

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HALOZYME, INC.,
Petitioner,

v.

ALTEOGEN INC.,
Patent Owner.

Case No. IPR2026-00176
U.S. Patent No. 12,221,638

PATENT OWNER'S PRELIMINARY RESPONSE

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Listing of Challenged Claims

1. [**Limitation 1.0**] A method for producing a recombinant protein that comprises at least one of hyaluronidase PH20 or a variant thereof, the method comprising:

[**Limitation 1.1**] first culturing host animal cells expressing the recombinant protein until an integral viable cell density of the host animal cells reaches 20×10^6 to 120×10^6 cells $\times$ day/mL, wherein first culturing is performed within a first temperature range from 35° C. to 38° C.; and

[**Limitation 1.2**] subsequently second culturing at least part of the host animal cells from first culturing for 2 to 18 days, which produces the recombinant protein, wherein second culturing is performed within a second temperature range from 28° C. to 34° C.,

[**Limitation 1.3**] wherein the second culturing maintains (a) a residual glucose concentration within a range from 0.001 g/L to 4.5 g/L and/or (b) pH within a range from 6.8 to 7.2 in a culture medium therefor,

[**Limitation 1.4**] wherein sialylation of N-glycan of the produced recombinant protein is 1 to 38%, and

[**Limitation 1.5**] wherein the produced recombinant protein has a hyaluronidase enzymatic activity at 10,000 units/mL or higher.

2. The method according to claim 1, wherein galactosylation of N-glycan is 1 to 68%, and mannosylation of N-glycan is 40 to 63%.

3. The method according to claim 1, wherein sialylation of N-glycan is 1 to 30%.

4. The method according to claim 1, wherein the recombinant protein has a specific enzymatic activity as hyaluronidase at least 10% higher than a specific enzymatic activity of a wild human PH20.

5. The method according to claim 1, wherein at least one of the first culturing or the second culturing are performed by one or more methods selected from the group consisting of batch culture, repeated batch culture, fed-batch culture, repeated fed-batch culture, continuous culture, and perfusion culture.

6. The method according to claim 1, wherein at least one of the first culturing or the second culturing are performed under one or more conditions selected from the group consisting of:

(i) a condition in which an ammonia concentration is maintained at 5 mM or higher in a culture medium thereof;

(ii) a condition in which one or more substances is added to the culture medium thereof, wherein the one or more substances are selected from the group consisting of glutamine, glucosamine, uridine, glucosamine, and sodium butyrate; and

(iii) a condition in which galactose and manNAc are not added to the culture medium thereof.

7. The method according to claim 1, wherein the recombinant protein comprises substitution of one or more amino acid residues when compared to an amino acid sequence of a wild human PH20.

8. The method according to claim 1, further comprising separating and purifying the produced recombinant protein.

9. The method according to claim 8, wherein separating and purifying the produced recombinant protein are performed using ionic bond and/or hydrophobic interaction characteristics thereof, rather than affinity binding.

10. The method according to claim 9, wherein separating and purifying the recombinant protein are performed using hydrophobic interaction chromatography and ion exchange chromatography, rather than affinity chromatography.

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| 11. The method according to claim 8, wherein purifying further comprises removing at least part of acidic recombinant protein. |
| 12. The method according to claim 11, wherein removing the acidic recombinant protein uses ion exchange chromatography. |
| 13. The method according to claim 7, wherein the recombinant protein further comprises truncation of at least one amino acid residue of N-terminus when compared to an amino acid sequence of a wild human PH20. |
| 14. The method according to claim 7, wherein the recombinant protein further comprises truncation of at least one amino acid residue of C-terminus when compared to an amino acid sequence of a wild human PH20. |
| 15. The method according to claim 7, wherein the recombinant protein further comprises truncation of at least one amino acid residue of N-terminus and at least one amino acid residue of C-terminus when compared to an amino acid sequence of a wild human PH20. |

Glossary

<i>Bold and italicized</i>	Emphasis added unless otherwise indicated
The '638 patent	U.S. Patent No. 12,221,638
IVCD	<i>integral viable cell density</i>
POSA	Person of ordinary skill in the art
Rule 42.104(b)(4) Enforcement Memo	Memorandum from Director Coke Morgan Stewart, Enforcement and Non-Waiver of 37 C.F.R. § 42.104(b)(4) and Permissible Uses of General Knowledge in Inter Partes Reviews, 1 (July 31, 2025) (uspto.gov/sites/default/files/documents/aapa_memo_final_signed.pdf)

List of Exhibits

Exhibit	Description
2001	European Patent No. EP 4 269 578 B1
2002	Excerpts from European Patent No. EP 4 269 578 B1 Opposition File History
2003	Excerpts from European Patent No. EP 4 269 578 B1 Prosecution History
2004	U.S. Patent Provisional Application No. 61/068,667
2005	International Application Publication No. WO 2019/222435 A1
2006	European Patent Application Publication No. EP 4 421 168
2007	EPO Notice for European Patent Application Publication No. EP 4 421 168
2008	European Patent No. EP 3 760 715 B1
2009	Excerpts from European Patent No. EP 3 760 715 B1 Opposition File History
2010	Kevin J.R. Clark et al., <i>Temperature Effects on Product-Quality-Related Enzymes in Batch CHO Cell Cultures Producing Recombinant tPA</i> , 20 BIOTECHNOL. PROG. 1888 (2004).
2011	H. Jonathan G. Lindström et al., <i>Inferring time-dependent population growth rates in cell cultures undergoing adaptation</i> , 21 BMC BIOINFORM. 583 (2020).
2012	J. Rodriguez et al., <i>High productivity of human recombinant beta-interferon from a low-temperature perfusion culture</i> , 150 J. BIOTECHNOL. 509 (2010).
2013	Hengameh Aghamohseni et al., <i>A semi-empirical glycosylation model of a camelid monoclonal antibody under hypothermia cell culture conditions</i> , 44 J. IND. MICROBIOL. BIOTECHNOL. 1005 (2017).

Exhibit	Description
2014-2099	Reserved
2100	Excerpts from Prosecution History of U.S. Application No. 17/907,538

I. INTRODUCTION

The challenged claims of U.S. Patent No. 12,221,638 (“the ’638 patent”) recite novel and inventive methods of producing recombinant PH20 hyaluronidase enzymes having specific properties using two specific culturing phases, each coupled with corresponding specific culturing conditions. The Petition fails to establish a reasonable likelihood of prevailing on either of its two obviousness grounds as it does not specify where each claim element is found in the prior art, does not provide a motivation for modifying its primary reference, and does not establish a reasonable expectation of success for the claimed invention.

Petitioner’s grounds are based on recycling Wei (EX1006), which describes Petitioner’s different and already optimized commercial method. EX2002, 64. Wei was twice overcome during prosecution for not teaching or suggesting the claimed combination of process and properties. EX1004, 8, 20, 23-26, 46-48. When elsewhere defending the patentability of Wei’s recombinant method, Petitioner described it as a combination of multiple interdependent “cell culture parameters [that] act synergistically to produce an improved hyaluronidase product.” EX2002, 8, 17, 65. According to Petitioner, again when self-servingly defending Wei’s method, “[c]hanging such cell culture parameters to enable large-scale production of a specific protein product is not trivial,” and it “needs to be ensured that enhanced productivity in one step does not have a negative effect on productivity

in other steps.” EX2002, 65. The Petition takes inconsistent and irreconcilable positions here, representing that changing cell culture parameters such as temperature, nutrients, and culturing periods was merely “routine,” “conventional,” and “predictable” with no regard to their interdependence, unpredictability, or complexity. *E.g.*, Pet. 21-26; *infra* §§IV.B-IV.C.

Beyond Petitioner’s inconsistent positions, Wei does not teach the claim limitations alleged in the Petition. *Infra* §IV.A. Most strikingly, for instance, limitation [1.1] is directed to a “first culturing” step to reach an integral viable cell density (“IVCD”) value of 20×10^6 to 120×10^6 cells $\times$ day/mL. Petitioner’s declarant admits that the claimed IVCD value is “not disclose[d]” in Wei and improperly attempts to fill this void with “assumed” conditions and “estimation[s]” to construct an “estimate[d] IVCD over time.” *Infra* §IV.A.1; EX1002, ¶¶111-112, 115-116. The Petition similarly relies on its declarant to supply missing elements of the “second culturing” step limitations [1.2]-[1.3]. *Infra* §IV.A.2. This is impermissible. “[E]xpert testimony ... may not be used to supply a missing claim limitation.” Rule 42.104(b)(4) Enforcement Memo (“Per 35 U.S.C. § 312(a)(4), the Board shall deny an IPR petition that fails to comply with Rule 104(b)(4).”).

The Petition further fails to establish a motivation to combine Wei and its secondary reference, Zmuda (EX1005), with a reasonable expectation of success. *Infra* §§IV.B-IV.C. Rather than proffer a problem with Wei to be solved, Petitioner

relied on and touted Wei's commercial-scale process for its "dramatic improvement" in PH20 production for more than a decade. *See* EX2004, 142:3-26; EX1006, [0360], [0373]; EX2002, 36; EX2005, cover, code (22) (filed May 15, 2019), 239:7-30; EX2001, 60; EX2006, cover (filed July 15, 2024), [0263]; *infra* §IV.B.1.

Zmuda is also unconnected to the production of hyaluronidase enzymes, which has unique considerations with respect to post-translational properties of glycosylation and sialylation that affect its folding and enzymatic activity. *Infra* §II.A. Zmuda teaches a "sharp" temperature drop from 37°C that is distinctly different from and incompatible with Wei's "acclimatizing" protocol using slow 0.5C temperature increments spread over 14 days. *Infra* §IV.B.2. The Petition ignores these differences, ignores that Zmuda's lower temperature is compared only to a fixed 37°C and offers no improvement over Wei's already reduced temperatures, and ignores Zmuda's disclaimer that temperature-shift effects vary with and "depend[] on the nature of the protein." EX1005, 82.

Rather than attempting to justify or reconcile the differences between Wei and Zmuda, much less state with particularity how they are to be combined, Petitioner hides behind generic "routine optimization" arguments. *See infra* §IV.B.2. These "fall[] short of [establishing a motivation to modify or combine with a reasonable expectation of success]. Missing from the [Petition's] analysis is

an explanation as to *why* it would have been routine optimization to arrive at the claimed invention.” *In re Stepan Co.*, 868 F.3d 1342, 1346 (Fed. Cir. 2017) (emphasis in original).

Institution should thus be denied under 35 U.S.C. § 314(a) and 37 C.F.R. § 42.104(b)(4).

II. TECHNOLOGY BACKGROUND

A. Hyaluronidase Enzymes and Recombinant Protein Production

Hyaluronidase enzymes, such as naturally occurring PH20, are proteins that enzymatically degrade hyaluronic acid in the extracellular matrix in the skin and other tissues. Because this can increase permeability, hyaluronidases have been used as biopharmaceutical products to enhance absorption of subcutaneous injections such as morphine, ceftriaxone, insulin, and immunoglobulin. EX1001, 1:39-57, 9:62-10:21; EX1006, [0002].

Proteins can be produced using recombinant techniques, generally entailing culturing cells transfected with genes encoding the protein under conditions causing them to express the protein. Recombinant proteins can differ from naturally produced proteins due to post-translational modifications that affect, for example, patterns and degrees of glycosylation (attaching glycan sugar molecules as N-linked and O-linked to certain amino acids via nitrogen and oxygen atoms, respectively) and related sialylation (sialic acid addition to glycans). These post-

translational modifications can, in turn, affect protein folding, activity, and immune response in the body. For recombinant human PH20 hyaluronidases (rHuPH20), N-glycosylation is particularly important to enable binding of the enzyme to its substrate, but this may be impaired by higher degrees of sialylation. Product consistency with respect to quality attributes such as glycosylation and sialylation is particularly important, especially for biopharmaceutical recombinant products. EX1001, 1:58-4:33, 4:14-55, 17:4-23; EX1006, [0029]-[0030], [0075]-[0077], [0114]-[0115] (“altering the type of glycan modifying a glycoprotein can have dramatic affects [sic] on a protein’s antigenicity, structural folding, solubility, and stability”), [0130], [0339] (“N-linked glycosylation is essential for proper folding and enzymatic activity of rHuPH20.”).

Post-translational modifications of recombinant proteins are known to be sensitive to changes in culturing conditions, such as the culturing media and temperature. EX1001, 3:32-49; EX2010, 1-2 (“the previously hypothesized advantages that lower culture temperatures have reduced protease activity and improved productivity do not appear to be universal”); EX2012, 2 (exposing cells to mild hypothermic conditions “can result in a variable glycosylation profile ... depending upon the cell line and culture conditions”). As represented by Petitioner and its declarant in an opposition proceeding before the EPO when defending patents related to Wei, “cell culture parameters act synergistically” such that

[c]hanging such cell culture parameters to enable large-scale production of a specific protein product is not trivial. Each of the steps needs to be improved to maximize productivity individually, and it also needs to be ensured that enhanced productivity in one step does not have a negative effect on productivity in other steps.

EX2002, 65; EX2009, 11 (“cell culture parameters in combination ... work together to achieve the increase in active rHuPH20”).

As a result, according to Petitioner, modifying cell culture parameters “gives rise to a distinct pattern of proportions of the individual C-terminally truncated polypeptides” with distinct “structural ‘fingerprint[s]’” that “include distinctive structural quality attributes, such as reproducibly different contents in product-related impurities.” EX2002, 66. As also represented by Petitioner, a difference in “feeding steps that are carried out in conjunction with adjusting the culture temperature ... results in a different composition” with different enzyme activity. EX2003, 5-11 (“It is not possible to define the claimed product appropriately other than in terms of a process of manufacture.”).

B. Asserted Ground References

1. Wei (EX1006)

Petitioner’s primary reference, Wei (EX1006), is from a series of Petitioner’s hyaluronidase-focused applications that were continuously filed with the same basic recombinant methods from as early as 2008 through 2026. *See, e.g.,*

EX1006, cover; EX2004, cover, 142:3-26; EX2001, [0270]; EX2005, 239:7-30; EX2006, cover (filed July 15, 2024), [0263]; EX2007, 1 (Mar. 5, 2026 Examination Notice). It describes recombinant methods of producing rHuPH20 using two protocols: Generation 1 (“Gen1”) and Generation 2 (“Gen2”).

Gen1, described in Examples 13A and 13B, entails culturing the recombinant cells at 37°C for at least 11 days (EX1006, [0354]) or using a four-step protocol that stepwise reduces culturing temperature from 37°C by 0.5C increments to 35.5°C over the course of approximately 14 days (EX1006, [0360]). Both Gen1 protocols “resulted in a final productivity of 1600 Units per ml.” EX1006, [0354], [0360], [0361] (Table 19).

Gen2, described in Example 15A, continues the scale-up process of Example 13B using the same 0.5C stepwise culturing temperature shifts but with different nutrient feedings. EX1006, [0373]. “The process resulted in a final productivity of 17,000 Units per ml with a maximal cell density of 12 million cells/mL.” EX1006, [0373], [0383] (Table 27). Wei demonstrates that PH20 hyaluronidase production depends on the interconnected parameters of at least nutrient feedings combined with temperature. *Infra* §IV.B.1.

Petitioner repeated and relied on these methods unchanged for over a decade, from Wei’s earliest possible priority date in 2008 to after both Zmuda (published January 19, 2017) and the ’638 patent (filed Aug. 7, 2020). EX1005,

cover, code (43); EX1001, cover, code (30). For example, approximately four years after Wei, Petitioner filed Wei 2013 (EX1037), which Petitioner admits relies on an identical protocol to Wei Gen2/Example 15A. Pet. 54; *compare* EX1006, [0373] (Example 15A), *with* EX1037, 228:34-229:20 (Example 1). As late as 2018, Petitioner continued to submit new applications that described the use of the Gen2 protocol to produce hyaluronidase. *See* EX2005, cover (noting a claim to a new provisional filed in 2018), 239:7-30 (describing the use of Wei’s Gen2 protocol). And to this day, Petitioner appears to be pursuing continuation applications that rely on Wei’s Gen2 protocol. *See, e.g.*, EX1006, [0373]; EX2002, 64; EX2006, [0263]; EX2007 (Mar. 5, 2026 Examination Notice).

Petitioner has touted Wei’s “Gen2” process as a unique combination of multiple “cell culture parameters [that] act synergistically to produce an improved hyaluronidase product.” EX2002, 8, 17, 65; EX1006, cover, code (73) (“Proprietor: Halozyme”); EX2009, 11 (“cell culture parameters in combination ... work together to achieve the increase in active rHuPH20”). According to Petitioner, this precise protocol was “sufficient to increase cell cycle arrest, increase cell viability and stabilize the soluble hyaluronidase” (EX1035, 2:30-32, 2:43-45), and its development was “not trivial” (EX2002, 65).

2. Zmuda (EX1005)

Petitioner's secondary reference, Zmuda (EX1005), includes a transfection protocol for the production of recombinant proteins in CHO cells. EX1005, 1. Petitioner relies on Zmuda in Ground 1 and Ground 2 to "disclose[] an overlapping range between 30°C and less than 37°C for recombinant protein production," and "teach[] that shifting the temperature down (e.g., to 32°C) improved titers" Pet. 2, 11; EX1005, 82.

Zmuda's "High Titer" and "Max Titer" transfection protocols involve a single sharp temperature drop from 37°C to 32°C one day post-transfection. EX1005, 82. For the tested antibodies and EPO protein, Zmuda reports 2-3x greater protein production (titer in g/L) in the High Titer and Max Titer protocols using the single sharp temperature drop as compared to a "standard" protocol where the culture is maintained at 37°C throughout. EX1005, 82, 90-91 (Example 2). Zmuda caveats this titer increase, noting that "some proteins will express similarly [to the Max Titer Protocol], or better, using the Standard Protocol without temperature shift depending on the nature of the protein." EX1005, 82.

3. Wei 2013 (EX1037)

Petitioner relies on Wei 2013 in Ground 2 only "[t]o the extent additional prior art support is needed to render claim 4 and/or claim 7 obvious," and not as a substitute for its reliance on Wei and Zmuda. Pet. 53. As Petitioner states, "Wei

2013 discloses the same method as Wei for production of ‘Gen2 soluble rHuPH20.’” Pet. 54; *compare* EX1006, [0373] (Example 15A), *with* EX1037, 228:34-229:20 (Example 1). Focusing only on claims 4 and 7, Petitioner does not rely on Wei 2013 for more than its teachings related to specific enzymatic activity (Pet. 55) and amino acid substitution of a wild human PH20 (Pet. 56-57).

III. THE ’638 PATENT

A. Overview of the ’638 Patent’s Specification and Independent Claim 1

Based on the finding that “the productivity and activity of recombinant hyaluronidase PH20 and variants thereof are affected by changes in the level of N-glycans,” the inventors of the ’638 patent sought and invented industrially useful methods for “production of a recombinant hyaluronidase PH20 protein or a variant thereof having high productivity and high enzymatic activity” by “controlling and maintaining the level of N-glycans [as] required for efficient mass-production.” EX1001, 4:25-32, 27:24-30.

To this end, the ’638 patent describes novel methods for producing rHuPH20 enzymes “capable of changing the N-glycan levels” through specific culturing conditions such as “concentration of glucose in the culture medium and a decreased culture temperature for a specific culture time period,” which leads to improved rHuPH20 proteins with increased activity. EX1001, Abstract, 4:49-64. In particular, the inventors “found that when the sialylation content of the N-glycan of

PH20 or the variant thereof is 1 to 38%, ... the enzymatic activity and productivity of hyaluronidase PH20 or a variant thereof were improved to unexpectedly high levels.” EX1001, 7:26-32; *see also* EX1001, 7:33-47, 15:39-16:53, Table 1, 18:15-24.

Across 11 examples, the '638 patent shows that cell culture conditions directly control the enzymatic activity of recombinant PH20 by modulating N-glycosylation, including sialylation, rather than by altering amino acid sequence.

Example 1 investigated the relationship between hyaluronidase activity, N-glycan levels, and isoelectric focusing patterns. It demonstrates that culture-generated acidic and basic fractions differ in activity and that “the acidic fraction exhibited the decreased enzymatic activity,” while complete deglycosylation abolished activity, showing that “the N-glycan level is closely related to enzymatic activity.” Example 1 further uncovered a “relationship between the content of sialic acid at the terminal [of N-glycans] and the enzymatic activity.” EX1001, 15:30-18:49, Figs. 1-2, Table 1.

Example 2 addresses the influence of additives to the culturing media. It shows that adding glycosylation precursors shifts glycan profiles but harms function, as galactose supplementation caused “a 24% increase in galactosylation and a 2% decrease in activity,” and ManNAc caused “a 35% increase in sialylation

and a 20% decrease in activity.” EX1001, 18:51-19:15, Figs. 3-6. Cell viability, VCD, pH, and lactate levels were measured daily. EX1001, 18:65-19:1, Fig. 3.

Example 3 establishes a time dependence of the culturing. It found that “[a]s the number of days of culture increased, the galactosylation and sialylation levels decreased and the activity increased.” EX1001, 19:16-47, Figs. 7-10. Cell viability, VCD, IVCD, and ammonium ion level were measured daily. EX1001, 19:37-41, Fig. 7. Example 4 investigated the effects of controlled glucose concentrations in the culturing medium. To this end, the glucose concentration was monitored daily and maintained at target levels (2, 4, or 6 g/L) by adding concentrated glucose only when levels fell below the set threshold. It shows glucose control is critical, because “as the concentration of glucose in the culture supernatant increased, the levels of galactosylation and sialylation increased and the activity decreased.” EX1001, 19:49-20:54, Figs. 11-14. Cell viability, VCD, pH, osmolality, and glucose and lactate concentration were measured daily. EX1001, 19:67-20:3, Fig. 11.

Example 5 is directed to the impact of pH control, with four setpoints (6.8, 7.0, 7.2, or 7.4 ± 0.1) and a pH control system, in which pH was continuously monitored, base was automatically added when pH fell below the lower limit, and CO₂ was added when pH exceeded the upper limit. Under these conditions, the highest activity and lowest sialylation were observed at pH 7.0 ± 0.1 compared to

the conventional pH 7.2 ± 0.4 condition. EX1001, 20:56-21:55, Figs. 15-17, Table 2. Cell viability, VCD, pH, and IVCD were measured daily. EX1001, 21:22-26, Fig. 15.

Examples 6-9 describe specific methods for purifying hyaluronidase proteins and analyzing the enzymatic activity, isoelectric focus, and glycan level of hyaluronidase proteins. EX1001, 21:56-24:20. Example 10 demonstrates that hyaluronidase sequences from other species, such as bonobo and sheep, expressed under the same conditions as rHuPH20 also exhibit activity differences related to glycosylation. EX1001, 24:21-26:5, Table 3.

Example 11 further investigated the activity and N-glycan level of hyaluronidase PH20, finding that “when the galactosylation and mannosylation levels fall within similar ranges and the sialylation level is low, the enzymatic activity ... is increased due to the high catalytic efficiency (k_{cat}/K_m).” From this, the inventors concluded that

- (1) “the activity of an enzyme having the same amino acid structure may be affected by the change in glycosylation, more specifically, by the change in the sialylation level”; and
- (2) “to produce industrially useful hyaluronidase by mass-producing wild PH20 hyaluronidase or a variant thereof using a recombinant method, an

enzyme having greater industrial applicability can be developed by controlling the sialy[l]ation level.”

EX1001, 26:6-56, Table 4.

Based on these detailed investigations and discoveries, the inventors of the '638 patent invented the controlled two-step process recited in independent claim 1 that recites interdependent steps for producing a *specific* protein (hyaluronidase PH20 or a variant thereof [1.0]) under *specific* first culturing conditions (IVCD, 35-38°C [1.1]) and *specific* second culturing conditions (maintaining glucose concentration and/or pH range, 2- to 18-day period, 28-34°C [1.2], [1.3]) that creates proteins having *specific* properties (percent sialylation [1.4]; hyaluronidase enzymatic activity [1.5]). EX1001, 8:4-21, 33:31-52 (claim 1).

B. Prosecution History Summary

The Examiner initially rejected the original claims as obvious over the combination of Wei (EX1006), Chen (122 J. BIOSCI. BIOENG. 673-78 (2016)), and Frost (EX1031), finding that they collectively taught all elements of the claimed method. EX1004, 46-48. This included 25% sialic acid (sialylation) from Wei, incubation for 2 days at 30°C from Chen, and enzymatic activity from Frost. *Id.* The Examiner understood Wei to teach everything *except the combination* of “the recited method steps of lowering the culture temperature to 28-34 °C *and* the

activity in a culture solution of the enzyme[] is 10,000 unit[s]/mL or more.”

EX1004, 47. The Examiner asserted it would have been obvious

to modify the teachings of [Wei] to include the method[] steps as taught and/or suggested by Chen et al. and Frost et al. for production of the human-derived pH20 hyaluronidase or any other PH20 variant[,] ***including lowering the culture temperature to 28-34 °C.***

EX1004, 48. The Examiner further asserted that a POSA “would have been motivated to do this in order to obtain a simple method for producing rHuPH20” based on “routine experimentation and/or as desired for efficient production of the PH20.” *Id.* The Examiner asserted “a reasonable expectation of success because recombinantly producing PH20 is known in the art as shown by the above reference teachings.” *Id.*

Applicant then amended the claims to, *inter alia*, narrow the culturing host to animal cells (EX1004, 33), submitted additional references (EX1004, 36; EX2100, 1-2), and traversed the obviousness rejection (EX1004, 37-40). Applicant responded that Wei and Chen do not disclose or suggest the combination of the 28--34°C second culturing together *with* controlled (“maintained”) glucose and pH conditions (“limitations (a) and (b)”), explaining that they

fail[] to disclose or provide [a] basis for deriving the step of “(2) decreasing the culture temperature to 28°C to 34°C and then culturing the host cells for 2 to 18 days[,],” and [Wei] fails to disclose

or provide [a] basis for deriving the limitations (a) and (b) specified in amended claim 1, viz., “(a) wherein the residual glucose concentration in the medium is maintained at 0.001 g/L to 4.5 g/L during the culture period” and “(b) wherein the pH of the culture medium is maintained at 6.8 ~ 7.2” in such step (2).

EX1004, 38-39. Applicant further relied on specification Examples 2-5 as demonstrating how these steps “can affect the highest activity and the lowest sialylation level of the recombinant PH20 hyaluronidase or a variant thereof.”

EX1004, 39-40.

The Examiner accepted these arguments. EX1004, 20, 30-31. After an additional amendment moving the claims closer to their present form, the Examiner allowed the claims because “[t]he prior art neither teaches nor suggests *the method* for producing a recombinant protein that comprises at least one of hyaluronidase PH20 or a variant thereof *as recited in the claims*.” EX1004, 20, 23-26. The Examiner’s allowance was based on the claimed method as a whole, notwithstanding previous findings that its two temperature conditions, sialylation, and enzymatic activity were individually known. See EX1004, 20, 46-48.

Following Applicant’s RCE, further minor amendments, and submission of additional references (EX1004, 10-13; EX2100, 5-10 (IDS), 14-16 (IDS), 20 (RCE), 23-35 (IDS), 39-42 (IDS)), the Examiner issued a second NOA. The

Examiner recognized the novelty and nonobviousness of the claimed method as a whole, including the combination of limitations [1.4] *and* [1.5]:

The prior art neither teaches nor suggests the *claimed method for producing a recombinant protein* wherein [1.4] sialylation of N-glycan of the produced recombinant protein is 1 to 38%, *and* wherein [1.5] the produced recombinant protein has a hyaluronidase enzymatic activity at 10,000 units/mL or higher.

EX1004, 8; *see also* Pet. 11-12 (agreeing that second NOA reason for allowance was based on “combination” of activity and sialylation).

IV. THE PETITION FAILS TO ESTABLISH A REASONABLE LIKELIHOOD THAT THE CHALLENGED CLAIMS ARE OBVIOUS

A. Petitioner Fails to Establish All Claim Limitations

The Petition argues that Wei discloses the first culturing IVCD limitation [1.1] (Pet. 28-29), the maintaining limitation [1.3] that is part of the second culturing limitation [1.2] (Pet. 29-35), and the sialylation [1.4] and enzymatic activity [1.5] limitations of the produced recombinant protein (Pet. 35-40).

Petitioner’s Grounds 1-2, however, fail to demonstrate that Wei discloses these limitations. Pet. 27-40, 53-57. Instead, Petitioner’s declarant admits that the limitation [1.1] IVCD value is “*not disclose[d]*” in Wei and improperly attempts to fill this gap with assumptions and estimations. *Infra* §IV.A.1; EX1002, ¶¶111-112.

The Petition continues to improperly rely on declarant testimony for

“maintain[ing]” glucose and pH according to limitation [1.3] during the second culturing [1.2], which are not disclosed in Wei. *Infra* §IV.A.2. Finally, the Petition ignores that Wei’s produced recombinant protein does not have both the claimed sialylation [1.4] *and* enzymatic activity [1.5] together, instead attempting to show them only in isolation from separate examples and not resulting from the claimed method. *Infra* §IV.A.3. The Petition should be denied for failing to establish each of these limitations.

1. Petitioner Improperly Relies on Declarant Assumptions and Estimations for Missing Limitation [1.1]

The Petition relies only on Wei for the “first culturing” “IVCD” limitation [1.1] but fails to specify where it is disclosed therein. Pet. 28-29; 37 C.F.R. § 42.104(b)(4). Relying on its declarant, Petitioner instead asserts that a POSA “*would have understood* Wei to teach that the first culturing continued until” reaching the claimed IVCD. Pet. 29. Petitioner’s declarant admits, however, that the IVCD value is “*not disclose[d]*” in Wei and then proffers speculative testimony—based on “assumed” conditions and “estimation[s]”—to supply this missing limitation as an “*estimate[d]* IVCD over time.” EX1002, ¶¶111-112, 115-116. Petitioner’s improper reliance on declarant testimony “to supply a missing claim limitation” is a dispositive basis to deny institution. Rule 42.104(b)(4) Enforcement Memo.

The admitted assumptions and estimations of Petitioner's declarant also preclude any basis to establish the claimed IVCD by inherency. *See Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1379 (Fed. Cir. 2005) (“[T]he district court’s inherency analysis goes astray because it assumes what Pereira neither disclosed nor rendered inherent.”); *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1194-95 (Fed. Cir. 2014) (“[T]he concept of inherency must be limited when applied to obviousness [when supplying a missing claim limitation], and is present only when the limitation at issue is the ‘natural result’ of the combination of prior art elements.” (citation omitted)). In this regard, Petitioner’s declarant relies on:

1. “***Assum[ed] exponential growth.***” EX1002, ¶¶113-114. Rather than exponential growth being inherent in recombinant cell culturing, the art shows that “factors such as cooperation or competition for resources creates ***a non-exponential population growth***.... In reality, the growth rate sometimes changes over time, either because of density-dependent effects or because the cells are evolving.” EX2011, 2. Unlike in the challenged ’638 patent, Wei does not include data tracking cell growth over days in culture, and without this data, a POSA does not know how the culturing methods of Wei affected cell growth rate. EX1001, Figs. 3A-B, 7A-B, 11A-B, 15A-B; *supra* §III.A.

2. “[A]ssumed that at maximum cell density the % *viability would likely be around 95%.*” EX1002, ¶115. Wei does not disclose percent cell viability at max cell density, which itself varies from batch to batch. EX1006, [0361] (Table 19, range of 5.65×10^6 to 9.70×10^6 cells/mL).

3. “[A]ssumed a gradual linear decrease in viable cell density.” EX1002, ¶116. “[G]radual linear decrease” is not inherent in cell culturing. As admitted by Petitioner’s declarant, “[i]n a fed-batch culture[,] the decline phase may be delayed or the rate of decline reduced through feeding of the cells. Delaying or reducing the decline rate has the effect of viable cells being maintained over a longer period of time and results in a higher overall product yield.” EX1002, ¶110. And, unlike the challenged ’638 patent, which tracks cell viability throughout the decline phase, the decline rate is unknowable in Wei because it does not provide sufficient information to determine the rate of decrease in viable cell density. EX1002, ¶111 (“Wei does not disclose values for viable cell density”); *see, e.g.*, EX1001, Figs. 3A-B, 7A-B, 11A-B, 15A-B; *supra* §III.A. As discussed in relation to the growth rate, without data tracking viable cell density over time, a POSA would not know how the culturing conditions of Wei affect decay rate.

4. “[E]stimate[d] IVCD over time.” EX1002, ¶111. Without data in Wei tracking viable cell density over time, Petitioner’s declarant resorted to “assumed”

growth and decay rates to calculate “estimate[d]” IVCD. EX1002, ¶¶111-116 (“Assuming exponential growth [A]ssumed a gradual linear decrease in viable cell density during the decline period ... to interpolate the data and calculate the cumulative IVCD”).

5. **Assuming** without support in Wei that one selected batch (HUA0420C) relied upon for his estimate is representative of Wei’s highly variable process. EX1002, ¶112; EX2002, 10 (Petitioner representing that “the process imparts a number of different properties on the product, each of which is affected by an extent of batch-to-batch variation” (emphasis in original)). The declarant ignores, for example, the significant variability in growth and decay characteristics and post-culture expansion activity among Wei’s various rHuPH20 batches even within a single process. *See* EX1006, [0361] (Example 13B, Table 19). The declarant further ignores Wei’s reported inter-process variability in post-culture expansion activity and other characteristics. *Compare* EX1006, [0360]-[0361] (Example 13B, Table 19), *with* EX1006, [0373] (Example 15A).

Petitioner’s assertion that its declarant’s “IVCD calculations are **consistent** with documentary evidence” is irrelevant given the admission that “**Wei does not disclose** values for viable cell density over time,” and that **Petitioner’s declarant is “estimat[ing] IVCD over time.”** Pet. 28-29; EX1002, ¶111. Even allegedly “consistent” declarant calculations are not a replacement for “specify[ing] where

each element of the claim is found in the prior art patents or printed publications relied upon.” 37 C.F.R. § 42.104(b)(4). “[E]xpert testimony ... may not be used to supply a missing claim limitation.” Rule 42.104(b)(4) Enforcement Memo.

The Director should reject Petitioner’s reliance on its declarant to manufacture IVCD limitation [1.1] from “assumed” conditions and “estimation[s]” where “Wei does not disclose”—either expressly or inherently—“values for [IVCD] over time.” EX1002, ¶¶111-112, 115-116; *BTC Corp. v. TG Biotech Co.*, IPR2022-00998, Paper 44, 42, 45-47 (P.T.A.B. Nov. 13, 2023); 37 C.F.R. § 42.104(b)(4).

2. Wei Does Not Teach Maintaining the Residual Glucose Levels and pH of Limitations [1.2] and [1.3]

The [1.3] “maintain[ing]” limitation requires that

the second culturing maintains (a) a residual glucose concentration within a range from 0.001 g/L to 4.5 g/L and/or (b) pH within a range from 6.8 to 7.2 in a culture medium therefor

EX1001, claim 1. “[*T*]he second culturing” is defined in [1.2] as, *inter alia*, “performed within *a second temperature range from 28° C. to 34° C.*” Petitioner alleges that “Wei teaches or suggests” [1.3] but fails to demonstrate where it discloses that “*the second culturing* [within a second *temperature range from 28° C. to 34° C.*] *maintains*” the recited glucose and/or pH conditions. Pet. 31-35.

a. Wei Does Not Disclose Glucose or pH Conditions for an Overlapping Temperature Range

Contrary the Petition's representations, Wei does not disclose a "second temperature range lower than ... 37°C" overlapping "with the recited range of 28°C-34°C" of limitation [1.2]. Pet. 30. Wei only "discloses decreasing ... to 35.5°C." EX1006, [0360] (37 to 35.5°C), [0373] (same). Wei's glucose and pH conditions relied upon by Petitioner are likewise at 35.5°C or higher. Pet. 30, 32-34 (citing EX1006, [0360], [0373]; EX1002, ¶134 ("35.5°C"), ¶135 (same)); *see also* EX1002, ¶¶53, 124, 219. Having misrepresented Wei's lower temperature range as overlapping "with the recited range of 28°C-34°C," the Petition provides no basis to rely on glucose and pH conditions at temperatures outside the claimed second culturing temperature range from 28 to 34°C. *See* Pet. 30.

Petitioner's declarant even admits that this limitation is not taught in Wei. The declarant states that "Wei does not disclose the amount of glucose in the media before or after feeding the cells." EX1002, ¶136. The declarant further admits that glucose utilization and pH change both depend on temperature and temperature-related culture conditions, precluding reliance on glucose and pH from Wei's temperature conditions outside of the limitation [1.2] range of 28°C-34°C. *See* EX1002, ¶¶31, 40, 43.

Petitioner also assumes, incorrectly and without explanation, that the initial pH 7.2 described in Wei's Example 13B is maintained throughout the culturing step. Pet. 34; EX1002, ¶141. In fact, Wei only discloses pH 7.2 as *a starting* pH. EX1006, [0360] (“[p]arameters were temperature setpoint, 37°C; pH: 7.2”); *see also* EX1006, [0354] (“pH 7.2 (starting Setpoint)”).¹ According to Wei, the culture media was at most *sampled* for “pH verification” but otherwise had “[n]o instrumentation” to monitor, much less control, pH. EX1006, [0360], [0373], Table 27 (describing process differences between Example 13B and Example 15A). The Petition's characterization of the process as “*allow[ing] for*” (Pet. 34) monitoring and controlling pH does not establish maintaining the pH 7.2 either (1) throughout the rest of its protocols *or* (2) within the claimed range during a second culturing step. *See ParkerVision, Inc. v. Qualcomm Inc.*, 903 F.3d 1354, 1363 (Fed. Cir. 2018) (upholding the PTAB's nonobviousness determination of a method when the petitioner failed to demonstrate that the prior art taught an element “even if [it was] capable of doing so”). Nor can monitoring and control be

¹ Example 15A of Wei does not describe any starting pH setpoints and does not report any pH data for this protocol. EX1006, [0373]. Petitioner omits this fact and baselessly suggests that Example 13B's pH is indicative of Example 15A. Pet. 34 (citing EX1006, [0360], [0373]).

inferred from Wei, which does not report any measurement of pH data. *Compare* EX1001, 20:56-21:37, Table 2, *with* EX1006, [0360], [0373], Table 27; *supra* §III.A. As such, Petitioner’s arguments are based on assumptions and fail to demonstrate that Wei discloses maintaining pH within the claimed range.

Wei does not disclose the combined “second temperature” [1.2] and “maintain[ing]” [1.3] limitations, including because it does not even teach the second temperature from 28 to 34°C. The Petition thus fails to “specify where each element of the claim is found in the prior art” 37 C.F.R. § 42.104(b)(4).

b. Declarant Opinions and Alleged “Conventional” Conditions Cannot Supply the Missing Limitation

After admitting that “Wei does not disclose the amount of glucose in the media before or after feeding the cells,” Petitioner’s declarant nevertheless asserts that a POSA “would have *expected* the concentration to be within the claimed range.” EX1002, ¶136. The declarant’s multiple assumptions as to what a POSA would have “expected” improperly “assumes what [Wei] neither disclosed nor rendered inherent.” *Perricone*, 432 F.3d at 1379; EX1002, ¶136 (“would have expected,” “would not have expected”), ¶137 (“would not have expected”), ¶139 (“would not expect”). Regardless, this declarant’s testimony “may not be used to supply a missing claim limitation.” Rule 42.104(b)(4) Enforcement Memo.

The Petition's assertion that "the recited pH range was conventional and routine in the art at the critical date" (Pet. 34) similarly falls short of establishing the pH maintaining according to limitation [1.3]. Rule 42.104(b)(4) Enforcement Memo ("General knowledge may not be used to supply a missing claim limitation.") (cleaned up). Indeed, merely having a starting pH of 7.2 that "is consistent with the literature" provides no explanation of how or why a POSA would have maintained the pH based on Wei. Pet. 34. *In re Stepan*, 868 F.3d at 1346 ("Stating that a person of ordinary skill in the art would have arrived at the claimed invention through routine optimization falls short of this standard. Missing from the Board's analysis is an explanation as to *why* it would have been routine optimization to arrive at the claimed invention." (emphasis in original)).

The Petition should thus be denied for failure to specify where the prior art discloses the glucose and/or pH "maintain[ing]" limitation [1.3] within the [1.2] second culturing temperature.

3. Wei Does Not Disclose the Claimed Sialylation Percentage and Hyaluronidase Activity of Limitations [1.4] and [1.5]

The claimed method comprises producing hyaluronidase PH20 having 1-38% sialylation [1.4] *and* activity above 10,000 U/mL [1.5] using steps [1.1]-[1.3]. The Petition relies on separate Wei Examples for allegedly teaching each of these elements. Pet. 35-36 (citing Example 6), 37-41 (citing Example 13

and 15A). The Petition does not, however, establish that hyaluronidase PH20 or processes with these combined properties was taught by Wei, much less one produced in accordance with limitations [1.1]-[1.3]. *Infra* §IV.A.3.a; *supra* §§IV.A.1-2. Indeed, Wei does not disclose a process or a product that is characterized with both sialylation and enzymatic activity. *Infra* §IV.A.3.b.

The Petition’s attempt to cobble together *separate* Wei Examples reflects its failure to identify where Wei teach a hyaluronidase PH20 process or product having **both** the claimed sialylation [1.4] *and* the claimed enzymatic activity [1.5]. *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1369 (Fed. Cir. 2016) (“It is of the utmost importance that petitioners in the IPR proceedings adhere to the requirement that the initial petition identify ‘with particularity’ the ‘evidence that supports the grounds for the challenge to each claim.’”) (citing and quoting 35 U.S.C. § 312(a)(3)); *see also Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 959 (Fed. Cir. 1986) (“That each element in a claimed invention is old or unpatentable does not determine the nonobviousness of the claimed invention as a whole.”).

a. Petitioner Fails to Connect Wei Examples

The Petition alleges that “Wei teaches element [1.4]” sialylation, relying on “general” and “about” disclosures of its Example 6 unconnected to any specific process or batch. Pet. 16, 35 (citing EX1006, [0322], [0324] (Wei Example 6));

EX1006, [0324] (“[i]n general,” and “[a]bout 35% of the total glycans are anionic...”). The Petition then *separately* relies on processes and selected batches from Wei Examples 13 and 15A for limitations [1.1]-[1.3] and for “teach[ing] Element [1.5]” enzymatic activity. Pet. 16, 37 (citing EX1006, [0373] Example 15A batch for 17,000 units/pl), 39-40 (citing EX1006, [0361] (Example 13B, Table 19 “Concentrated enzyme assay”)), [0362] (Example 13B, “Eluate Enzyme Assay”); *supra* §§IV.A.1-2.

The Petition, however, fails to connect these separate Wei Examples to establish that it teaches a process for recombinant hyaluronidase PH20 having *both* the required sialylation [1.4] *and* the required enzymatic activity [1.5]. The Petition does not show, for example, that Wei’s Example 6 “[i]n general” and “[a]bout” glycosylation and sialylation approximations apply to or are reflective of the Example 13 or Example 15A process or its specific batches. Nor does the Petition show that the Wei Example 13 or Example 15A processes or specific batches meet the same “[i]n general” and “[a]bout” properties of Wei Example 6. *See* Pet. 35-40.

The Petition’s reliance on Wei for separately teaching sialylation in Example 6 and activity in Examples 13 and 15A thus fails to establish a teaching of the claimed combination of limitations [1.4] and [1.5] using steps [1.1]-[1.3]. *See In re Stepan*, 868 F.3d at 1346 (For “a rejection is based on ... combining multiple

embodiments from a single reference ... there must be a motivation to make the combination and a reasonable expectation that such a combination would be successful, otherwise a skilled artisan would not arrive at the claimed combination.”).

b. Wei Makes It Impossible to Connect Its Examples

The Petition’s only arguable attempt to link the different Wei Examples is its statement that “Wei discloses performing a ‘glycan analysis study’ on the rHuPH20 made according to Example 15,” citing to Wei Example 6. Pet. 35-36 (citing and quoting EX1006, [0322] (Example 6, “Briefly, rHuPH20 (as produced in Example 15C)”). On its face, “made according to Example 15” precludes a link to Example 13, cited in the Petition for limitation [1.5]. *See* Pet. 39-40 (citing EX1006, [0361] (Tables 19), [0362] (Table 20)); *see also* Pet. 29-31. It also does not even attempt to link Example 6 to the relied upon process or batches of Examples 15A specifically. *See* Pet. 37 (citing EX1006, [0373], Example 15A). Wei, in fact, precludes making any such link.

While Wei Example 6 refers to “rHuPH20 (as produced in Example 15C),” Wei Example 15C, titled “***Comparison*** of production and purification ***of Gen1*** soluble rHuPH20 ***and Gen2*** soluble rHuPH20,” does not describe a specific process or batch. EX1006, [0383]. It instead contrasts two materially different processes, Gen1 (Example 13B) and Gen2 (Example 15A), with at least 14

categorized differences. EX1006, [0383] (“Table 27 sets forth exemplary differences, in addition to simple scale up changes between the methods.”); EX2002, 10 (“the process imparts a number of different properties on the product, each of which is affected by an extent of batch-to-batch variation” (emphasis in original)), 65 (“*[c]hanging such cell culture parameters* to enable large-scale production of a specific protein product *is not trivial*”); EX2003, 5-11 (“feeding steps that are carried out in conjunction with adjusting the culture temperature ... results in a different composition”). It is, therefore, unknowable what process or batch the Example 6 “[i]n general” and “about” characterizations apply. *See Perricone*, 432 F.3d at 1379 (“[T]he district court’s inherency analysis goes astray because it assumes what Pereira neither disclosed nor rendered inherent.”).

Wei’s description of Example 6 as “a glycan analysis study of rHuPH20 (**SEQ ID NO:122**)” further precludes linking it to Examples 13 or 15A. *See* EX1006, [0321]. According to Wei, SEQ ID NO:122 is a specific 447 ammino acid rHuPH20. EX1006, [0386], p. 292-93. By contrast, Wei’s processes and its Examples 13 or 15A are described as producing heterogenous mixtures of rHuPH20 with various C-terminal truncations. EX1006, [0029] (“As produced in the culture medium, there is heterogeneity at the C-terminus so that the product includes a mixture of species that can include any one or more of SEQ ID NO:122 to SEQ ID NO:127 in various abundance.”), [0205] (“[C]ulture of soluble PH20 in

CHO cells can result in a mixture of heterogeneous polypeptides. An exemplary protocol for the generation, production and purification of a soluble PH20 (e.g. rHuPH20) is described in Examples 13–15 below”), [0383] (Table 19, 3D35M and 2B2 cell lines), [0385] (Example 17, “C-terminal heterogeneity of soluble rHuPH20 from 3D35M and 2B2 cells”); EX2002, 66 (modifying cell culture parameters “gives rise to a distinct pattern of proportions of the individual C-terminally truncated polypeptides” with distinct “structural ‘fingerprint[s]’” that “include distinctive structural quality attributes, such as reproducibly different contents in product-related impurities.”). Thus, there is no basis to link Wei’s “in general” and “about” characterizations for SEQ NO:122 to the Examples 13 or 15A processes and their heterogeneous products.

The express “in general” and “about” limitations of Example 6 also make clear that they are at best approximations and not reflective of any specific batch or process, such as those of Example 13 and 15A.² This is consistent with the art

² Beyond the Example 6 “in general” and “about” approximations, Wei does not include specific sialylation measurements for any PH20 enzyme, including SEQ ID NO:122. To the contrary, while Wei Example 16 is described as “[d]etermination of *sialic acid* and monosaccharide content” for batch HUB0701E, it again fails to provide any measure of sialic acid content. EX1006, [0384].

teaching that sialylation can depend on and vary with culture conditions. *See, e.g.*, EX2012, 510 (sialylation may increase, remain stable, or “decrease[] depending upon the *cell line and culture conditions*”) (citations omitted); *see also* EX2013, 1006 (“[E]ffects of mild hypothermia on *glycosylation* appear to be *highly dependent on cell line, protein types[,] and temperature*”). And Wei itself teaches variable activity, ranging from 991 to 29,826 U/mL depending on the process, batch, and stage. *See* EX1006, [0361] (Table 19), [0367]. Consequently, Wei’s disclosure precludes even assuming, let alone establishing, that Wei’s Examples are connected in such a way that Wei “general” and “about” characterizations for SEQ NO:122 are representative of the relied upon Example 13 and 15A processes or products.

At bottom, Wei’s at best ambiguous disclosure is insufficient for the Petition to establish a teaching of these combined limitations. *See W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1554 (Fed. Cir. 1983) (rejecting teachings that were “unacceptably vague concerning characteristics of products produced by their respective processes”).

B. Petitioner Fails to Establish Motivation to Modify Wei According to Zmuda

The Petition fails to articulate a problem to be solved with Wei, which Petitioner elsewhere describes as an optimized, commercial-scale process with

synergistic culturing parameters. *Infra* §IV.B.1. Nor does it address the incompatibility of Wei’s four-step acclimatizing protocol with Zmuda’s single sharp temperature drop, the only purported benefit of which is relative to fixed 37°C conditions irrelevant to Wei. *Infra* §IV.B.2. The Petition further fails to establish the bases for any presumption based on allegedly overlapping ranges, having misrepresented Wei as teaching a “second temperature range ... [that] is an overlapping range with the recited range of 28°C-34°C” and ignored the interdependence of Wei’s process parameters. *Infra* §IV.B.3; Pet. 30. The Petition thus fails to establish a motivation to combine Wei with Zmuda, on which all grounds rely.

1. The Petition Fails to Identify Any Problem to Be Solved for Wei’s “Synergistic” Combination of Processes Parameters

The Petition fails to identify any problem to be solved in Wei, its primary reference for all grounds. *See* Pet. 15-16. It thus fails to establish a “reason for one of ordinary skill in the art to attempt to improve upon” Wei by modifying it with Zmuda or Wei 2013. *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1354 (Fed. Cir. 2013) (“The ordinary artisan would first have needed to recognize the problem”); *Samsung Elecs. Co. v. Mojo Mobility Inc.*, IPR2023-01102, Paper 11, 19-20 (P.T.A.B. Jan. 10, 2024) (“Petitioner has failed to establish ... a known problem in the art.”); *see* Pet. 14 (“modification to Wei”).

Inconsistent with any problem to be solved, Petitioner touted Wei's "Gen2" process—Petitioner's own "successful commercial" process—as a unique combination of multiple "cell culture parameters [that] act synergistically to produce an improved hyaluronidase product." EX2002, 64-65; EX1006, cover, code (73) ("Proprietor: Halozyme"). According to Petitioner, Wei's four specific steps of "[g]radually reducing the temperature by specific amounts at specific times throughout the culturing process" with defined 0.5C temperature shifts from 37°C to 35.5°C was "sufficient to increase cell cycle arrest, increase cell viability[,] and stabilize the soluble hyaluronidase." EX1006, [0360], [0373]; EX2002, 65; EX1035, 2:30-32, 2:43-45.

Petitioner first disclosed its Gen2 process as early as 2008 and then continued to rely on it for more than a decade, including after Zmuda, for its "dramatic improvement" in PH20 production. *See* EX2004, 142:3-26; EX1006, [0360], [0373]; EX2001, [0270]; EX2002, 36; EX2005, 239:7-30; EX2006, [0263]. Petitioner's ongoing reliance and "the substantial number of intervening years between the publication of" Wei's Gen2 method in 2008 and the '638 patent filing date in 2020 "speak[] volumes to the nonobviousness of" the '638 patent. *Leo Pharm.*, 726 F.3d at 1357-59.

Having articulated no problem in Wei's successful commercial process or its synergistic combination of multiple cell culture parameters, the Petition fails to

establish a motivation to modify or a reasonable likelihood that any claim is unpatentable.

2. The Petition’s Generic Motivation Ignores Incompatible Differences Between Wei and Zmuda

Ignoring incompatible differences between Wei and Zmuda, the Petition “provides no persuasive explanation, reasoning, or evidence for concluding that one of skill in the art would have combined these particular references to produce the claimed invention.” *RPX Corp. v. Collision Avoidance Techs. Inc.*, IPR2017-01336, Paper 35, 71 (P.T.A.B. Nov. 13, 2018). The Petition’s generic “good reason[s]” to “optimiz[e] protein product[s]” are not a “motivation to combine particular references [(Wei and Zmuda)] to reach the particular claimed method.” *Innogenetics, N.V. v. Abbott Lab ’ys*, 512 F.3d 1363, 1373 (Fed. Cir. 2008); Pet. 23, 26, 31. The Petition further fails to state with “particularity ... how the combination of [Wei and Zmuda] renders the challenged claims unpatentable” as required to meet its 35 U.S.C. § 312(a)(3) burden. *TikTok Inc. v. Advanced Coding Techs. LLC*, IPR2022-01546, Paper 9, 8 (P.T.A.B. June 15, 2023).

First, the Petitioner’s generic “good reason[s]” to combine Wei and Zmuda fail to address, much less reconcile, that the “[f]undamental differences between the references are central to [the] motivation to combine inquiry.” *Adidas AG v. Nike, Inc.*, 963 F.3d 1355, 1359 (Fed. Cir. 2020) (affirming Board on absence of

motivation to combine where petitioner relied on generic consideration of “cost reduction and garment production” without addressing the references’ “fundamental differences”); *see* Pet. 23, 26, 31. The Petition thus fails as it “did not reconcile the conflict between” the “incompatible” Wei and Zmuda processes. *Intel Corp. v. Koninklijke Philips N.V.*, Nos. 2022-2034, -2035, 2024 WL 725243, at *1 (Fed. Cir. Feb. 22, 2024).

More specifically, Petitioner has described Wei as an optimized commercial-scale recombinant hyaluronidase protocol with multiple synergistic “acclimatizing” 0.5C temperature shifts. EX1006, [0373]; EX2002, 64-65; EX1014, 2-3. By contrast, Zmuda’s “High Titer” and “Max Titer” protocols are based on a single “sharp” temperature drop from 37°C to 32°C one day post-transfection. EX1005, 82, 88; EX1005, 82, 89-91; EX1014, 2-3.

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Wei GEN1	37°C					36.5°C			36°C		35.5°C			
Wei GEN2	37°C						36.5°C		36°C		35.5°C			
Zmuda	37°C	32°C												

Table 1. Comparison of temperature-shifts in Wei and Zmuda.

The Petition makes no effort to reconcile the incompatible timing and magnitudes of Wei’s “acclimatizing” method and Zmuda’s “sharp” temperature drop. *See* Pet. 23-24, 26, 31.

The irreconcilability of these differences is, instead, highlighted in Petitioner's references and admissions elsewhere. Becerra, for one, explains that *results “can vary substantially* depending on whether the mild hypothermia is induced by means of a *sharp* temperature change or by means of *acclimatizing* cells to the operational temperature.” EX1014, 3. Reflecting that Wei's 0.5C temperature steps and Zmuda's 10x large 5C temperature drop are materially different, Xu warns that “a minor difference in temperature (1-1.5 °C) caused significant differences in cell culture performance such as cell growth rates ... and quality attributes” EX1012, 200. And contradicting its allegedly “simple modification to Wei” (Pet. 14), Petitioner has elsewhere argued that “[c]hanging *such cell culture parameters* to enable large-scale production of a specific protein product *is not trivial*,” and that “it also *needs to be ensured that enhanced productivity in one step does not have a negative effect on productivity in other steps*.” EX2002, 65.

Second, the Petition fails to address “[t]he proper question” for motivation of “whether a designer of ordinary skill in the relevant technology, facing the wide range of needs created by developments in the field of endeavor, would have seen a benefit to modifying” Wei's acclimatizing protocol with Zmuda's sharp temperature drop. *RPX*, IPR2017-01336, Paper 35, 71. It “provides no persuasive

explanation, reasoning, or evidence for concluding that one of skill in the art would have combined these particular references to produce the claimed invention.” *Id.*

The *only* alleged benefits of Zmuda’s High Titer and Max Titer protocols are relative to its “Standard Protocol” comprising a “[s]ingle feed on Day 1 post-transfection, [with] flasks ***maintained at 37°C throughout*** the expression run.” Pet. 23-24; EX1005, 82, Fig. 6A. This “standard” protocol is not used in or shown to be relevant to Wei’s four-step 0.5C temperature shifts over 14 days to “acclimatiz[e] cells to the operational temperature.” EX1014, 2-3; EX2002, 64-65; *supra* Table 1. Thus, even if Zmuda could support a general motivation to modify a “standard” 37°C incubation with a “sharp temperature change,” the Petition does not show this to support a motivation to modify Wei’s materially different acclimatizing method comprising temperature already reduced to 35.5°C.

Zmuda also does not teach or suggest that any potential benefits of its single “sharp temperature change” are universal, much less applicable, to Wei’s hyaluronidase PH20 enzymes. Zmuda instead states that “some proteins will express similarly, or better, using the Standard Protocol [(37°C incubation)] without temperature shift depending on the nature of the protein.” EX1005, 82. The protein-specific nature of recombinant conditions was also recognized in

Clark,³ which teaches that “the previously hypothesized advantages that lower culture temperatures have reduced protease activity and improved productivity do not appear to be universal,” and that “a slow temperature decrease does not always result in increased cell viability.” EX2010, 1-2. These express disclaimers against extrapolating results with one protein to another further preclude Petitioner’s generic motivation to combine.

Finally, on top of the foregoing, the Petition fails to state with “particularity ... how the combination of [Wei and Zmuda] renders the challenged claims unpatentable,” as required to meet its burden under 35 U.S.C. § 312(a)(3). *TikTok*, IPR2022-01546, Paper 9, 8; *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (“Thus, it was Harmonic’s burden to explain to the Board how Haskell combined with Rossmere rendered the challenged claims unpatentable.”).

To start, Petitioner mischaracterizes Wei as having a “second temperature range of lower than 37°C [that] is an overlapping range with the recited range of 28°C-34°C.” Pet. 30. This is false. As Petitioner elsewhere acknowledges, “Wei

³ Clark is cited in the specification (EX1001, 3:43-49), but ignored by Petitioner and its declarant.

discloses decreasing the temperature in a stepwise fashion to 35.5°C” (*id.*), which is not overlapping with the [1.2] range of 28°C-34°C. *See* EX1006, [0360], [0373].

Building on its mischaracterization, the Petition alleges it would have been routine “to apply Zmuda’s overlapping range temperature shift ... in combination with Wei.” Pet. 24; *see also* Pet. 21-23, 25, 30-31; EX1014, 2. Yet it fails to articulate any basis as to how the two would be combined, e.g., how to incorporate Zmuda’s sharp temperature drop or otherwise modify Wei’s already purportedly optimized four-step acclimatizing protocol. *See, e.g., supra* Table 1.

Thus, not only does the Petition fail to show “that a skilled artisan, once presented with [Wei and Zmuda], would have understood that they *could be* combined”—which itself is “not enough”—it fails to provide specific “motivation to pick out those two references and combine them to arrive at the claimed invention.” *Pers. Web Techs., LLC v. Apple, Inc.*, 848 F.3d 987, 993-94 (Fed. Cir. 2017) (emphasis in original).

3. The Petition Fails to Establish Any “Overlapping Ranges” Presumption

The Petition fails to justify its asserted “presumption of obviousness” based on references that “overlap with the claimed numerical amount” or are “close enough to warrant an inference of having similar properties” Pet. 19-20; *Janssen Pharms., Inc. v. Teva Pharms. USA, Inc.*, 141 F.4th 1367, 1378 (Fed. Cir.

2025) (holding “there is an insufficient basis in the record evidence for us to apply the invoked presumption”). Nor can Petitioner rely on nonspecific “optimization of the lower second culturing temperature to improve yields,” which fails to account for irreconcilable differences between Wei and Zmuda. Pet. 24-25. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Pat. Litig.*, 676 F.3d 1063, 1072-73 (Fed. Cir. 2012) (“[W]here the prior art, at best, gives only general guidance as to the particular form of the claimed invention or how to achieve it, relying on an obvious-to-try theory to support an obviousness finding is impermissible.” (cleaned up) (citation omitted)); Pet. 24; *supra* §IV.B.2.

a. No Basis to Combine Multiple Ranges

The Petition fails to establish a basis to create overlapping from “a plurality of prior art references [to] together ... teach[] a range.” *Janssen*, 141 F.4th at 1375; Pet. 19-20; *supra* §§IV.B.1-IV.B.2. It instead boldly misrepresents Wei as “teach[ing] ... [a] second temperature range of lower than 37°C [that] is an overlapping range with the recited range of 28°C-34°C.” Pet. 30. Wei’s lowest temperature of 35.5°C is not “overlapping” with the claimed [1.2] range of 28°C-34°C. *See* EX1002, ¶¶53, 85, 91, 124, 134, 135.

Moreover, unlike *Iron Grip* (Pet. 20), the Petition does not assert that “***the prior art affirmatively suggests*** combining” Wei and Zmuda. *Janssen*, 141 F.4th at 1375 (citing *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322

(Fed. Cir. 2004)); Pet. 20, 22-25, 31. It instead relies on generic “good reason[s]” divorced from Wei’s hyaluronidase processes. Pet. 20, 22-26, 31; *supra* §IV.B.2.

b. No Presumption for Interacting Variables

Petitioner ignores that a presumption of obviousness based on overlapping ranges does not apply to combinations of *interacting* variables. *Janssen*, 141 F.4th at 1378-79 (rejecting a presumption for claimed “*combination* of loading doses” and distinguishing it from “variables [that] are properly considered separately from each other” (emphasis in original)). In this regard, the Petition fails to show that “the variables are properly considered separately from each other,” as would be necessary to invoke any presumption. *Id.* To the contrary, and even more so than *Janssen*, Petitioner and its references recognized the unpredictable *interdependency* of cell culturing process conditions.

For example, Becerra teaches that “it is not easy to evaluate the effect of the operational variables independently from the specific growth rate.” EX1014, 3. Due to this interdependency, results “can vary substantially depending on whether the mild hypothermia is induced by means of a sharp temperature change or by means of acclimatizing cells to the operational temperature.” *Id.*

Similarly, also inconsistent with the Petition, Petitioner represented and apparently has extensive evidence that Wei’s combination of multiple “cell culture

parameters act synergistically.”⁴ EX2002, 65. Petitioner further emphasized this interdependency, representing that “it also needs to be ensured that enhanced productivity in one step does not have a negative effect on productivity in other steps.” *Id.*

Thus, the Petition failed to establish any presumption as it “failed to address the interdependence of the claimed” cell culture parameters “and how adjustments would affect” the recombinant process “as a whole.” *ModernaTx, Inc. v. Arbutus Biopharma Corp.*, 18 F.4th 1364, 1376-77 (Fed. Cir. 2021) (affirming “the Board’s finding that optimizing the four interdependent lipid components in the prior art nucleic acid-lipid particles would not have been routine”).

⁴ Petitioner’s “extensive evidence” of synergistically interdependent cell culture parameters and variable results based on “a long-term research project that took several years to complete” (EX2002, 8, 17, 28-30, 65) should have been served with its Petition. 37 C.F.R. § 42.51(b)(1)(iii); *Spectrum Sols. LLC v. Longhorn Vaccines & Diagnostics, LLC*, IPR2021-00847, Paper 107, 4 (P.T.A.B. May 3, 2023) (discussing previous order to serve any relevant inconsistent information as required by 37 C.F.R. § 42.51(b)(1)(iii)).

c. Wei's and Zmuda's Temperatures Are Materially Different

Rather than present evidence that the conditions are “close enough to warrant an inference of having similar properties” (Pet. 19-20), Petitioner’s references and representations establish the opposite. “Where,” as here, “differences clearly exist and there is no evidence that they are either not meaningful or one of skill in the art would know to discard the limits set by the prior art, proximity alone is not enough to establish a prima facie case of obviousness.” *In re Patel*, 566 F. App’x 1005, 1010 (Fed. Cir. 2014).

Evidencing that “meaningful” “differences clearly exist,” *id.*, Xu reported that “*a minor difference in temperature (1-1.5 °C) caused significant differences in cell culture performance such as ... quality attributes*” EX1012, 200, Fig. 7. Petitioner’s combination significantly exceeds Xu’s 1-1.5C “minor” but “significant” difference, as there is a 3x greater difference between Wei’s 35.5°C lowest temperature and Zmuda’s 32°C second culturing temperature. EX1006, [0360], [0373]; EX1005, 82.

Amplifying the significance of this difference, Zmuda teaches that effects of its sharp temperature drop are “highly dependent on the specific protein expressed and relative yields achieved with the three different protocols may not reflect the results observed in this study.” EX1005, 91. And further precluding any “inference

of having similar properties” when modifying Wei’s precise temperatures (Pet. 19-20), Petitioner itself asserts that Wei’s “cell culture parameters act synergistically” such that any changes may have significant negative effects. EX2002, 65 (“[I]t also needs to be ensured that enhanced productivity in one step does not have a negative effect on productivity in other steps.”).

Thus, rather than establishing that conditions are “close enough to warrant an inference of having similar properties” (Pet. 19-20), Petitioner’s evidence demonstrates the opposite. *In re Patel*, 566 F. App’x at 1010.

C. Petitioner Fails to Establish a Reasonable Expectation of Success in Modifying Wei with Zmuda

The Petition has not established a reasonable expectation of success as it “failed to adequately explain ‘how [Wei’s recombinant hyaluronidase] process would be changed to use [Zmuda’s sharp temperature-shift recombinant process], which is formed in a quite different manner than’” Wei. *Samsung Elecs. Co. v. Elm 3DS Innovations LLC*, 925 F.3d 1373, 1381 (Fed. Cir. 2019) (citation omitted); *infra* §IV.C.1. Ignoring their incompatibilities, the Petition further fails to establish a reasonable expectation of success for its purported “improved yield” motivation, as Zmuda, at best, only shows improved yield relative to fixed 37°C culturing not shown relevant to Wei’s already reduced PH20 hyaluronidase temperature conditions. *Infra* §IV.C.2. Finally, the Petition fails to establish a reasonable

expectation of success for the claimed method, which is directed to PH20 hyaluronidase enzymes having *combined* sialylation and activity properties not taught by Wei in the first place. *Infra* §IV.C.3.

1. The Petition Ignores Wei and Zmuda’s Incompatibility

Wei’s four-step “acclimatizing” temperature shifts are distinct from and facially incompatible with Zmuda’s single sharp temperature drop.

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Wei GEN1	37°C					36.5°C			36°C		35.5°C			
Wei GEN2	37°C						36.5°C		36°C		35.5°C			
Zmuda	37°C	32°C												

Table 1. Comparison of temperature-shifts in Wei and Zmuda.

EX1006, [0360], [0373]; EX1005, 82, 88; *supra* §IV.B.2. EX1014, 2-3; EX1012, 200 (“a minor difference in temperature (1-1.5 °C) caused significant differences”). The Petition’s purported motivation based on unspecified “routine optimization” and “optimiz[ing] recombinant protein yield” fails on its own terms for not addressing these incompatible differences. *See* Pet. 22-23, 31; *supra* §IV.B.2.

The Petition’s “routine optimization” assertions, for example, do not address how a POSA would modify Wei without “fundamentally alter[ing]” its incremental, temperature-acclimatizing “principle of operation.” *Plas-Pak Indus.*,

Inc. v. Sulzer Mixpac AG, 600 F. App'x 755, 758-59 (Fed. Cir. 2015) (affirming Board on nonobviousness). For instance, the Petition fails to address why or how a POSA would modify Wei's combination of multiple "cell culture parameters [that] act synergistically to produce an improved" hyaluronidase product without "a negative effect on productivity in other steps." EX2002, 8, 17, 65. The Petition's failure in this regard is particularly glaring in view of its prior inconsistent representations that "[c]hanging such cell culture parameters to enable large-scale production of a specific protein product is not trivial." EX2002, 65.

The Petition further fails to establish a reasonable expectation of success as, contrary to the art and Petitioner's prior representation, it only considers temperature changes in isolation. For example, the Petition is irreconcilable with its own evidence recognizing that "*it is not easy to evaluate the effect of the operational variables independently* from the specific growth rate." EX1014, 3. Considering temperature in isolation is further irreconcilable with Petitioner's prior representation that Wei's combination of multiple "cell culture parameters act[s] synergistically."⁵ EX2002, 8, 17, 65 ("[I]t also needs to be ensured that enhanced

⁵ In addition to gradually reducing temperature, Petitioner stated that factors such as "the composition of the feed media," "the number of feeds," and the "time for harvesting" may impact Wei's hyaluronidase product. EX2002, 65.

productivity in one step does not have a negative effect on productivity in other steps.”).

Thus, the Petition fails to establish a reasonable expectation of success for its proposed combination of Wei and Zmuda, as it “failed to adequately explain how [Zmuda’s sharp temperature-shift] process would be changed to use [Wei’s purportedly optimized hyaluronidase protocol], which is formed in a quite different manner” *Samsung*, 925 F.3d at 1381 (cleaned up) (citation omitted) (affirming the Board’s lack of “reasonable expectation of success” finding where method of secondary reference (Leedy) was incompatible with the primary reference (Bertin)).

2. The Petition Fails to Establish a Reasonable Expectation of Improved Yield

The Petition further fails to establish a reasonable expectation for its alleged “improve[d] yield[]” motivation in view of the differences and incompatibility of Wei and Zmuda, and the art recognized protein-dependent unpredictability of temperature shifts. *See* Pet. 24-25, 37-38.

First, Zmuda’s only purported improvement in yield (greater “titer”) for its 5C “Max Titer” temperature drop is relative to a steady state “Standard Protocol” that “maintain[s] at 37°C throughout the expression run.” EX1005, 82. Any improvement relative to a *fixed* 37°C is irrelevant to Wei’s four-step *acclimatizing*

37°C → 36.5°C → 36°C → 35.5°C process. *See* EX1006, [0360], [0373]; EX1014, 3; EX1012, 200 (“[A] minor difference in temperature (1-1.5 °C) caused significant differences in cell culture performance such as cell growth rates ... and quality attributes”). Indeed, the Petition does not even allege Zmuda to teach or suggest improvement in yield for an allegedly optimized acclimatizing protocol as in Wei. *See* Pet. 24-25, 37-38. Thus, the Petition fails to support its proffered motivation to improve the yield of Wei with “a reasonable expectation of success in doing so.” *Intelligent*, 821 F.3d at 1367-68 (citation omitted).

Second, rather than supporting an expectation of increased yield for modifying Wei’s acclimatizing protocol, Petitioner’s references, including Zmuda, describe the effect of temperature shifts on yield as unpredictably varying depending on the protein. The Petition fails to account for this “highly unpredictable art,” precluding a reasonable expectation of success for improved yield. *OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1384-85 (Fed. Cir. 2019) (“Thus, there is not only a complete absence of data regarding the effect of erlotinib on NSCLC, but also a complete absence of an indicator or mechanism on which a person of ordinary skill could rely to reasonably expect success.”).

To start, Zmuda states that “some proteins will express similarly, or better, using the Standard Protocol [(37°C incubation)] without temperature shift

depending on the nature of the protein.” EX1005, 82. The unpredictable protein-dependent effects of temperature are further documented in Xu, which teaches that:

- “[t]he effects of temperature on productivity ... are ... protein specific” and “may also have interactions with other cell culture parameters,”
- “productivity *decreased* after temperature downshift,”
- “some produced lower q_p [(specific productivities)] under TS conditions (compared to that at 36.5 °C),”
- “ q_p decreased with temperature decrease from 36.5 to 32 °C,” and
- “mixed results on q_p ..., depending on shift timing and glutamine concentrations.”

EX1012, 198-200 (“We also found that a minor difference in temperature (1-1.5 °C) caused significant differences in cell culture performance”). This protein-dependent unpredictability is affirmed in Becerra, which teaches that “[a] general analysis of the background shows that the magnitude of the effect of reducing the culture temperature over the specific production rate depends markedly on ... the r-protein itself.” EX1014, 2.

Ignoring these unpredictable protein- and condition-dependent effects of temperature shifts, the Petition makes no effort to articulate a reasonable basis to expect increased yield for PH20 hyaluronidase specifically or even enzymes more generally. Pet. 24-25, 37-40. Rather, it relies on literature addressing various antibodies and hormones that do not even exhibit enzymatic activity. EX1005, 17,

81 (studying antibodies); EX1012, 192 (studying antibodies); EX1014, 2 (studying non-PH20 recombinant proteins).

Without a basis to extrapolate effects of Zmuda's sharp temperature drop on antibody production to Wei's allegedly optimized acclimatizing method of producing distinctly different hyaluronidase PH20 enzymes, the Petition fails to establish a reasonable expectation of success for its improved yield motivations.

3. The Petition Fails to Provide a Reasonable Expectation of Success for the Claimed Sialylation and Enzymatic Activity

Claim 1 requires, *inter alia*, that the produced recombinant hyaluronidase has [1.4] 1 to 38% N-glycan sialylation *and* [1.5] 10,000 units/mL or higher hyaluronidase enzymatic activity. The Petition's failure to articulate a reasonable expectation of success for this "*claimed* invention" is dispositive of not even a reasonable likelihood of prevailing on obviousness. *Janssen*, 141 F.4th at 1379-80 ("It is bedrock law that the inquiry of motivation and reasonable expectation of success must focus on arriving at the *claimed* invention" (emphasized in original)); 35 U.S.C. § 314(a).

First, as noted above in Section IV.A.3, Wei nowhere reports any batch having both the sialylation level and the claimed hyaluronidase enzymatic activity. The enzymatic activity associated with the reported sialylation also cannot be inferred from Wei's other examples due to their high degree of variability and

ambiguous disclosure. *Supra* §IV.A.3.b. Thus, even if a POSA could have expected to maintain the same sialylation and enzymatic activity, there is no disclosure in Wei of rHuPH20 enzymes with the combination of [1.4] sialylation and [1.5] enzymatic activity to be maintained.

Second, the Petition’s assertion that “no detrimental change ... would have been expected” (Pet. 26) fails to account for Wei’s highly variable process based on a combination of synergistically interacting variables. *Supra* §§IV.B.1-2. This unpredictability precludes any reasonable expectation for the claimed combination of properties not even taught in Wei in the first place. *See, e.g., Honeywell Int’l Inc. v. Mexichem Amanco Holding S.A. DE C.V.*, 865 F.3d 1348, 1354-55 (Fed. Cir. 2017) (finding the Board erred in relying on inherency to dismiss evidence showing unpredictability in the art); *Grunenthal GMBH v. Alkem Lab’ys Ltd.*, 919 F.3d 1333, 1342-43 (Fed. Cir. 2019) (finding nonobviousness where the prior art taught that “a POSA could alter any number of variables and still fail to find a polymorph of a particular compound”). This is not cured by Petitioner’s other literature (Pet. 35-40), which (1) fails to overcome Wei’s deficiency in disclosing the combination of sialylation and hyaluronidase activity, and (2) is silent on how sharp temperature drops would affect the combination of sialylation and enzymatic activity of PH20 hyaluronidase. *Supra* §§IV.A.3, IV.B.

Lacking any argument or evidence as to how a sharp temperature drop would affect the sialylation and enzymatic activity (not taught in Wei in the first place), the Petition is left without bases to establish a reasonable expectation of success in achieving the claimed invention.

V. CONCLUSION

The Petition fails to establish a reasonable likelihood of prevailing on either of its two obviousness grounds as it does not specify where each claim element is found in the prior art, does not provide a motivation for modifying its primary reference, and does not establish a reasonable expectation of success for the claimed invention. Accordingly, Patent Owner requests that the Director deny institution.

Dated: March 16, 2026

By: /Mark J. Feldstein/
Mark J. Feldstein, Lead Counsel
Reg. No. 46,693

CERTIFICATION OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24, Patent Owner certifies that the word count of
PATENT OWNER'S PRELIMINARY RESPONSE as measured by Microsoft
Word is 11,124.

Dated: March 16, 2026

By: /Mark J. Feldstein/
Mark J. Feldstein, Lead Counsel
Reg. No. 46,693

CERTIFICATE OF SERVICE

The undersigned certifies that a copy of the foregoing PATENT OWNER'S
PRELIMINARY RESPONSE and EXHIBITS 2001-2013 were served
electronically via email on March 16, 2026, in their entirety on the following:

Michael T. Rosato
Sonja R. Gerrard
Jad Mills
Aubrey Haddach
WILSON SONSINI GOODRICH & ROSATI
701 Fifth Avenue, Suite 5100
Seattle, WA 98104-7036
mrosato@wsgr.com
sgerrard@wsgr.com
jmills@wsgr.com
ahaddach@halozyme.com

Petitioner has consented to electronic service.

Dated: March 16, 2026

/ William Esper /
William Esper
Senior Litigation Paralegal
Finnegan, Henderson, Farabow,
Garrett & Dunner, LLP