synthetic Corp. v. Int’l Trade Comm’n*, 128 F.4th 1272, 1285 (Fed. Cir. 2025) (quoting *Amgen Inc. v. Sanofi*, 598 U.S. 594 (2023)).

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).

Petitioner’s assertion that undue experimentation would be required cannot be squared with the Federal Circuit’s decision in *Wands*. *Wands* involved hybridoma technology and commercial screening assays whereby antibodies were produced from hybridomas and then screened for the desired characteristics. 858 F.2d at 740. The Federal Circuit held the claims were enabled “because the monoclonal antibodies needed to perform the immunoassays can be made from readily available

starting materials using methods that are well known in the monoclonal antibody art.” *Id.* at 736.

Similarly, the '767 Application teaches the skilled artisan (i) how to recombinantly produce Factor C proteins in HEK293 cells and (ii) how to measure the residual activity in the claimed salt solution concentrations. As in *Wands*, a skilled artisan carrying out the disclosed process in the '767 Application, particularly given the knowledge in the art, could have successfully made recombinant Factor C in HEK293 cells with the claimed residual activity without undue experimentation.

A proper analysis of the *Wands* factors further demonstrates that undue experimentation would **not** have been required, and the '767 Application enables the full scope of claim 21. Ex. 2038 ¶ 106.

1. Claim 21 is Not Broad (*Wands* Factor 8)

Petitioner asserts that claim 21 of the '318 Patent “broadly encompasses Factor C proteins satisfying a wide range of values of residual activity in the presence of certain ions.” Pet. at 37. But neither Petitioner nor its expert offers evidence quantifying the size of the genus. Instead, they summarily assert without citation that the genus is “broad.” Pet. at 37-38; Ex. 1002 ¶¶ 130-134. Moreover, Petitioner’s argument that claim 21 “encompasses Factor C proteins” ignores that claim 21 is **narrowly** confined to a specific species of horseshoe crab (*Limulus polyphemus*) recombinantly expressed from a specific host cell (HEK293) with

minimum threshold residual activity values in specifically claimed concentrations of specific salt solutions. *Id.* Petitioner provides no support for its conclusion that “Claim 21 is Broad.” *Id.*

As for the assertion that the claim requires a “wide claimed range” of residual activity values, as discussed in Section VI.A.1, *supra*, a POSA would have understood the residual activities in claim 21 as simply requiring the minimum threshold of relative reactivity in different salt solutions (*i.e.*, sodium citrate and magnesium sulfate) that must be present for the recombinantly produced Factor C to exhibit the inventive concept: low susceptibility to inhibition of activity by an ion. It would not be understood as requiring a “wide claimed range” of residual activities as Petitioner argues. A POSA would not have considered claim 21 to be broad as Petitioner asserts. Ex. 2038 ¶¶ 107-110.

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

Petitioner lumps together *Wands* factors 1-3 but then ignores factors 1 and 2, focusing instead only on the lack of a specific example of Factor C from *Limulus polyphemus* exhibiting the claimed residual activity. But, as discussed, 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 Petitioner ignores that 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. Ex. 2038 ¶ 114-118.

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 meet the minimum residual activity threshold required by Claim 21. 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 minimum residual activity threshold claimed. Ex. 2038 ¶ 116. The lack of the examples using *Limulus polyphemus* Factor C does not change the conclusion. Given what was well known in the prior art (as discussed in Section II, VI, *supra*) and the admitted 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.

In sum, the specification would have enabled a skilled artisan to make and use Claim 21 because (i) undue experimentation would not have 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)**

Relying on its unsupported assertion that Claim 21 is broad, Petitioner asserts that “[r]eaching the full scope of claim 21 therefore requires an *extensive amount of experimentation* across multiple fronts: (1) to discover and characterize the gene and amino acid sequence for *Limulus polyphemus* Factor C itself, which was not known as of 2013 . . . , (2) to use this as-yet undiscovered genetic information to recombinantly generate Factor C across the full scope of residual activity function characteristic as defined by claim 21.” Pet. at 38. As shown below, the record proves otherwise. 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 in Section II, *supra*, 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]. Further, in 2009, it was reported that “[t]he rFC protein derived from *C. rotundicauda* shares a 90.5% identical amino acid sequence with the native Factor C protein derived from *L. polyphemus*.” Ex. 2049 at 2. 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 claim 21 without undue experimentation. *Id.* ¶¶ 111-112.

Further, the Opposition to EP '670 and Professor Frohman's declaration submitted with the Opposition confirm, a POSA would *not* have had to unduly experiment to discover and characterize *Limulus polyphemus* Factor C and recombinantly express it in HEK293 cells.

For example, in the Opposition, the Opponent stated that “the skilled person merely had to determine the sequence of the *Limulus* Factor C protein, or cDNA sequence encoding the same, to carry out its recombinant production. . . it would have merely been a matter of routine analysis to obtain the sequences.” Ex. 1048 ¶31; *see also id.* ¶116 (emphasis in original). The Opponent further stated “the problem in view of **D1** may thus be formulated as the determination of the full-length *Limulus* Factor C sequence. . . . Deriving the solution to this problem (i.e., one of the sequences recited in claim 1) does not require any inventive skill. As we have already noted above, it is a matter of routine practice for a person skilled in the art to determine the sequence of a known protein.” *Id.* ¶¶58-59 (emphasis in original).

Moreover, when discussing D1, which has the same specification as the '767 Application, critically, the Opponent noted that “**D1** already discloses ‘a recombinant Factor C protein derived from *Limulus polyphemus*.’” Ex. 1048 ¶155.

The Opponent also argued that by “reading the description of” the ’767 Application, a POSA “would not only be able to produce a *Limulus* Factor C without undue burden, but that they would further expect the invention of [the ’767 Application] to ‘also work when Factor C is the Factor C of *Limulus polyphemus*.’” *Id.* ¶50 (emphasis in original). The Opposition further stated, when addressing statements that appear in the ’498 PCT, that “the mere statement in par. [0012] . . . which alleges that the determination of this sequence ‘*could not be achieved by general techniques*’ is entirely unsupported.” Ex. 1048 ¶75.

The Opponent’s retained expert Dr. Frohman also noted that claim 1 in EP ’670 “relates to a method for producing an endotoxin detecting agent comprising a step of artificially expressing a protein using a cDNA [...], wherein the *cDNA encodes [a limulus Factor C sequence]*.” Ex. 2004 ¶ 4. In his declaration, Professor Frohman opined on “questions from the perspective of a [POSA] charged with the determination of the full-length *Limulus* Factor C sequence before October 18, 2016,” including whether it would have been difficult to obtain the cDNA sequence of *Limulus polyphemus* and express it after the sequence had been obtained. *Id.* ¶ 5 (emphasis in original). As Professor Frohman explained, a POSA would have been able to do these things with little difficulty.

To obtain the cDNA sequence of *Limulus polyphemus*, Professor Frohman explained a POSA “would have most likely used Rapid Amplification of cDNA

Ends (RACE) to obtain the sequence of the cDNA encoding Factor C from *Limulus polyphemus*.” Ex. 2004 ¶ 7. Although he focused his analysis on what a POSA would have known in 2016, Professor Frohman pointed exclusively to publications and knowledge available well before 2013.

Specifically, Professor Frohman explained that he developed RACE in **1988** “as a quick approach to obtain full-length cDNA sequences in cases where a partial stretch of the mRNA sequence was known” and that it “can be used to obtain a full-length cDNA sequence *in a matter of days*.” Ex. 2004 ¶ 8. He also stated it would “have been entirely straightforward for the skilled person to design RACE primers based on the available *Limulus* sequence information listed in items (i)-(iii) above.” *Id.* ¶ 10. Notably, item (iii) is the **1991** Tokunaga publication (Ex. 1022).

Professor Frohman also explained that a POSA could have also used protocols described in publications from the 1990s to obtain the cDNA sequence for *Limulus polyphemus*. Ex. 2004 ¶¶ 11-16. Relying on U.S. 5,716,384, which published in **1998** (Ex. 1012), and *Ding* in **1995**, Professor Frohman opined that obtaining the sequence is “very straightforward” such that the “approach [used in these references] would have been successful to obtain the *Limulus* Factor C cDNA” with “no reason to expect any technical difficulties for repeating this protocol for *Limulus*.” Ex. 2004 ¶ 14.

After obtaining the cDNA sequence of *Limulus polyphemus*, as Professor Frohman explained, expressing it also would have involved routine experimentation. Ex. 2004 ¶¶ 44-48. Professor Frohman opined that “the cDNA sequence of the *Limulus* Factor C is *very similar* to the other known species of horseshoe crabs, which had been successfully expressed in Sf9, CHO DG44 and HEK 293 cells,” pointing to “D1 (’241).” *Id.* ¶ 45. According to Professor Frohman, by following the “example of **D1** using the *Limulus* sequence,” he would “not anticipate experiencing any difficulties.” *Id.* ¶ 47.

As such, and contrary to Petitioner and Dr. Jain, a skilled artisan would not have had to conduct undue experimentation to discover and characterize the gene and amino acid sequence for *Limulus polyphemus* Factor C and recombinantly express it in HEK293 cells, as claim 21 requires. Ex. 2038 ¶¶ 109-112.

**b. Undue Experimentation Would Not Have Been
Required to Practice the Full Scope of Residual
Activity in Claim 21 Before 2013**

Petitioner’s assertion that a POSA would have had to unduly experiment to “recombinantly generate Factor C protein across the full scope of residual activity function characteristic as defined by claim 21” likewise fails. Pet. at 38. As noted above, Petitioner’s assertion that the claim requires enablement of a “wide” range of residual activities is misplaced.

The '767 Application details how to measure residual activity of Factor C recombinantly expressed in HEK293 cells, including in the salt solution concentrations of Claim 21, and provides results showing the requisite minimum threshold of residual activity had been achieved. Ex. 1006 at 96-99, Figs. 4, 7. The '767 Application also discloses that these results “indicate that Factor C expressed in mammalian cells can have low susceptibility to activity inhibition by ions,” noting that specific examples include the claimed minimum thresholds. Ex. 1006 at 99. It further identifies *Limulus polyphemus* in the “Modes for Carrying Out the Invention” section. Ex. 1006 at 40.

Given this and a POSA's knowledge (as Professor Frohman's declaration confirms), undue experimentation would not have been required to practice the full scope of claim 21. *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%).

As evidenced by data discussed more fully below in Section IX, the residual activity of *Limulus polyphemus* Factor C recombinantly produced in HEK293 cells when tested in the claimed salt solutions nears and exceeds 100%. Ex. 2033 at Figs. 4, 6. This demonstrates that, even if the claimed residual activity values require a range and not merely a minimum threshold, this range would have been enabled as

of December 10, 2013. *See, e.g., Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1344 (Fed. Cir. 2003).

4. *Wands* Factor 6 Supports a Finding that Challenged Claim 21 is Enabled

Although Petitioner admits the level of skill would have been high, it still argues that making “a recombinant Factor C protein that actually has *any* desired activity. . . was known to be difficult.” Pet. at 39. Yet, 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”); *see also* Ex. 2038 ¶ 113.

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 meets the claimed residual activity minimum thresholds 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 Claim 21 without undue experimentation and thus enables the claim.

Accordingly, contrary to Petitioner's assertion, the '767 Application provides written description support and enables the full scope of claim 21 of the '318 Patent such that it should be afforded its December 10, 2013 priority date.

VII. THE PETITION FAILS TO ESTABLISH THAT CLAIM 21 IS OBVIOUS OVER MIZUMURA IN VIEW OF THE '498 PCT (GROUND 1)

A. Neither Mizumura Nor the '498 PCT is Prior Art

Petitioner asserts that claim 21 is obvious over Mizumura (Ex. 1009) in view of the '498 PCT (Ex. 1005). Pet. at 45. As Petitioner concedes, however, its obviousness argument hinges on its assertion that the '318 Patent is not entitled to its earliest priority date because Mizumura and the '498 PCT have an effective filing date after December 10, 2013. Pet. at 42-43. As Petitioner failed to make this showing, as described in Section VI, *supra*, neither Mizumura nor '498 PCT is prior art to claim 21. Ground 1 thus fails for this reason alone.

B. Even if Mizumura and the '498 PCT were Considered Prior Art, Petitioner Has Failed to Meet its Burden to Demonstrate Unpatentability of Claim 21

To the extent the Board determines that the '318 Patent is not entitled to the December 10, 2013 priority date such that Mizumura and the '498 PCT are prior art, Petitioner's invalidity challenge still fails because Petitioner failed to meet its burden to demonstrate claim 21 is unpatentable.

As Petitioner concedes, Mizumura's disclosure "is identical to both the '767 Application and the '318 patent specification." Pet. at 45. As discussed, claim 21 requires "wherein the Factor C protein exhibits a residual activity of at least one selected from the group consisting of: (1) 10% or higher in the presence of 21 mM sodium citrate; and (2) 15% or higher in the presence of 16 mM magnesium sulfate." Ex. 1001 at cl. 21.

As evidenced by Petitioner's claim chart in its Petition, it relies solely on Mizumura to disclose this claim limitation. Pet. at 51-52. Specifically, it points to the data presented in Figure 7 of Mizumura showing residual activity in various salt solutions for Factor C derived from *Tachypleus tridentatus*, not the claimed *Limulus polyphemus* Factor C. *Id.* at 52. Thus, Petitioner has failed to demonstrate anything in the prior art disclosing the claimed residual activity for the specifically claimed *Limulus polyphemus* Factor C expressed in HEK293 cells.

Recognizing this deficiency, Petitioner asserts that a POSA nonetheless would have been motivated to modify Mizumura with the teaching of the '498 PCT to "develop recombinant *Limulus polyphemus* Factor C via HEK293 cells with the 'residual activity' described in Mizumura" and would have had a reasonable expectation of success in using *Limulus* constructs to generate the claimed residual activity. Pet. at 53-60. This assertion, however, directly contradicts Petitioner's and its expert's arguments that residual activity data in *Tachypleus tridentatus* Factor C

is insufficient to show that the claimed residual activity would be maintained for *Limulus polyphemus* Factor C. Thus, Petitioner has failed to show where the prior art teaches the claimed residual activity values.

Petitioner also fails to demonstrate a reasonable expectation of success in modifying Mizumura based on the '498 PCT to arrive at the claimed invention. Ex. 1002 ¶ 123. To support its argument that a POSA would have had a reasonable expectation of success, Petitioner argues that “[i]t would have been within the skill and experience of a POSA as of 2019 to compare amino acid sequences from the then-known *Limulus polyphemus* horseshoe crab and the well-studied *Tachypleus tridentatus* horseshoe crab, and, given similarities overall, ***reasonably expect the two to be comparable*** in terms of residual activity.” Pet. at 58. As noted, this argument contradicts Petitioner’s (and its expert’s) position relating to a lack of Section 112 support. Moreover, Petitioner’s argument is nothing more than conclusory assertions with no support.

Petitioner bears the burden of demonstrating unpatentability and that a POSA would have had a reasonable expectation of success in arriving at the claimed invention. *Eli Lilly & Co. v. Teva Pharms. Int'l GmbH*, 8 F.4th 1331, 1348 (Fed. Cir. 2021) (“[T]he law places ***the burden of proof on the petitioner*** to prove a proposition of unpatentability by a preponderance of the evidence” such that at all times, it remains Petitioner’s burden to “show that the claims would have been

obvious, including that a skilled artisan would have had a reasonable expectation of success in achieving the claimed invention.”).

Petitioner's reliance on a statement made by Dr. Mizumura in a declaration submitted during prosecution of the '767 Application fails to fill the gap in the analysis. Pet. at 59-60. Dr. Mizumura offers a conclusory assertion that in his opinion “a person skilled in the art would readily recognize that the *presently claimed invention* could also work when Factor C is the Factor C of *Limulus Polyphemus*.” But, while his declaration states that the “similarity between the amino acid sequence of TtFC [*Tachypleus tridentatus* Factor C] and that of LpFC [*Limulus polyphemus* Factor C] is 99.5%” and mentions that “the amino acid residues which can undergo N-type sugar chain modification are conserved,” his declaration nonetheless offers no evidence of the percentage of conserved amino acid substitutions that exist to support the conclusion that a POSA would have expected the residual activity to be maintained between *Tachypleus tridentatus* and *Limulus polyphemus*.

In arguing against the December 10, 2013 priority date of the '318 Patent , Petitioner and its expert assert that non-conservative mutations between the species would have had the “potential to cause structure and function differences between the recombinantly produced Factor C proteins.” Pet. at 28 (citing Ex. 1002 ¶¶ 95-101). Given this, and Petitioner's failure to present any analysis of the percentage

of non-conservative mutations between species, Petitioner has failed to meet its burden to demonstrate a reasonable expectation of success in modifying Mizumura based on the '498 PCT to arrive at the claimed invention.

As such, Petitioner has failed to meet its burden to show that claim 21 of the '318 Patent is unpatentable as obvious.

**VIII. THE PETITION FAILS TO ESTABLISH THAT CLAIM 21 IS
OBVIOUS OVER MIZUMURA IN VIEW OF MCCLYMONT
(GROUND 2)**

A. Neither Mizumura Nor McClymont is Prior Art

Petitioner asserts that Claim 21 is obvious over Mizumura (Ex. 1009) in view of McClymont (Ex. 1010). Pet. at 60. As with Ground 1, Petitioner's obviousness argument hinges on its priority date argument. As Petitioner failed to make this showing, as described in Section VI, *supra*, neither Mizumura nor McClymont is prior art to claim 21. Ground 2 thus fails for that reason alone.

**B. Even if Mizumura and McClymont were Considered Prior Art,
Petitioner Has Failed to Meet its Burden to Demonstrate
Unpatentability of Claim 21**

To the extent the Board determines that the '318 Patent is not entitled to the December 10, 2013 priority date such that Mizumura and McClymont are prior art, Petitioner's invalidity challenge still fails because Petitioner failed to meet its burden to demonstrate claim 21 is unpatentable.

Petitioner relies on McClymont for its discussion of the *Limulus polyphemus* Factor C sequence, noting that “[f]or the same reasons discussed in [Ground 1], POSAs would have had reason to utilize the sequence information from McClymont to generate a recombinant Factor C protein of the *Limulus polyphemus* species in HEK293 cells as disclosed for *Tachypleus tridentatus* in Mizumura, and would have reasonably expected the resulting proteins to have residual activity described in Mizumura and falling within the claimed range.” Pet. at 60-61.

For the same reasons as discussed in Ground 1, incorporated here, Petitioner has failed to meet its burden to demonstrate a reasonable expectation of success in modifying Mizumura to arrive at the claimed invention. As such, Petitioner has failed to meet its burden to show that claim 21 of the '318 Patent is unpatentable.

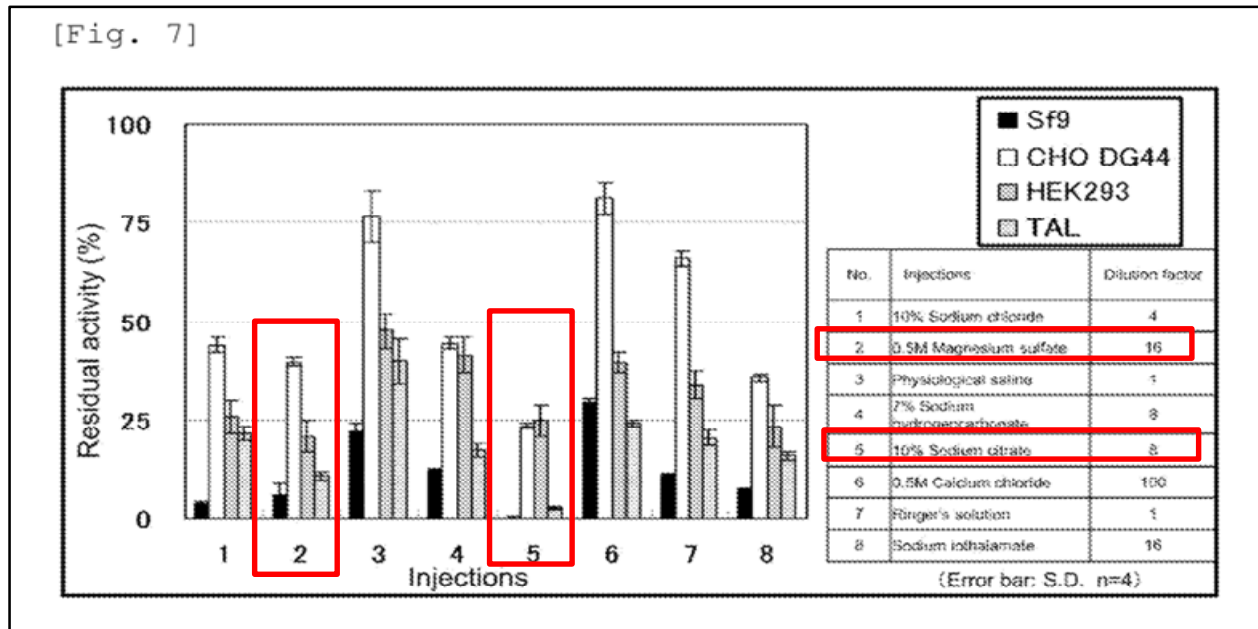
IX. SECONDARY CONSIDERATIONS OF NON-OBVIOUSNESS EXIST

Assuming the '318 Patent is not entitled to its December 10, 2013 priority date, Petitioner has not only failed to demonstrate the unpatentability of claim 21 of the '318 Patent for the reasons described in Sections VIII.A-B, but secondary considerations of non-obviousness, specifically unexpected results, also support a finding that claim 21 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. Claim 21, 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 122 (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. Ex. 2042 ¶ 44. 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. *Id.*

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). "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 with 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.

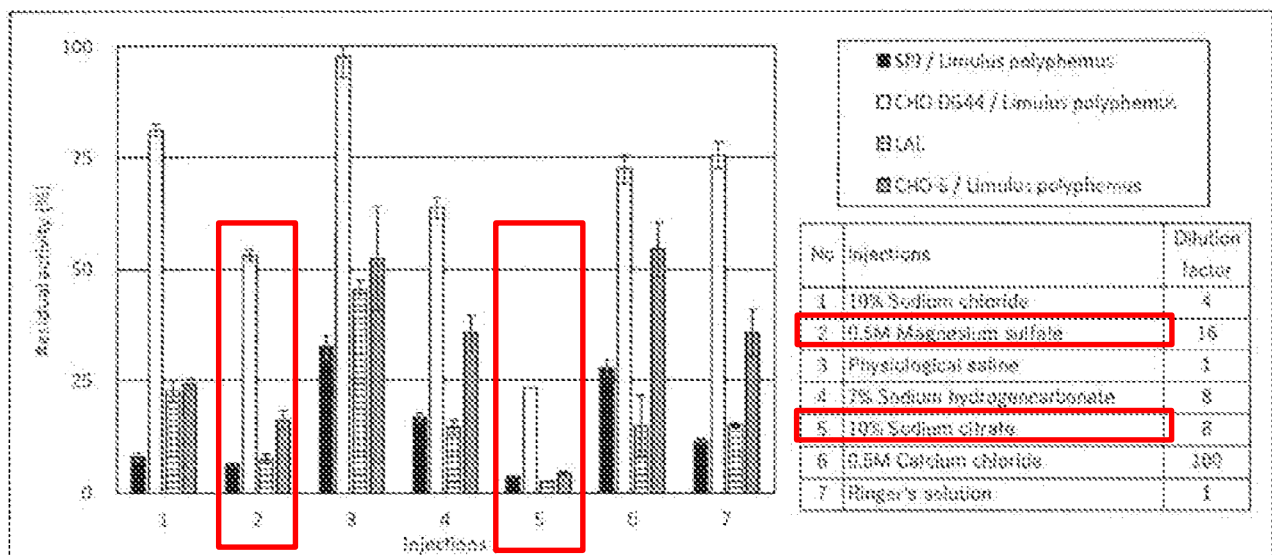
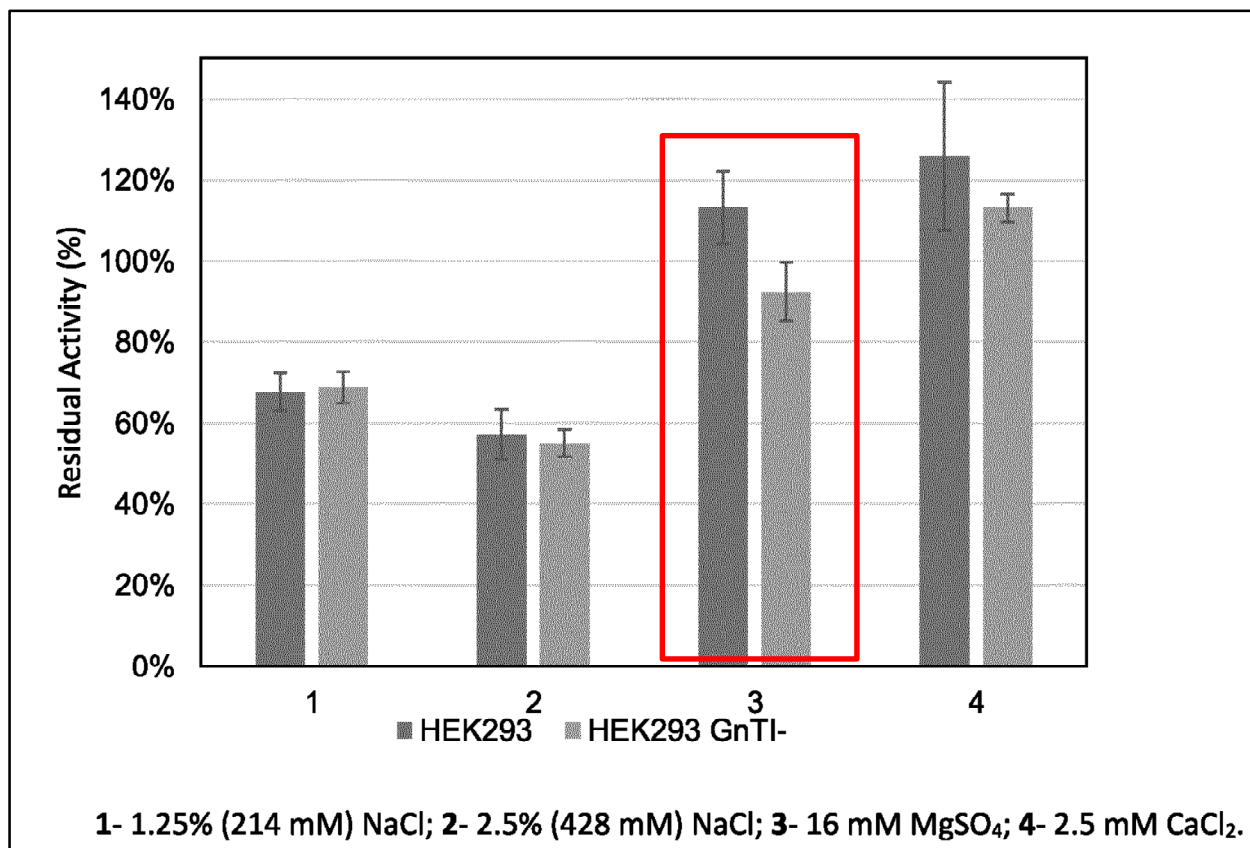


Fig. 1. Residual Activity of *L. polyphemus* Factor Cs in the Presence of Salt

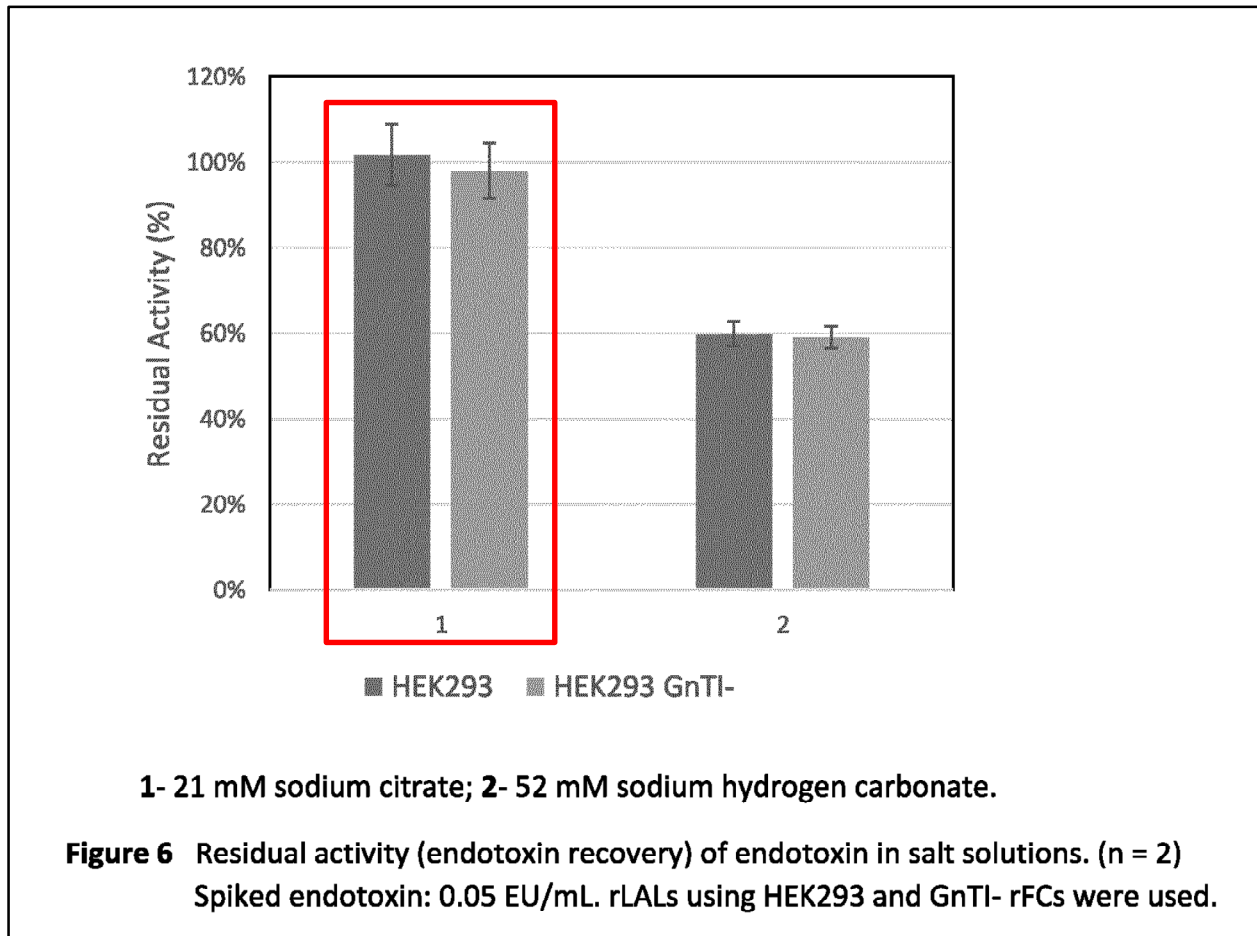
Ex. 1004 at 85 (annotated).

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 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. 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. 2042 ¶¶ 52-53.



Ex. 2033 at Fig. 4 (annotated).



Ex. 2033 at Fig. 6 (annotated).

Comparing this for *Limulus polyphemus* Factor C to the data observed in Figure 7 of Mizumura further confirms 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). *Id.* This is far superior to the residual activity observed 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 citrate (Mizumura Fig. 7, column 5). *Id.*

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 in Mizumura of *Tachypleus tridentatus* Factor C recombinantly expressed in HEK293 cells. 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. 2042 ¶¶ 49-50. Given this, the claimed invention exhibits unexpected results, which weighs in favor of finding claim 21 of the '318 Patent not unpatentable as obvious.

X. CONCLUSION

For the reasons discussed above, the Board should maintain the patentability of claim 21 of the '318 Patent.

Respectfully Submitted,

Dated: December 1, 2025

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

CERTIFICATE OF COMPLIANCE

I, the undersigned, certify that the foregoing Patent Owner Response complies with the applicable type-volume limitations of 37 C.F.R. § 42.24(b)(2). Exclusive of the portions exempted by 37 C.F.R. § 42.24(a)(1), this Petition, including footnotes, contains 11,556 words, as counted by the word count function of Microsoft Word. This is less than the limit of 14,000 words as specified by 37 C.F.R. § 42.24(b)(2).

Respectfully Submitted,

Dated: December 1, 2025

/ Alexander B. Stein /
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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 RESPONSE was served via the email correspondence address of record for Petitioner's counsel of record:

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