

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 REQUEST FOR DISCRETIONARY DENIAL

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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.

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
IVCD	<i>integral viable cell density</i>
'638 Patent	U.S. Patent No. 12,221,638
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 (July 31, 2025), uspto.gov/sites/default/files/documents/aapa_memo_final_signed.pdf

List of Exhibits

Exhibit	Description
2001-2099	Reserved
2100	Excerpts from Prosecution History of U.S. Appl. No. 17/907,538

I. Introduction

The claimed methods of producing *specific* recombinant proteins include two *specific* culturing temperature phases, each coupled with *specific* conditions¹ to provide *specific* properties² following the second culturing conditions. The claims were *twice* allowed over Petitioner's same primary reference (Wei, EX1006), same attempt to combine with lower-temperature conditions from a secondary reference, and same "obvious to optimize" arguments. The Examiner correctly found that "[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, 8.

Rather than showing that the method "as recited in the claims" is taught or suggested in art not already considered, Petitioner argues that the Examiner failed to appreciate protein properties *from different conditions* in Wei and low temperatures *for different proteins* in other references. Pet. 10-12. By relying on alleged disclosure of partial elements, Petitioner contravenes the fundamental principle that "[t]he determination of obviousness is made with respect to the

¹ "Integral viable cell density" (IVCD) in first temperature phase [1.1] and maintaining glucose level and/or pH ranges in second temperature phase [1.2, 1.3].

² Percent sialylation [1.4] and enzymatic activity [1.5].

subject matter as a whole, not separate pieces of the claim.” *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008). Regardless of the alleged “separate pieces”—none of which are connected to the claimed method’s specific conditions and specific properties at the specific temperature—the file history shows that the Examiner properly examined the claims and prior art as well as Petitioner’s “obvious to optimize” rationale.

Petitioner further relies on declarant testimony to manufacture multiple claim limitations, including the IVCD value limitation [1.1] it admits is “not disclose[d]” in the asserted prior art. EX1002, ¶¶111-112. The declarant’s testimony goes beyond permissible expert explanations, instead generating the claimed property from his own “assumed” conditions and “estimation[s].” *Id.*, ¶¶111-116. Petitioner thus fails to “specify where each element of the claim is found in the prior art,” as required. 37 C.F.R. § 42.104(b)(4); Rule 42.104(b)(4) Enforcement Memo, 1.

Because the Petition seeks to relitigate issues already resolved by the Office and flouts the Rules, Patent Owner requests that the Director deny institution.

II. Petitioner’s Art and Arguments Were Examined and Overcome Without Material Error

Examination of the Application of the ’638 Patent twice properly found the claimed method as a whole nonobvious. *See* Section II.A. The Petition’s two

Grounds rely primarily on Wei (EX1006), which was applied and overcome during prosecution and does not teach or suggest the claimed second temperature range enzymatic activity of combined limitations [1.2] and [1.5]. *See* Section II.B. The Petition relies on secondary reference Zmuda (EX1005) as disclosing and motivating the claimed second temperature range [1.2], but Zmuda is cumulative of references and rationale previously applied by the Examiner that were entirely ignored in the Petition. *See* Sections II.C-D. Petitioner's tertiary Wei 2013 (EX1037) reference for Ground 2 was already considered and is not, in any event, asserted to overcome the deficiencies of Wei and Zmuda. *See* Section II.E. The Office should not waste resources addressing issues already considered and overcome—particularly as the Petition fails to specify where all elements are found in the prior art. *See* Section III.

A. Prosecution History Summary

The claimed method 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]).

The Examiner initially rejected the original claims as obvious over the

combination of Wei (EX1006), Chen (122 J. Biosci. Bioeng. 673-678 (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 claim 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).

B. Wei Was Considered Without Material Error

Wei (EX1006), Petitioner's lead reference, was previously applied by the Examiner as a primary obviousness reference. EX1004, 46-48; Pet. 9-12; 35 U.S.C. § 325(d); *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6, 7-8 (P.T.A.B. Feb. 13, 2020) (precedential). Petitioner nevertheless argues that the Examiner overlooked Wei's

disclosure of enzymatic activity within limitation [1.5]. Pet. 9, 11-12. The Examiner, however, expressly considered Wei in its entirety multiple times. EX1004, 47 (“see entire [Wei] publication”), 55 (“see entire [Wei] publication”); *cf. Yeda Rsch. v. Mylan Pharms. Inc.*, 906 F.3d 1031, 1046 (Fed. Cir. 2018) (“As we have said numerous times, failure to explicitly discuss every fleeting reference or minor argument does not alone establish that the Board did not consider it.”).

Rather than materially err with respect to Wei, the Examiner properly evaluated the claimed method “as a whole, [and] not separate pieces of the claim.” *Sanofi-Synthelabo*, 550 F.3d at 1086. As noted above, limitations [1.2] and [1.5] together require, *inter alia*, a “second culturing,” “performed within a second temperature range from 28° C. to 34° C.,” “which produces the recombinant protein ... ha[ving] a hyaluronidase enzymatic activity at 10,000 units/mL or higher.” In this regard, the Examiner determined that

[Wei] does not teach 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. In other words, the Examiner found that Wei does not teach the *combination* of the limitation [1.2] lower, second temperature range of 28-34°C *with* the limitation [1.5] enzymatic activity. *See also* Pet. 11-12 (allowance based on “combination” of activity and sialylation).

The Petition does not dispute this key finding. In fact, Petitioner concedes that *Wei does not teach* the second 28-34°C temperature range at all. EX1004, 47; Pet. 30 (“Wei discloses decreasing ... to 35.5°C”); EX1002, ¶124 (“Wei discloses decreasing ... to 35.5°C”), ¶219 (“Wei ... uses 35.5°C as a lower ... temperature.”); EX1006, [0360], [0373]. The undisputed absence of the 28-34°C temperature range confirms no error in the Examiner’s conclusion that Wei “does not teach 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.

Rather than showing error with respect to combined *second* 28-34 °C temperature [1.2] and enzymatic activity [1.5] limitations, the Petition instead improperly relies on enzymatic activity from a concentrated and purified Wei batch produced within the distinct limitation [1.1] “*first* temperature range from 35° C. to 38° C.” See Pet. 28-29, 37 (EX1006, [0360]-[0362] (37° to 35.5°C), [0373] (same)). While Petitioner points to Wei’s disclosure of a temperature decrease, that decrease only reaches 35.5°C—within the *first* 35 to 38°C temperature range defined by limitation [1.1]. Then, without scientific explanation or legal basis, the Petition stealthily applies this high-temperature batch activity as if it were produced at a “second temperature range from 28° C. to 34° C.” of limitations [1.2] and [1.5] read together. See Pet. 37. Notwithstanding the Petition’s sleight of

hand, the Wei high-temperature batch is not produced in a “second culturing,” “performed within a second temperature range from 28° C. to 34° C.,” and is not a recombinant protein produced under those conditions “ha[ving] a hyaluronidase enzymatic activity at 10,000 units/mL or higher,” as recited in limitations [1.2] and [1.5]. *See* EX1006, [0360]-[0362] (37° to 35.5°C), [0373] (same)

Given the Petition’s (1) admission that Wei only “discloses decreasing the temperature in a stepwise fashion to 35.5°C” (Pet. 30) and (2) reliance on enzymatic activity of a high-temperature batch *not* produced at the second temperature range, Petitioner has no basis to allege error in the Examiner’s finding that Wei “does not teach 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; *see also* EX1004, 8, 20. Disagreement with the Examiner’s determination of nonobviousness does not establish material error. *See Ascentcare Dental Prods., Inc. v. Solmetex, LLC*, IPR2025-01065, Paper 11, 2-3 (Director Oct. 17, 2025).

C. Zmuda Is Cumulative of Previously Presented Art Examined Without Material Error

The Petition relies on Zmuda for a second culturing temperature within the claimed 28-34°C range [1.2] and alleges as error that the Examiner was “unaware of the overlapping prior art range, and never asserted any rejection in view of

overlapping ranges.” Pet. 3, 31. However, “the same or substantially the same prior art or arguments previously were presented to the Office.” 35 U.S.C. § 325(d); *Advanced Bionics*, Paper 6, 7-8. Rather than material error in this regard, the Petitioner’s redundant rationale reflects, at most, disagreement. *Advanced Bionics*, Paper 6, 8-9; *Ascentcare*, Paper 11, 2-3.

In asserting that the Examiner was “unaware” and “never asserted any rejection in view of overlapping ranges” (Pet. 3, 31), Petitioner overlooks that the Examiner initially rejected the pending claims as obvious, relying on Chen for a temperature within and lowering to the [1.2] claimed range:

Chen et al. teach ... incubation for 2 days at 30°C Therefore, 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, 47-48 (citing Chen). Petitioner’s assertion that the Examiner was “unaware of the overlapping prior art range and never asserted any rejection in view of overlapping ranges” (Pet. 3, 31) is plainly false. Indeed, Petitioner’s reliance on Zmuda is cumulative of the Examiner’s rejection.

First, Petitioner relies on Zmuda for allegedly disclosing a temperature within the range of 28-34°C. Pet. 30-31. This is cumulative of the Examiner’s

reliance on Chen for teaching “*incubation ... at 30°C.*” EX1004, 47; *Helena Lab ’ys Corp. v. Sebia*, IPR2024-00801, Paper 10, 12, 15 (P.T.A.B. Oct. 23, 2024) (finding art cumulative when an asserted reference was not identical but relied on for the same teachings as considered art). Petitioner’s contention that the Examiner was “unaware of the overlapping prior art range” (Pet. 3) simply ignores the Examiner’s express reliance on Chen. The Examiner specifically cited Chen for teaching “incubation ... at 30°C” and expressly considered the obviousness of “lowering the culture temperature to 28-34°C.” EX1004, 47. Thus, Zmuda adds nothing new to the Examiner’s analysis of the temperature conditions.

Second, any argument that the Examiner would have “benefit[ted]” from Zmuda (or any of Petitioner’s secondary references) with respect to “reduction of the culture temperature to 34°C or below” is also cumulative. *See* Pet. 10-11. For example, the Petition asserts that “[b]oth Wei and Zmuda thus provide good reason to optimize recombinant protein yield through routine operation of the lower second culturing temperature” Pet. 31. Petitioner’s contention that Wei—previously considered by the Examiner—already provided its alleged “good reason” renders Zmuda cumulative in this regard. Indeed, the Examiner already considered the argument that a POSA “would have been motivated” to modify Wei “including lowering the culture temperature to 28-34 °C.” EX1004, 47-48; *LG Elecs. Inc. v. Image Processing Techs., LLC*, IPR2023-00104, Paper 11, 26-27

(P.T.A.B. May 11, 2023) (finding a proposed combination cumulative because a modification was done “in substantially similar a manner as that which was previously considered”).

Given that the Petition’s proffered “good reason” is at least substantially the same as the Examiner’s, the Petition again at best reflects disagreement but not material error. *Advanced Bionics*, Paper 6, 8-9; *Ascentcare*, Paper 11, 2-3.

D. Petitioner’s Rationale to Modify Wei Was Considered and Traversed Without Material Error

The Petition’s rationale for modifying Wei is based on purported routine optimization and conventional teachings. *E.g.*, Pet. 22-26 (“routine optimization”), 30-31 (“optimize”), 32-34 (“routine and conventional”). Indeed, Petitioner alleges that five out of six limitations of claim 1 are “routine” or “conventional.” Pet. 28 ([1.1]), 30-31 ([1.2]), 32-34 ([1.3]), 35-36 ([1.4]), 37-39 ([1.5]). The Office, however, already considered and withdrew rejection based on these theories. That Petitioner relies on Wei again with additional references and declarant testimony to make the same or substantially the same argument fails to support material error or provide reason to reconsider. *See, e.g., LG Elecs.*, Paper 11, 22-27 (denying institution where the Petitioner presented a new secondary reference filling the same gap in a primary reference as two previously considered secondary references).

In making its initial obviousness rejection, the Examiner expressly considered routine experimentation and conventional teachings. *See* Section II.A; EX1004, 47-48 (motivation based on “routine experimentation and/or as desired for efficient production of the PH20,” expectation of success where “recombinantly producing PH20 is known in the art as shown by the above reference teachings”). Applicant overcame this rejection by explaining that the references—individually or in combination—failed to disclose or provide any basis for deriving the combined limitations [1.2] (“second culturing ... within a second temperature range from 28° C. to 34° C.”) and [1.3] (“the second culturing maintains”). EX1004, 37-39. Applicant further directed the Examiner to specification Examples 2-5 that demonstrate the interdependence of multiple variables (additives, culturing duration, glucose control, and pH control) with respect to PH20 activity and sialylation levels:

Examples 2 to 5 of the present application ... sufficiently demonstrate[] that [a] culture dependent on additives (Example 2), culturing duration (Example 3), controlled glucose concentration in culture medium (Example 4), and controlled pH (Example 5) can affect the highest activity and the lowest sialylation level of the recombinant PH20 hyaluronidase or a variant thereof.

EX1004, 39-40. The Examiner properly withdrew the rejection in view of these arguments. EX1004, 8, 20; *see ModernaTx, Inc. v. Arbutus Biopharma Corp.*,

18 F.4th 1364, 1376-77 (Fed. Cir. 2021) (rejecting routine optimization arguments based on “general considerations” that failed to address the interdependence of individual components).

Petitioner does not demonstrate error by restating the Examiner’s original rationale with different references. *See Fortinet Inc. v. Brit. Telecomms. Pub. Ltd.*, IPR2019-01326, Paper 8, 9 (P.T.A.B. Jan. 7, 2020) (failing “to describe *any* difference between [the references] that would provide a reason to obtain a different result from the obviousness analysis previously performed by the Examiner”). Nor does Petitioner have a basis to demonstrate error where the combined “second temperature” “maintain[ing]” limitations [1.2]-[1.3] are not disclosed in Wei, as addressed in Section III.B, *infra*.

The Examiner, thus, did not “misapprehend[] or overlook[]” Petitioner’s rationale to modify Wei. *Advanced Bionics*, Paper 6, 9 (“If reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to patentability.”), 21.

E. Wei 2013 Was Also Previously Presented to the Office and Examined Without Material Error

Petition Ground 2 utilizes Wei 2013 (EX1037) as a tertiary reference against dependent claims 4 and 7. *See* Pet. 53-57. Petitioner fails to disclose, however, that (1) Wei 2013 was previously presented to the Office; (2) Wei 2013 is substantially

similar to Wei, describing the same experiments in places; and (3) the Examiner allowed the challenged claims over both Wei and Wei 2013. EX2100, 29 (July 22, 2024 IDS); EX1004, 8; *compare* EX1006, [0001]-[0002], [0019], Example 11, Example 15, *with* EX1037, 1:18-2:3, 51:1-52:11, Example 1.

In addition to having already been considered, Wei 2013 is only asserted against dependent claims 4 and 7 and is not relied upon to overcome the deficiencies of its Ground 1 combination. *See* Pet. 53-57. Wei 2013 is, therefore, of no consequence to the Examiner’s overall determination of nonobviousness.

III. The Petition Fails to Demonstrate Where the IVCD [1.1] and Second Culturing Temperature Maintains [1.3] Limitations Are Found in the Asserted Prior Art

The Petition fails to identify prior art disclosure of (A) the claimed IVCD [1.1] and (B) “maintain[ing]” pH and/or glucose during the second temperature step [1.3]. Pet. 28-29, 31-34. Petitioner’s improper reliance on its declarant’s “assumed” conditions, “estimated” numbers, and “expected” results to fabricate these elements warrants denial. Pet. 28-29; EX1002, ¶¶111-116; Rule 42.104(b)(4) Enforcement Memo, 1.

A. Petitioner Improperly Relies on Declarant Assumptions and Estimates for Missing IVCD Limitation [1.1]

Petitioner’s declarant admits that the IVCD value of limitation [1.1] is “*not disclose[d]*” in Wei. EX1002, ¶¶111-112. Petitioner instead relies on speculative

testimony—based on “assumed” conditions and “estimation[s]”—to generate an “estimate[d] IVCD over time.” *Id.*, ¶¶111-116; Pet. 29. Petitioner’s reliance on its declarant to attempt to supply this missing limitation is a dispositive basis to deny institution. Rule 42.104(b)(4) Enforcement Memo, 1.

Petitioner alleges that a POSA “would have understood Wei to teach that the first culturing continued until” the claimed IVCD. Pet. 29. This alleged understanding is contradicted by its declarant, who admits that “*Wei does not disclose* values for [IVCD]” and that *he can only “estimate IVCD over time.”* EX1002, ¶111.

To the extent Petitioner newly argues that its declarant is calculating an inherent property from Wei, that argument is precluded by the declarant’s admitted reliance on assumptions and estimations. *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:

- “[a]ssum[ed] exponential growth” (EX1002, ¶113);

- “*assumed* that at maximum cell density[,] the % viability would likely be around 95%” (EX1002, ¶115);
- “*assumed* ... gradual linear decrease in viable cell density” (EX1002, ¶116); and
- “*estimate[d]* IVCD over time” (EX1002, ¶111).

Thus, Petitioner’s alleged “underst[anding]” is really its declarant self-selecting data from Wei and adding assumptions and estimates not found therein. Pet. 28-29.

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” IVCD 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, 1.

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, ¶¶111-116; *BTC Corp. v. TG Biotech Co.*, IPR2022-00998, Paper 44, 30-31, 35-36 (P.T.A.B. Nov. 13, 2023); 37 C.F.R. § 42.104(b)(4).

B. Petitioner Fails to Identify Prior Art Disclosure of the Second Culturing Temperature Maintains Limitation [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.

“*The second culturing*” is defined in element [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. Petitioner’s reliance on what, according to its declarant, a POSA would have “expected” further contravenes Rule 42.104(b)(4).

First, Wei only “discloses decreasing ... to 35.5°C,” and the Wei glucose conditions relied upon by Petitioner were likewise at temperatures of 35.5°C and higher. Pet. 30, 32-34 (citing EX1006, [0360] (37° to 35.5°C), [0373] (same)); EX1002, ¶53 (“35.5°C”), ¶124 (same), ¶134 (same), ¶135 (same). The same is true for Wei’s pH conditions. Pet. 34 (citing EX1006, [0360] (37° to 35.5°C), [0373] (same)); EX1002, ¶¶141-142 (citing the same Wei disclosures). Inconsistent with its reliance on Wei’s higher ($\geq 35.5^{\circ}\text{C}$) temperature culturing conditions in place of the required conditions during the second temperature range from 28° to 34°C,

Petitioner's declarant admits that both glucose utilization and pH changes depend on temperature. EX1002, ¶¶31, 40, 43. Thus, because the Wei glucose concentrations and pH conditions were not at a second temperature from 28° to 34°C, Wei does not and cannot disclose the combined "second temperature" [1.2] and "maintain[ing]" [1.3] limitations. For the same reasons, the Petition fails to "specify where each element of the claim is found in the prior art" 37 C.F.R. § 42.104(b)(4).

Second, Petitioner's declarant admits that "Wei does not disclose the amount of glucose in the media before or after feeding the cells," but then 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" again improperly "assume[] 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"). Petitioner's arguments regarding pH are even more deficient. Rather than asserting that the pH conditions would have been "expected" to be maintained, Petitioner's declarant relies on "instrumentation that *allows for* monitoring and control of pH" without disclosure of controlling or maintaining within the claimed range. EX1002, ¶141.

Finally, the Petition's alternative "conventional ... to maintain" arguments

(Pet. 33-34) again fail to address the combined [1.2] and [1.3] limitations of maintaining glucose or pH in the claimed ranges *and* at a temperature between 28°C to 34°C. *See id.*

The Petition should thus be denied for failure to specify where the prior art discloses limitation [1.3] that “the second culturing [within a second temperature range from 28° C. to 34° C.] maintains” the recited glucose and/or pH conditions.

IV. Conclusion

Petitioner (1) attempts to relitigate art and arguments that the Office previously considered without error, and (2) inappropriately relies on declarant testimony to supply missing elements. Accordingly, Patent Owner respectfully requests that the Director discretionarily deny the Petition.

Dated: February 17, 2026

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

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d) and Interim Director Discretionary Process (§ II.C.iii), I, Mark J. Feldstein, certify that **PATENT OWNER'S REQUEST FOR DISCRETIONARY DENIAL** complies with the 20-page limit, excluding those portions identified in 37 C.F.R. § 42.24(c).

Dated: February 17, 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 REQUEST FOR DISCRETIONARY DENIAL AND EXHIBIT 2100** were served electronically via email on February 17, 2026, in its entirety on the following:

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Dated: February 17, 2026

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