

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

WUHAN HEALTHGEN BIOTECHNOLOGY CORP.,
Petitioner,

v.

VENTRIA BIOSCIENCE INC.,
Patent Owner.

IPR2023-00684
Patent 11,492,389 B1

Before TINA E. HULSE, DAVID COTTA and MICHAEL A. VALEK,
Administrative Patent Judges.

VALEK, *Administrative Patent Judge.*

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Wuhan Healthgen Biotechnology Corporation (“Petitioner”) filed a Petition (Paper 2, “Pet.”), seeking *inter partes* review of claims 1–29 of U.S. Patent No. 11,492,389 B1 (Ex. 1001, “the ’389 patent”). Ventria Bioscience Inc. (“Patent Owner”) filed a Preliminary Response. Paper 6 (“Prelim. Resp.”).

In its Preliminary Response, Patent Owner asks the Board to apply discretion to deny institution under 35 U.S.C. § 325(d). *See* Prelim. Resp. 11–34. Patent Owner also challenges the merits of the grounds in the Petition. *Id.* at 31–58.

After considering the arguments and evidence presented at this stage of the proceeding, we are not persuaded that Petitioner has demonstrated a reasonable likelihood that it would prevail with respect to at least one claim challenged in the Petition. Accordingly, *inter partes* review is denied.

II. BACKGROUND

A. *Real Parties in Interest*

The parties identify themselves as the only real parties in interest. Pet. 65; Paper 5, 1.

B. *Related Matters*

The parties do not identify any other matter involving the ’389 patent. *See* Pet. 66; Paper 5, 1. However, the parties identify the following matters involving U.S. Patent No. 10,618,951 (“the ’951 patent”), which is related to the ’389 patent: *Ventria Bioscience Inc. v. Wuhan Healthgen Biotechnology Corp.*, DKS-5-21-cv-04008 (D. Kan.) and *Wuhan Healthgen Biotechnology Corp. v. Int’l Trade Comm’n*, No. 2023-1389 (Fed. Cir.), which is an appeal

from: *Certain Plant-Derived Recombinant Human Serum Albumins (“rHSA”) and Products Containing Same*, U.S.I.T.C. Inv. No. 337-TA-1238. Pet. 66; Paper 5, 1.

Moreover, Petitioner previously challenged certain claims of the ’951 patent in IPR2022-00712 (“the 712 IPR”). Institution was denied in that proceeding. Ex. 2015 (Decision Denying Institution of *Inter Partes* Review in IPR2022-00712).

C. The ’389 Patent and Related Background

The ’389 patent issued on November 8, 2022 from a continuation in a series of applications dating back to Application No. 12/708,462, filed on February 18, 2010 and Provisional Application No. 61/154,204, filed on Feb. 20, 2009. Ex. 1001, codes (60), (63). The ’951 patent issued from an earlier continuation of Application No. 12/708,462 and can be considered the great-grandparent to the ’389 patent. *Id.*, code (63).

The ’389 patent relates to “cell culture media” and more specifically to a media comprising albumin and other proteins that aid in the growth of cultured cells. Ex. 1001, Abstr, 1:29–33, 3:8–12.

Albumin is a naturally-occurring protein that may be obtained from different sources. *See* Ex. 1003 ¶¶ 64–76, 89–96 (providing background). For example, human serum albumin (“HSA”) may be derived from human plasma (“pHSA”) or it may be expressed as a recombinant protein (“rHSA”) in a host organism such as yeast or a plant like rice. *See* Ex. 1001, 14:23–67 (describing comparisons of pHSA with rHSA from yeast and rice); *see also* Pet. 1 (noting that recombinant proteins, such as rHSA, “are expressed in hosts that would not naturally produce them”).

The '389 patent describes a cell culture media supplement comprising a recombinant albumin produced in a plant and having less than about 1 EU¹ of endotoxin/mg of albumin. *See* Ex. 1001, 5:4–8, 45:43–47. In some embodiments, the albumin also contains less than about 10 ppm detergent. *Id.* at 45:43–57. This albumin is “expressed within a plant cell, and then purified from host cells proteins and lipids.” *Id.* at 26:28–31. The '389 patent explains that albumin may be purified using a variety of techniques. *Id.* at 49:60–67. In particular, the '389 patent describes two processes for purifying rHSA from rice grain, i.e., the “B000” process, which the patent refers to as the “old process,” and the “B0000C” process. *Id.* at 14:11–16, 65:53–69:20 (Ex. 5), 69:24–67 (Ex. 6). During prosecution of the '951 patent, the Applicants submitted a declaration explaining that the old B000 process is the same process for preparing purified rHSA described in Deeter.² Ex. 2010 ¶¶ 4–8; *see also* Ex. 1002, 281 (referring to the same declaration in the Examiner’s reasons for allowing the '389 patent).

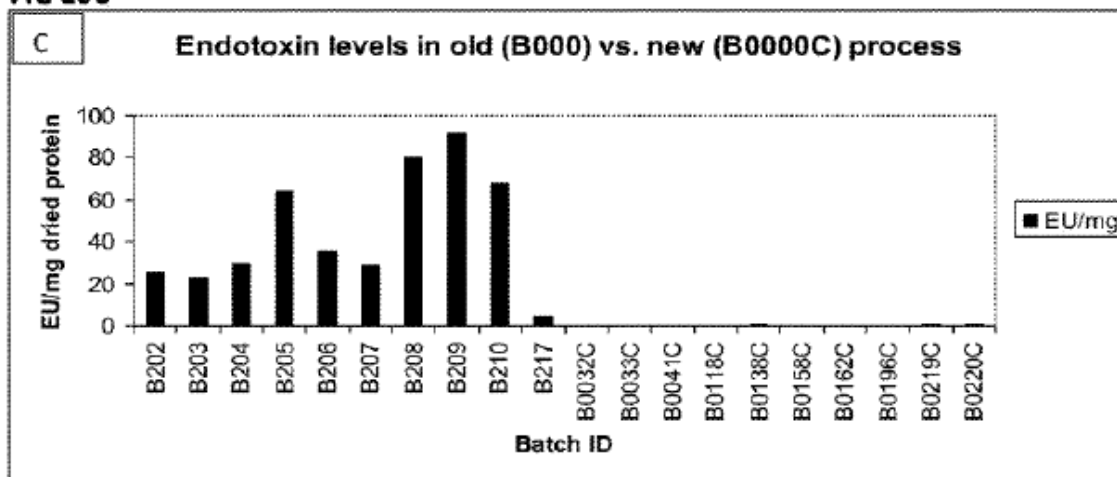
According to the '389 patent, “[r]e-engineering the old process to create the new process described in Example 5 [i.e., B0000C] resulted in significant changes in both overall product purity, and performance,” including “an average 100-fold less endotoxin, and 100[-]fold less detergent than the old process” as well as an “an average batch to batch 100 percent improvement in cell viability.” Ex. 1001, 73:39–67. Figure 10C of the '951

¹ EU stands for “endotoxin unit.” *See, e.g.*, Ex. 1003 ¶¶ 116, 157; Ex. 1027, 2, Ex. 1040, 544, Ex. 1042, 389. “Endotoxin Units, rather than units of weight, were developed by the U.S. Food and Drug Administration (FDA) for testing comparisons because the potency of an endotoxin for causing pyrogenic effects depends on a variety of factors.” Ex. 1027, 2.

² WO 2007/002762 A2, published January 4, 2007 (Ex. 1005) (“Deeter”).

patent is reproduced below and is a bar graph showing endotoxin levels in rHSA expressed in rice grain and purified using the “old (B000)” and “new (B0000C)” processes.

FIG 10C



The bars on the left side of Figure 10C depict endotoxin levels in batches prepared according to the old process. The average amount of endotoxin in these batches was about 45 EU/mg. *Id.* at 72–73 (Table E3). In contrast, the labels on the right side of Figure 10C, and the corresponding data in Table E4 of the ’389 patent, show that all of the batches of rHSA produced using the new process contain less than 1 EU endotoxin/mg of albumin. *Id.* at 73 (Table E4).

D. Challenged Claims

The Petition challenges claims 1–29. Claims 1, 24, and 26 are the only independent claims and are reproduced below:

1. A cell culture media supplement or complete media composition for improving the growth, viability, and/or productivity of cultured cells as compared to cells grown without said supplement or complete media composition, said cell culture media or complete media composition comprising a plant-produced heterologous protein, wherein said plant-

produced heterologous protein is recombinant human albumin, said recombinant human albumin comprising:

- i) less than 1 EU of endotoxin/mg of albumin; and
- ii) less than 10 ppm detergent.

24. A cell culture media supplement or complete media composition for improving growth, viability, and/or productivity of cultured cells as compared to cells grown without said supplement or complete media composition, said cell culture media or complete media composition comprising a plant-produced heterologous protein, wherein said plant-produced heterologous protein is recombinant human albumin, said recombinant human albumin comprising:

- (i) less than 1 EU of endotoxin/mg of albumin; and
- (ii) a monocot seed component, wherein said monocot seed component is a plant carbohydrate or plant lipid.

26. A cell culture media supplement or complete media composition for improving the growth of a cell in cell culture comprising:

a recombinant mammalian albumin wherein said albumin is:

- (i) produced in a transgenic plant; and
- (ii) has less than 1 EU of endotoxin/mg of albumin.

Ex. 1001, 123:47–57, 126:9–21, 126:24–31. As shown above, each of the independent claims recites a cell culture media supplement or complete media composition comprising rHSA, or another recombinant mammalian albumin (claim 26), that is plant-produced and “has less than 1 EU of endotoxin/mg of albumin” (the “endotoxin limitation”). All of the other claims challenged in the Petition are dependent claims and thus incorporate the endotoxin limitation from their respective independent claim.

E. Asserted Ground of Unpatentability

Petitioner asserts the following ground of unpatentability:

Claims Challenged	35 U.S.C. § ³	Reference(s)/Basis
1–29	103(a)	Hatsuyama, ⁴ Deeter, and the General Knowledge of a Person of Ordinary Skill in the Art (“POSA”) that Purified Proteins Should Contain Less than 10 ppm Detergent

Pet. 5. Petitioner further relies on the declaration of Douglas S. Clark, Ph.D. (Ex. 1003) submitted with the Petition.

III. ANALYSIS OF THE ASSERTED GROUND

A. Legal Standards

A claim is unpatentable for obviousness if, to one of ordinary skill in the pertinent art, “the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.” 35 U.S.C. § 103(a); *see also KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) when in evidence, objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

³ The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) (“AIA”), included revisions to 35 U.S.C. § 103 that became effective after the filing of the applications to which the ’389 patent claims priority. Therefore, we apply the pre-AIA version of § 103.

⁴ US 2007/0166825 A1, published July 19, 2007 (Ex. 1004) (“Hatsuyama”).

B. Level of Ordinary Skill in the Art

Petitioner contends that a person of ordinary skill in the art (POSA) “would have had a Ph.D. in chemistry, biochemistry, or chemical engineering, with at least two years of experience involving production and/or purification of proteins such as a rHSA and/or experience with compositions suitable for use in cell culture media.” Pet. 14. Patent Owner does not address Petitioner’s description of a POSA in its Preliminary Response. *See generally* Prelim. Resp.

We find that Petitioner’s description of the level of ordinary skill in the art is supported by the record. For purposes of this decision, we apply Petitioner’s description of a POSA.

C. Claim Construction

Neither party suggests that the issues presented in the Petition turn on claim construction. *See* Pet. 16 (noting the parties’ competing constructions in a related proceeding, but urging that the prior art discloses the limitations “[r]egardless of which interpretations are applied”); Prelim. Resp. 19 (“validity of the ’951 patent does not hinge on claim construction”). We agree that no formal claim construction is necessary for this decision. *Realtime Data, LLC v. Iancu*, 912 F.3d 1368, 1375 (Fed. Cir. 2019) (“The Board is required to construe ‘only those terms that . . . are in controversy, and only to the extent necessary to resolve the controversy.’”) (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

D. References Relied Upon

i. Hatsuyama

Hatsuyama was published July 19, 2007. Ex. 1004, code (43). Petitioner asserts, and Patent Owner does not dispute, that Hatsuyama qualifies as prior art under 35 U.S.C. § 102(b). Pet. 4.

Hatsuyama describes a serum-free medium comprising “recombinant human serum albumin.” Ex. 1004, Abstr. Hatsuyama states:

The recombinant human serum albumin (hereinafter abbreviated as rHSA as necessary) used in the present invention is not subject to limitation, as long as it has been prepared using gene recombination technology, for example, one that has been purified to a sufficient extent to permit its use as a pharmaceutical (injection) is preferred.

Id. ¶ 24. Hatsuyama explains that the rHSA is “produced by an HSA-producing host prepared via gene manipulation” and “preferably one prepared by culturing an rHSA-producing host by a known means, and then collecting and purifying the rHSA from the resulting culture filtrate or bacteria or cells by a known means of separation and purification.” *Id.* ¶ 25. According to Hatsuyama, “[t]ransgenic animals and transgenic plants can also be used.” *Id.*

In Reference Example 1, Hatsuyama describes rHSA prepared in “rHSA-producing yeast” that is cultured, recovered, and purified according to certain previously-described methods. Ex. 1004 ¶ 69 (referring to methods described in Japanese Patent Unexamined Publication Nos. HEI-5-317079 and HEI-8-116985). Hatsuyama reports properties for the rHSA produced according to these methods in Table 1, which is reproduced below.

TABLE 1

<u>Properties of Recombinant HSA (-comprising Composition)</u>	
Analytical item	Results
HPLC	Single peak of HSA monomer
Yeast-derived components	
(based on proteins)	less than 0.1 ng/mL
(based on polysaccharides)	less than 1 ng/mL
Molecular weight	Approx. 67000
Isoelectric point	Approx. 4.9
Degree of coloring (A_{350}/A_{280})	Approx. 0.015
(A_{450}/A_{280})	Approx. 0.01
(A_{500}/A_{280})	Approx. 0.002
Pyrogen	less than 0.5 EU (per 250 mg rHSA)

Id. ¶ 76. Table 1 above lists various properties of the yeast-derived rHSA in Reference Example 1, including a “Pyrogen” result of “less than 0.5 EU (per 250 mg rHSA).” *Id.*

In addition to a serum-free medium, Hatsuyama states that “[t]he composition of the present invention contains rHSA and a carrier,” which is preferably a “pharmaceutically acceptable carrier” used to prepare “a pharmaceutical composition in the form of an injection, liquid and the like.” Ex. 1004 ¶ 41; *see also id.* ¶¶ 42–43 (describing preparation and sterilization of “an injection”).

ii. Deeter

Deeter is a publication of a PCT application filed by Patent Owner on June 27, 2006, and published January 4, 2007. Ex. 1005, codes (22), (43). Petitioner asserts, and Patent Owner does not dispute, that Deeter qualifies as prior art under 35 U.S.C. § 102(b). Pet. 4.

Deeter describes “the production of components of cell culture media produced from plant cells and cell culture media comprising the same.” Ex. 1005, Abstr. Deeter explains that “[h]eterologous DNA comprising genes encoding the desired component are introduced into plant cells, especially rice, which then produce the desired component.” *Id.* “The component can be isolated from the plant cell and combined with other components to form the required cell culture medium.” *Id.*

Deeter provides examples describing rHSA produced from rice grain. Ex. 1005 ¶¶ 103–105, 116–120 (Examples 3, 7–9). Example 3 describes the transformation and generation of transgenic rice plants to express rHSA. *Id.* at ¶¶ 103–105. Example 7 describes a process for purifying that rHSA:

To purify rHSA from rice grain, rice grain expressing rHSA was dehusked, ground to flour and mixed for 30 min. with rHSA extraction buffer (Sodium Acetate, pH 4.9). After clarification by filtration, the filtrate was loaded onto an anion-exchange column (Q-Sepharose; GE Healthcare) at a rate of approximately 150 cm/hr. Once loaded, the resin was then washed with equilibration buffer to remove any unbound protein. The eluted rHSA is approximately 90% pure as analyzed by SDS-PAGE. BlueSepharose (GE Healthcare) can then be used to increase the purity from 90% to approximately 98% based on scanning analysis of SDS-PAGE gels.

Id. at ¶ 116.

Deeter describes “a range of biochemical and biophysical characterizations” comparing its purified rHSA to pHSA. Ex. 1005 ¶ 117 (Table 3). According to Deeter, “[t]hese tests indicate that rHSA expressed in rice is equivalent to pHSA.” *Id.*

Deeter also describes tests to determine the effectiveness of its purified rHSA “to stimulate cell growth.” Ex. 1005 ¶¶ 118–120. Deeter

reports that “cells grown in media with rHSA supplementation grew equivalently or better than cells grown in media with plasma derived HSA” and “grew much faster and reached a higher density in [common media] rHSA than in [common media] without any HSA.” *Id.* at ¶ 118; *see also id.* at ¶ 120 (reporting similar results for the serum-free media experiment in Example 9). According to Deeter, these tests “show[] that plant derived recombinant human serum albumin can promote cell growth” and “replace animal derived albumin for use in tissue culture.” *Id.* at ¶ 120.

E. Alleged Obviousness over Hatsuyama and Deeter

The only ground of unpatentability in the Petition is premised on modifying Hatsuyama’s cell medium composition to include Deeter’s rice-derived rHSA. *See* Pet. 3, 35–36. Petitioner explains that “Hatsuyama exemplifies its invention with rHSA expressed in yeast, while teaching that the rHSA for use in its cell culture medium may be expressed in transgenic plants.” *Id.* at 2. Petitioner articulates various reasons why, in its view, a POSA would have been motivated to use Deeter’s rice-derived rHSA instead of the yeast-derived rHSA exemplified in Hatsuyama and would have had a reasonable expectation of success in doing so. *Id.* at 35–37. Petitioner contends this combination teaches or suggests all of the limitations recited in independent claims 1, 24, and 26. *See id.* at 37–42, 57–58.

Because our decision turns on the sufficiency of Petitioner’s showing for the endotoxin limitation, we focus on that limitation and the parties’ arguments regarding the same. Petitioner presents the same showing for the endotoxin limitation in each of the independent claims. *See* Pet. 38–40 (analysis for claim 1), 57–58 (asserting claims 24 and 26 would have been

obvious for the same reasons). That is, Petitioner relies on: (1) Hatsuyama’s teaching of “the use of rHSA comprising only 0.002 EU endotoxin/mg albumin” as evidenced by the pyrogen result for Hatsuyama’s yeast-derived rHSA in Table 1⁵; and (2) Hatsuyama’s statement “that the rHSA for use in its cell culture media be ‘purified to a sufficient extent to permit its use as a pharmaceutical (injection),’ which Petitioner contends “necessarily requires far less than 1 EU endotoxin/mg albumin.”⁶ *Id.* at 38–39 (quoting Ex. 1004 ¶¶ 24, 76 (Table 1) and citing Ex. 1003 ¶¶ 159, 198–199). Based on these teachings, Petitioner contends:

a POSA would have been motivated to ensure that the plant-derived rHSA for use in Hatsuyama’s cell culture media had well below 1 EU endotoxin/mg albumin. A POSA would have appreciated the importance of avoiding and/or removing endotoxin contamination from cell culture media components such as rHSA, as the problems associated with endotoxin contamination in cell culture media were widely reported. *Supra*, § V.E.

Id. at 39–40 (citing Ex. 1003 ¶¶ 199–200, 202; Ex. 1004 ¶ 25).

⁵ Hatsuyama’s Table 1 states that the amount of “Pyrogen” in the exemplified rHSA was “less than 0.5 EU (per 250 mg rHSA).” Ex. 1004 ¶ 76 (Table 1). Petitioner’s analysis equates the amount of pyrogen with the amount of endotoxin. *See* Pet. 30 (stating that Hatsuyama exemplified its cell culture medium with “rHSA expressed in yeast having less than 0.5 EU endotoxin/250 mg rHSA”).

⁶ The Petition does not rely on any teaching in Hatsuyama regarding methods for purifying rHSA. *See* Pet. 38–40. Instead, Petitioner asserts that it would have been obvious to use “routine purification processes” not taught or exemplified in Hatsuyama, “e.g., by using a simple phase-separation using Triton that had proven extremely successful for [bovine serum albumin]” citing the testimony of Dr. Clark. *Id.* at 39–40 (citing Ex. 1003 ¶¶ 121–126, 140–154); *see also id.* at 17–18 (describing techniques).

Patent Owner disputes Petitioner's contentions, urging that Hatsuyama does not teach or suggest the endotoxin limitation. *Id.* at 39–42. According to Patent Owner, the data in “Hatsuyama’s Table 1 (which merely reports pyrogen levels for its yeast-derived rHSA) would [not] motivate the POSA to further reduce endotoxin levels in Deeter’s plant-derived rHSA,” since “Hatsuyama itself does **not** actually highlight or emphasize its pyrogen levels, indicate any particular protocol for reducing pyrogen levels to the reported values, or even provide any target threshold for pyrogen levels.” *Id.* at 39–40. Moreover, Patent Owner contends Petitioner’s argument that Hatsuyama teaches that the rHSA in its cell culture medium should be purified to an extent sufficient to use it as a pharmaceutical injection “is a mischaracterization of what Hatsuyama actually teaches.” *Id.* at 40–41 (internal quotations omitted). According to Patent Owner, “as is clear by the entire context, Hatsuyama teaches that in certain embodiments it contemplates using the rHSA ***in a pharmaceutical injection***, and ***those versions*** of the rHSA need to be sufficiently purified.” *Id.* at 41. However, urges Patent Owner, “[a]t no point does Hatsuyama teach or imply that rHSA ***to be used in cell culture media*** should have ***any*** particular pyrogen thresholds.” *Id.* For these reasons, Patent Owner argues that “nothing about the teachings of Hatsuyama would motivate a POSA to ensure that Deeter’s rHSA has any particular endotoxin levels for cell culture, let alone less than 1EU/mg albumin” as recited in the endotoxin limitation. *Id.* at 42 (internal quotations omitted).

Based on the record before us, Patent Owner has the better argument. As an initial matter, Petitioner’s reliance on the properties of the rHSA in Hatsuyama’s Table 1 is misplaced because that is not the rHSA

Petitioner relies upon for its asserted combination of references. The rHSA exemplified in Hatsuyama's Reference Example 1 and described in Table 1 is produced in and purified from yeast according to methods described in other publications not cited or relied upon in the Petition. Ex. 1004 ¶ 69. The Petition does not address those methodologies or suggest that it would have been obvious to employ them in combination with Deeter. Rather, Petitioner alleges that it would have been obvious to substitute the yeast-derived rHSA exemplified in Hatsuyama with Deeter's rHSA, which is produced in rice and purified according to a different process. *See* Ex. 1005 ¶¶ 116–117. Petitioner has not demonstrated that a POSA would have understood Deeter's rice-derived rHSA to have the same properties as the yeast-derived rHSA in Hatsuyama's Table 1. Indeed, the data in the Specification of the '389 patent shows that Deeter's rHSA had substantially higher levels of endotoxin than the rHSA in Hatsuyama's Table 1. *Compare* Ex. 1001, Fig. 10C (showing greater than 20 EU endotoxin levels in old (B000) process) *with* Ex. 1004, Table 1 (less than 0.5 EU); *see also* Ex. 2010 ¶¶ 4–8.

Petitioner's assertion that a POSA would have been motivated to further purify Deeter's rHSA based on the pyrogen result in Hatsuyama's Table 1 is unpersuasive. As Patent Owner points out, Table 1 merely reports properties of the yeast-derived rHSA in Reference Example 1; none of the paragraphs Petitioner cites in Hatsuyama highlight or specifically discuss any of those properties. *See* Prelim. Resp. 40. Indeed, other than reporting the pyrogen result in Table 1, Hatsuyama does not mention pyrogens or endotoxins, much less suggest that any particular level of such is desirable or preferred with the use of rHSA in a cell culture medium.

Moreover, we agree with Patent Owner that the statement Petitioner relies on from paragraph 24 of Hatsuyama pertains to the use of rHSA in a pharmaceutical injection rather than a cell culture medium. *See* Prelim. Resp. 41 (quoting Ex. 1004 ¶ 24). Hatsuyama describes several different embodiments, including a “serum-free medium containing rHSA” (*see* Ex. 1004 ¶¶ 34–40, 44–59) and a “pharmaceutical composition” that “contains rHSA and a carrier” (*id.* ¶¶ 41–43). The paragraphs describing the former consistently refer to the “serum-free medium” of the “present invention” and say nothing about the purity of the rHSA or its use in an injection. *See id.* ¶¶ 34–40, 44–59). In contrast, the only paragraphs describing rHSA in an injection or pharmaceutical composition do not refer to a serum-free medium. *See id.* ¶¶ 24, 41–43. Instead, these paragraphs describe a composition containing a carrier and other excipients that is used to prepare a sterile injection. *Id.* ¶¶ 41–43. Petitioner does not reconcile these distinctions, much less explain why a POSA would read Hatsuyama’s statement about the rHSA being sufficiently pure to permit its use as a pharmaceutical injection to apply to a cell culture medium that is not injected. Thus, Petitioner has not shown that Hatsuyama teaches or suggests that the rHSA used in its serum-free medium should be purified to an extent sufficient to permit its use as a pharmaceutical injection and the premise for Petitioner’s theory that Hatsuyama teaches a cell culture medium that meets the endotoxin limitation because “suitability for use as an injectable would necessarily require far less than 1 EU/mg rHSA given the FDA’s stringent requirements” has not been established. *See* Ex. 1003 ¶ 160.

Because the teachings Petitioner relies upon in Hatsuyama are inapposite, Petitioner has not sufficiently demonstrated that the prior art

cited in its ground teaches or suggests the endotoxin limitation. Indeed, it is undisputed that the other reference in the ground, Deeter, does not teach the endotoxin limitation. Petitioner's ground also includes the "General Knowledge of a POSA that Purified Proteins Should Contain Less than 10 ppm Detergent." Pet. 5, 33–34. But such knowledge pertains to the detergent limitation in claim 1, not the endotoxin limitation.

The other references cited in the Petition's background section do not fill this gap. *See* Pet. 13–17. For instance, Petitioner cites references it says show "that endotoxin contamination should be avoided in cell culture media, as endotoxins may contaminate a biological product of interest and/or otherwise complicate biological research." *See* Pet. 13–15. But endotoxin is derived from "the outer membrane of gram-negative bacteria such as *E-coli*." Ex. 1003 ¶ 97. And Deeter's rHSA was not produced in bacteria, had already undergone purification, and was reported to be "functionally equivalent to pHSA in enhancing . . . cell growth." *See* Ex. 1005 ¶¶ 116–120. As such, Petitioner has not sufficiently shown that further purification to remove endotoxin from Deeter's rHSA would have been obvious.

Petitioner's citation to other background references it contends show that it was known that endotoxins "may" contaminate recombinant proteins produced in plants is also unpersuasive. *See* Pet. 15–17. Some of the references Petitioner cites appear to support its contention. *See* Ex. 1038, 169 ("transgenic plant cell cultures in bioreactors have advantages over whole plants . . . including . . . reduced potential for endotoxin and mycotoxin contamination derived from the plant and soil source"); Ex. 1039, 90 ("since the processed plant or seed was probably grown in

dirt, or some similarly unclean stratum, one may anticipate the presence of a diverse bioburden”). Others, however, appear to say the opposite or undermine Petitioner’s argument by suggesting that additional purification to remove endotoxin is unnecessary for plant-derived proteins. *See* Ex. 1031, 206 (“All plant expression platforms, including whole plants . . . have safety benefits over microbial and animal cells . . . because they lack endotoxins produced by bacterial cells”); Ex. 1040, 545 (“small amounts of residual endotoxin will be removed easily during purification without dedicated removal protocols”); Ex. 1041 (“removal of endotoxins is unnecessary if the extraction and purification procedures are performed carefully”). In any event, even the references that arguably support Petitioner’s position merely suggest that endotoxin contamination was a possibility for plant-produced recombinant proteins. As Patent Owner points out, “nowhere can [Petitioner] point to any particular thresholds or endpoints” taught in these background references, nor does the Petition allege that any of these references teach the particular threshold recited in the endotoxin limitation. *See* Prelim. Resp. 40 n. 6.

For these reasons, we find that Petitioner has not met its burden with respect to the endotoxin limitation. Because that limitation is required by all of the challenged claims, Petitioner has not met its burden for any of the challenged claims.

IV. CONCLUSION

Based on the current record, Petitioner has not shown a reasonable likelihood of establishing that any of the challenged claims are unpatentable on any of the grounds in the Petition. Accordingly, institution of *inter partes* review is denied. Because we determine that Petitioner has not met the

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burden for institution on the merits, we do not reach Patent Owner's arguments for discretionary denial under 35 U.S.C. § 325(d).

V. ORDER

Accordingly, it is:

ORDERED that the Petition is denied, and no *inter partes* review is instituted.

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For PETITIONER:

Maximilienne Giannelli
Joshua Goldberg
Ningling Wang
Jessica L. Roberts
FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, LLP
Maximilienne.Giannelli@finnegan.com
Joshua.Goldberg@finnegan.com
Ningling.Wang@finnegan.com
Jessica.Roberts@finnegan.com

For PATENT OWNER:

Scott R. Brown
Crissa A. Cook
HOVEY WILLIAMS LLP
sbrown@hoveywilliams.com
ccook@hoveywilliams.com