

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

WUHAN HEALTHGEN BIOTECHNOLOGY CORP.,
Petitioner,

v.

VENTRIA BIOSCIENCE INC.,
Patent Owner.

IPR2022-00712
Patent 10,618,951 B1

Before JACQUELINE WRIGHT BONILLA, *Deputy Chief Administrative Patent Judge*, and 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 1–9 and 11–13 of U.S. Patent No. 10,618,951 B1 (Ex. 1001, “the ’951 patent”). Ventria Bioscience Incorporated (“Patent Owner” or “Ventria”) 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) and 314(a). *See* Prelim. Resp. 7–17. Patent Owner also challenges the merits of the grounds in the Petition. *Id.* at 17–50.

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. 61; Paper 5, 1.

B. *Related Matters*

Petitioner and Patent Owner identify the following matters involving the ’951 patent: *Ventria Bioscience Inc. v. Wuhan Healthgen Biotechnology Corp.*, DKS-5-21-cv-04008 (D. Kan.) and *Certain Plant-Derived Recombinant Human Serum Albumins (“rHSA”) and Products Containing Same*, U.S.I.T.C. Inv. No. 337-TA-1238 (“the ITC proceeding”). Pet. 62; Paper 5, 1.

C. The '951 Patent

The '951 patent issued on April 14, 2020, and is a continuation of an application filed on February 18, 2010. Ex. 1001, code (63).

The '951 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, 2:66–3:12.

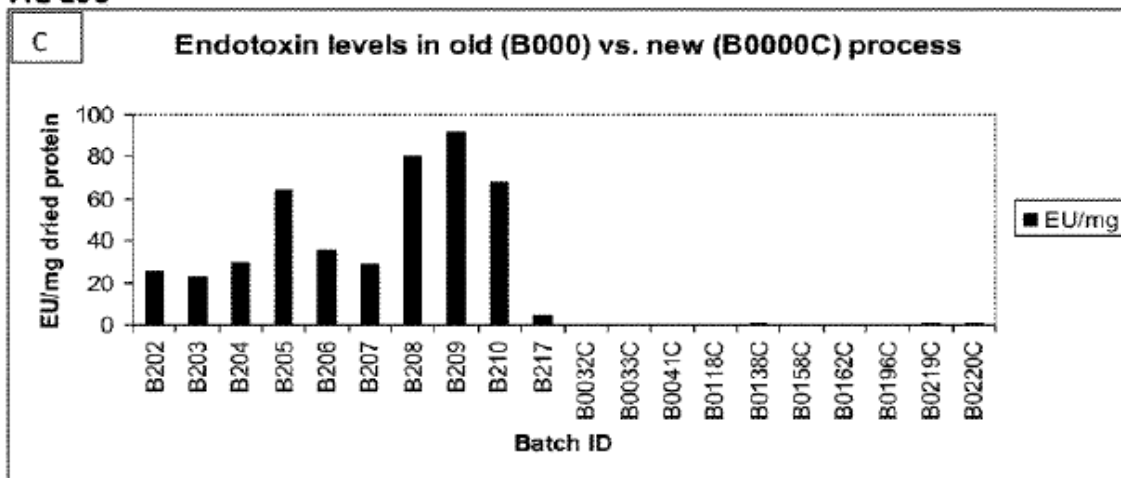
Albumin is a naturally-occurring protein that may be obtained from different sources. *See* Ex. 1002 ¶¶ 15, 18. For example, human serum albumin (“HSA”) may be derived from human plasma (“pHSA”) or it may be expressed as a recombinant protein (“rHSA”) in a host organism such as yeast or a plant. *See* Ex. 1001, 14:10–51 (describing comparisons of pHSA and 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 '951 patent describes a cell culture supplement comprising a recombinant albumin produced in a plant and having less than about 1 EU of endotoxin/mg of albumin and less than about 2% aggregated albumin. Ex. 1001, 4:62–5:2. This albumin is “expressed within a plant cell, and then purified from host cells proteins and lipids.” *Id.* at 26:14–17. The '951 patent explains that albumin may be purified using a variety of techniques. *Id.* at 50:1–12. In particular, the '951 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 13:65–67, 14:28–31, 65:54–69:22 (Ex. 5), 69:24–67 (Ex. 6). During prosecution, the Applicants explained that the old B000 process is the same process for

preparing purified rHSA described in Deeter,¹ a reference Petitioner relies upon in each of the four grounds in this proceeding. Ex. 1042, 693–94; *see also id.* at 699–701 (Declaration Under 37 C.F.R. 1.132 ¶¶ 4–8).

According to the '951 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 “improvement in cell viability.” *Id.* at 73:40–67. Figure 10C of the '951 patent is reproduced below and shows 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. Ex. 1001, 73 (Table E3). In contrast, the labels on the right side of Figure 10C, and the corresponding data in Table E4 of the '951 patent, show that all of the batches of rHSA produced using

¹ WO 2007/002762 A2, published January 4, 2007 (Ex. 1003) (“Deeter”).

the new process contain less than 1 EU endotoxin/mg of albumin. *Id.* at 73 (Table E4).

D. Challenged Claims

The Petition challenges claims 1–9 and 11–13. Claim 1 is the only independent claim and is representative for purposes of this decision. It reads as follows:

1. 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;
 - ii) has less than 1 EU of endotoxin/mg of albumin; and
 - iii) less than 2% aggregated albumin.

Ex. 1001, 123:46–53.

E. Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability:

Claim(s) Challenged	35 U.S.C. §²	Reference(s)/Basis
1–8, 11–13	103(a)	Deeter, Tanaka ³
9	103(a)	Deeter, Tanaka, Meng ⁴

² 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 ’951 patent claims priority. Therefore, we apply the pre-AIA version of § 103.

³ K. Tanaka *et al.*, “Purification of human albumin by the combination of the method of Cohn with liquid chromatography,” 31 Brazilian J. of Med. and Bio. Research 1383–88 (1998) (Ex. 1053) (“Tanaka”).

⁴ EP 2,177,602 B1, published April 21, 2010 (Ex. 1054) (“Meng”). Because this decision turns on Petitioner’s showing for claim 1 and Meng is only asserted for the additional limitations of dependent claim 9, we need not address the disclosure in Meng.

Claim(s) Challenged	35 U.S.C. § ²	Reference(s)/Basis
1–8, 11–13	103(a)	Deeter, Van Urk ⁵
9	103(a)	Deeter, Van Urk, Meng

Petitioner further relies on the declaration of Douglas S. Clark, Ph.D. (Ex. 1002) submitted with the Petition.

III. ANALYSIS OF THE ASSERTED GROUNDS

A. Legal Standards

A claim is unpatentable for obviousness if, to one of ordinary skill in the pertinent art, “the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains.” 35 U.S.C. § 103; *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).

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

⁵ PCT/GB00/00257, published August 3, 2000 (Ex. 1004) (“Van Urk”).

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.

We find that Petitioner’s description of the level of ordinary skill in the art is supported by the record. Thus, 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. Deeter

Deeter is a publication of a PCT application filed by Patent Owner on June 27, 2006, and published January 4, 2007. Ex. 1003, codes (22), (43). Petitioner asserts that Deeter qualifies as prior art under 35 U.S.C. § 102(b). Pet. 3. At this point in the proceeding, Patent Owner does not dispute that Deeter is prior art to the challenged claims.

Deeter describes “the production of components of cell culture media produced from plant cells and cell culture media comprising the same.” Ex. 1003, 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. 1003 ¶¶ 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 SOS-PAGE. BlueSepharose (GE Healthcare) can then be used to increase the purity from 90% to approximately 98% based on scanning analysis of SOS-PAGE gels.

Id. at ¶ 116.

Deeter describes “a range of biochemical and biophysical characterizations” comparing its purified rHSA to pHSA. Ex. 1003 ¶ 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. 1003 ¶¶ 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.

ii. Tanaka

Tanaka is an article from a scientific journal with a 1998 publication date on its face. Ex. 1053, 1. Petitioner asserts that Tanaka qualifies as prior art under 35 U.S.C. § 102(b). Pet. 3. At this point in the proceeding, Patent Owner does not dispute that Tanaka is prior art to the challenged claims.

Tanaka describes a method for purifying HSA from plasma. Ex. 1053, Abstr. Tanaka’s method involves a number of steps, including “[t]he use of two different processes in the chromatography step, i.e., ion-exchange on DEAE-Sepharose FF (Figure 2) and gel filtration on Sephacryl S-200 HR (Figure 3).” *Id.* at 5; *see also id.* at 2 (Figure 1 depicting a “[f]low diagram” of Tanaka’s purification method).⁶

Tanaka describes the results of tests conducted on pHSA purified according to this methodology. *See* Ex. 1053, 4. According to Tanaka, “[t]he tests carried out to determine *in vivo* pyrogenicity and toxicity yield

⁶ To be consistent with the citations in the parties’ papers, our citations to Tanaka refer to the page numbers added in the footer of Ex. 1053, rather than the page numbers of the original reference.

satisfactory results.” *Id.*; *see also id.* (Table 3 reporting “satisfactory” results of pyrogens). In its discussion of these results, Tanaka states that the use of its two processes in the chromatography step “resulted in a high quality, pyrogen-free product with a reduction of viruses . . . associated with the process of viral inactivation by pasteurization for 60°C for 10 h.” *Id.* at 5.

iii. Van Urk

Van Urk is a PCT application filed on January 31, 2000, and published August 3, 2000. Ex. 1004, codes (22), (43). Petitioner asserts that Van Urk qualifies as prior art under 35 U.S.C. § 102(b). Pet. 3. At this point in the proceeding, Patent Owner does not dispute that Van Urk is prior art to the challenged claims.

Van Urk describes “[a] process . . . for the preparation of a highly pure albumin solution[,] the process comprising subjecting albumin (preferably expressed and secreted by transformed yeast) to a series of chromatographic steps,” including ion-exchange chromatography. Ex. 1004, Abstr. Van Urk further states that its process may be used to purify albumin “produced using transgenic animals or plants.” *Id.* at 3.⁷

Van Urk’s examples describe a process for expressing and purifying rHSA from yeast. *See* Ex. 1004, 34–57 (Example 1). This process involves a series of chromatographic steps, which Van Urk characterizes as novel because they provide “increased yeast antigen clearance.” *Id.* at 45–46; *see also id.* 48, 51, 56 (describing removal of yeast proteins and antigens in various steps). In Example 10, Van Urk describes assays “on albumin which

⁷ Our citations to Van Urk refer to the page numbers added in the footer of Ex. 1004, rather than the page numbers at the top of the page.

has been purified according to Example 1 and formulated according to Example 9.” *Id.* at 65. According to Van Urk, “[n]o endotoxin was detected” in the assay conducted there. *Id.* at 74–75.

E. Grounds 1 and 2: Obviousness over Deeter and Tanaka

Grounds 1 and 2 rely on the combination of Tanaka’s purification processes with Deeter’s rice-derived rHSA. Because Petitioner’s argument for each of the claims in these grounds is premised on its showing for independent claim 1, we focus our analysis on claim 1.

Petitioner contends that it would have been obvious to purify Deeter’s rHSA, which is expressed in rice, “using the guidance of Tanaka” and that doing so would result in the composition of claim 1. *See* Pet. 17–20. More specifically, Petitioner asserts:

While Deeter’s rHSA would have been recognized as a beneficial alternative to traditional, animal-sourced albumin, it contained undesirable levels of endotoxin, which would have been readily detected and known to a skilled artisan. EX1002, ¶¶ 171-72; EX1030; EX1026, 292; EX1027, 1:49–52; EX1028, 261; EX1029, 3. Indeed, as acknowledged by [Patent Owner] during prosecution of the ’951 patent, “[t]he average endotoxin level in Deeter et al.-produced albumin was 44.97 EU/mg.” EX1042, 693–94 (emphasis in original); EX1042, 693 (identifying Deeter et al. as WO 2007/002762).

Pet. 35. According to Petitioner, “a POSA would have sought to reduce the endotoxin level in Deeter’s rHSA and would have looked to Tanaka for guidance, as Tanaka discloses a simplified process for purifying pHSA to provide albumin free of endotoxins.” *Id.*

Moreover, Petitioner contends that Tanaka teaches albumin containing “less than 1 EU endotoxin/mg of albumin” as recited in claim 1 because

Tanaka states that the pHSA produced by its process is “pyrogen-free,” which a “POSA would have understood means free of pyrogens including endotoxins.” Pet. 19 (quoting Ex. 1053, 5). Thus, urges Petitioner, “when purified using the guidance of Tanaka, Deeter’s rHSA would have been reasonably expected to contain less than 1 EU endotoxin/mg albumin.” *Id.*

Patent Owner contends that Petitioner’s argument for combining the references “ignores that Deeter already discloses purified rHSA, and yet fails to arrive at a plant-derived rHSA having the properties claimed.” Prelim. Resp. 30. According to Patent Owner, “the rHSA in Deeter is *purified* rHSA from a plant, which represented the best product specifications that Ventria was able to achieve at that time in plant-derived albumin.”⁸ *Id.* at 23. Patent Owner urges that “[g]iven that Deeter is *already purified*, [Petitioner] fails to prove why, given the general knowledge in the art, one of ordinary skill in the art would even look . . . to further reduce endotoxin and/or aggregated albumin in Deeter’s plant-based rHSA.” *Id.*

Patent Owner also contends that Deeter and Tanaka fail to teach the “less than 1 EU endotoxin/mg albumin” limitation of claim 1. Prelim Resp. 33–34. According to Patent Owner, the description of Tanaka’s pHSA as “pyrogen-free” is only “a shorthand for what is actually reported in the table of results. For pyrogens, that table’s specifications—the apparent targeted value for the characteristic listed—identifies only ‘satisfactory’ with the results matching that desired target: ‘satisfactory.’” *Id.* at 33. Patent Owner

⁸ This argument first appears in the section of the Preliminary Response addressing the merits of the grounds based on Deeter and Van Urk. Patent Owner cross-references the arguments in that section to explain why, in its view, the Deeter and Tanaka grounds are also deficient. *See* Prelim. Resp. 30–32.

contrasts this with the result for “polymers” in the table where “the result was reported as ‘not detected.’” *Id.* at 34. According to Patent Owner this “suggests *some* amount of pyrogen was detected” and therefore Petitioner has not shown that Tanaka, in fact, teaches a process for purifying albumin to have less than 1 EU endotoxin/mg albumin. *Id.*

Based on the record before us, Patent Owner has the better argument. Regarding the alleged motivation to combine Tanaka’s purification “guidance,” Petitioner has not articulated persuasive reasoning with rational underpinning to explain why a POSA would have sought to further purify Deeter’s rHSA. Deeter already teaches that its rHSA is purified using ion-exchange chromatography and reports that such rHSA is equivalent to or better than pHSA in stimulating cell growth. Ex. 1003 ¶¶ 116–120 (Examples 7–9). In view of these disclosures, Petitioner has not sufficiently explained why a POSA would be have been motivated to apply a different purification process or to add additional purification steps to Deeter’s existing process.

Petitioner’s obviousness position is premised on the notion that a POSA would have recognized that Deeter’s rHSA “contained undesirable levels of endotoxin.” But Petitioner’s support for this assertion is based primarily on data from the ’951 patent itself and arguments Patent Owner made regarding that data during prosecution to distinguish Deeter. *See* Pet. 35 (citing Ex. 1042, 693–94); *see also* Ex. 1002 ¶ 171 (Petitioner’s declarant referring to the same). Petitioner has not shown that this information, or other evidence suggesting that Deeter’s rHSA contained undersirable levels of endotoxin, was in the prior art. Indeed, during prosecution the Examiner reached the opposite conclusion when the Applicants presented the same

information from the '951 patent that Petitioner relies upon now, finding “that the levels of endotoxins in the culture medium *were not appreciated at the time of Deeter’s invention.*” Ex. 1042, 717 (Examiner’s Reasons for Allowance) (emphasis added).

Our reviewing court has long cautioned that “[c]are must be taken to avoid hindsight reasoning to avoid hindsight reconstruction by using ‘the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit.’” *In re NTP, Inc.*, 654 F.3d 1279, 1299 (Fed. Cir. 2011) (quoting *Grain Processing Corp. v. Am. Maize Prods. Co.*, 840 F.2d 902, 907 (Fed. Cir. 1988) and *Orthopedic Equip. Co. v. United States*; see also *Purdue Pharma L.P. v. Depomed, Inc.*, 643 Fed. Appx. 960, 966 (Fed. Cir. 2016) (“[t]o the extent [Petitioner] relies on the problem to be solved to supply the reason to combine the prior art, it failed to demonstrate to the Board that the problem was known in the art”). Here, however, the Petition relies on information from the challenged patent, and not the prior art, showing that Deeter’s rHSA had high endotoxin levels to guide the combination of references. This invites improper hindsight. Thus, Petitioner’s reliance on such information is misplaced.

Without the information from the '951 patent itself, Petitioner is left with a string-cite of exhibits, cited with no additional explanation, to support its argument that Deeter’s rHSA “contained undesirable levels of endotoxin, which would have been readily detected and known to a skilled artisan.” Pet. 35 (citing Ex. 1030; Ex. 1026, 292; Ex. 1027, 1:49–52; Ex. 1028, 261; Ex. 1029, 3.). Petitioner does not sufficiently explain how any of these exhibits

suggest that Deeter's purified rHSA contained undesirable levels of endotoxin.

At most, these references suggest that endotoxins may be harmful in certain contexts and teach that methods of testing for endotoxins were generally known in the art. For example, Exhibit 1026 states that endotoxins "must be removed from pharmaceutical products, biologicals for injection and some media for tissue cultures" and that "ion exchange resins are the most common depyrogenation method for proteins." Ex. 1026, 292.

Petitioner's other citations similarly evidence a desire to minimize endotoxins in biological products generally or discuss methods for detecting them.⁹ Such generalized teachings do not suggest that Deeter's rHSA contained undesirable levels of endotoxin, much less that a POSA would have been motivated to use Tanaka's process for preparing pHSA to further purify Deeter's rHSA. This is particularly so because Deeter's rHSA has already been purified using an ion-exchange resin and been shown to stimulate cell growth as well as or better than pHSA. *See* Ex. 1003 ¶¶ 116–120 (Examples 7–9).

The Petition also cites Dr. Clark's declaration, which states that "[g]iven Deeter's lack of description for use of sterile techniques, a person of ordinary skill would have recognized that endotoxins would be present in Deeter's rHSA." Ex. 1002 ¶ 172. This additional rationale is not clearly

⁹ *See* Ex. 1027, 1:42–52 ("The presence of endotoxins in biologically derived products (biologicals) prepared for therapeutic use is of major concern."); Ex. 1028, 261 ("Endotoxin contamination of cell culture . . . should be avoided"); Ex. 1029, 3 ("Endotoxin contamination of products should be minimized"); Ex. 1030 (discussing various "LAL test methods" for detecting endotoxins).

presented in the Petition itself. Even if it were, Dr. Clark’s testimony does not sufficiently address why a POSA would have expected undesirable levels of endotoxin to remain *after* undergoing the purification process taught in Deeter. Thus, it does not fill the gap in Petitioner’s rationale for combining the references. Because the Petition does not establish a sufficient motivation for combining the references, Petitioner has not met the burden for institution.

In addition, Petitioner has not sufficiently shown that Tanaka teaches the “less than 1 EU of endotoxin/mg of albumin” limitation of claim 1. Petitioner relies on Tanaka’s statement that its processes resulted in a “pyrogen-free product,” interpreting it to mean that Tanaka’s pHSA “contains no endotoxins.” Pet. 12; Ex. 1002 ¶ 61 (“A POSA would have understood that Tanaka’s ‘pyrogen-free’ albumin would be free of pyrogens, including endotoxin.”). Patent Owner presents a different interpretation, arguing that “pyrogen-free” is “shorthand” for the “satisfactory” pyrogenicity test results reported elsewhere in the reference. Prelim. Resp. 33–34.

Patent Owner’s interpretation is more persuasive. Tanaka teaches that the “tests carried out to determine *in vivo* pyrogenicity . . . yielded satisfactory results.” Ex. 1053, 4. This is consistent with the “characteristics of the final product” reported in Table 1 of Tanaka, which also state that the pyrogen test results were “satisfactory” and within specifications set forth in the Pharmacopée Européenne requiring a “satisfactory” level of pyrogens. *Id.* Tanaka’s later statement that its product is “pyrogen-free” is premised on those results. *Id.* at 5. Thus, we agree with Patent Owner that, when read in context of the entire reference, Tanaka’s statement that the product is

“pyrogen-free” means that it yields satisfactory results according to Tanaka’s tests and specifications.

Petitioner does not attempt to explain what a POSA would have understood a “satisfactory” result to mean within the context of Tanaka’s testing, or how such a result might relate to the “less than 1 EU of endotoxin/mg of albumin” recited in claim 1. As Patent Owner points out, the fact that Tanaka reports “not detected” for the polymers entry in Table 1, whereas the results reported for pyrogens are just “satisfactory,” suggests that some amount of pyrogens were detected in Tanaka’s pHSA. *See* Prelim. Resp. 34 (quoting Ex. 1053, 4). In addition, Table 1 refers to specifications in the “Pharmacopée Européenne.” Ex. 1053, 4, 6. Those specifications may shed light on the pyrogenicity testing and results in Tanaka. But neither Petitioner, nor Dr. Clark, address these issues. Instead, Petitioner premises the whole of its argument on its interpretation of “pyrogen-free,” which, as explained above, is unpersuasive because it does not take into account Tanaka’s other teachings. Thus, even if Petitioner had shown a sufficient rationale for combining the references, it has not sufficiently shown that combining the references would result in a product with less than 1 EU of endotoxin/mg of albumin.¹⁰

¹⁰ Petitioner contends that if the levels of endotoxin remained too high after utilizing Tanaka’s process “the rHSA could simply be run through either a fresh column or a larger column until the level of endotoxin was lowered to desired levels.” Pet. 40 (citing Ex. 1002 ¶ 188). As explained above however, Petitioner has not sufficiently shown that a POSA would have been motivated to apply Tanaka’s teachings to further purify Deeter’s rHSA. This is even more the case for Petitioner’s argument that even after combining the references a POSA would have been motivated to undertake still more purification steps.

For these reasons, we determine that Petitioner has not demonstrated a reasonable likelihood that it will succeed in showing that claim 1 is unpatentable over Deeter and Tanaka. Petitioner's showing for each of the other claims in grounds 1 and 2 relies on its showing for claim 1. Therefore, Petitioner's showing for these other claims does not meet the burden for institution for the same reasons explained above.

F. Grounds 3 and 4: Obviousness over Deeter and Van Urk

Petitioner's grounds 3 and 4 are similar to the first two grounds, but instead of Tanaka, these grounds rely on the combination of Van Urk's purification process with Deeter's rice-derived rHSA. As before, Petitioner's argument for each claim in these grounds is premised on its showing for claim 1 so we focus our analysis there.

Petitioner contends it would have been obvious to purify Deeter's rHSA, "using the guidance of Van Urk" and that doing so would result in the composition of claim 1. *See* Pet. 45–48. Petitioner argues a POSA would be motivated to combine the references because:

Deeter's rHSA . . . had an undesirably high level of endotoxin, which would have been detected by and known to a POSA. Accordingly, a POSA would have been motivated to reduce the endotoxin level in Deeter's rHSA and would have naturally looked to Van Urk for guidance, as Van Urk details a process for purifying rHSA, including rHSA produced in transgenic plants, to achieve a product with no detectable endotoxins.

Pet. 52 (citations omitted). Petitioner also asserts that Van Urk's process "provides rHSA beneficially containing up to 1% aggregated albumin," which is an "added benefit [that] would have further motivated a POSA to use the guidance of Van Urk to remove endotoxins from Deeter's rHSA." *Id.*

at 53.

As before, Patent Owner contends that Petitioner's motivation for combining the references is lacking because Deeter's rHSA is already purified. According to Patent Owner,

[Petitioner] points to a generalized statement by Van Urk purporting to suggest its applicability to plants; however . . . Van Urk in reality only has disclosure relating to its yeast system. Given that Deeter is *already purified*, Healthgen fails to prove why, given the general knowledge in the art, one of ordinary skill in the art would even look to a yeast-based expression system as the solution to further reduce endotoxin and/or aggregated albumin in Deeter's plant-based rHSA.

Prelim. Resp. 23.

Patent Owner further relies on testimony¹¹ and findings from the ITC proceeding that it contends show "there are vast differences between plant-derived and yeast-derived products such that a person of ordinary skill in the art, concerned with plant-derived recombinant proteins, would not consider Van Urk's purification steps, which are specific to yeast-derived impurities."

Prelim. Resp. 24 (quotations omitted); *see also id.* at 24–27 (citing Ex. 2002). According to Patent Owner,

[s]ince there are multiple platforms, expression strategies and extraction and purification processes which result in different outcomes depending on the methods used, a person of ordinary

¹¹ The testimony Patent Owner cites is sworn testimony from the parties' experts in a multi-day, evidentiary hearing that took place several months before the Petition was filed; it addresses the same asserted combination of Deeter and Van Urk against claim 1 of the '951 patent. The Petition does not mention this testimony, but Patent Owner provides a copy of the transcript from that proceeding in Exhibit 2002. Our citations to Exhibit 2002 herein refer to the page numbers added in the exhibit footer, rather than the page number at the top right corner of the page.

skill in the art would have understood that plant and yeast-derived rHSA are not interchangeable, and that any finding or technique used with yeast would not inform or read on plants.

Id. at 27 (quotations omitted).

Based on the record before us, Patent Owner has the better argument. Petitioner's rationale for combining the references again rests on its assertion that Deeter's rHSA "had an undesirably high level of endotoxin, which would have been detected by and known to a POSA." Pet. 52. Petitioner relies on the same showing to support that assertion that it does for the grounds based on Deeter and Tanaka. *Id.* (citing Ex. 1002 ¶ 244 (referring back to the testimony and exhibits cited in paragraphs 171–72)). For the same reasons explained above, this showing is also not persuasive for the grounds based on Deeter and Van Urk. *See supra* § III(E). Thus, Petitioner has not articulated sufficient reasoning with rational underpinning to explain why a POSA would have sought to further purify the rHSA taught in Deeter using the purification "guidance" described in Van Urk.

This is particularly so because, as Patent Owner points out, all of the specific guidance Van Urk provides relates to purifying rHSA expressed in yeast, which is markedly different from Deeter's rice-based rHSA. *See* Prelim. Resp. 23–27. Patent Owner identifies expert testimony from the ITC proceeding, explaining that there are numerous differences between Van Urk's yeast-based system and the transgenic rice taught in Deeter that result in "a different profile of impurities" that must be addressed in the downstream processing such that it "would not be suitable to apply one particular system to the other." Ex. 2002, 495:8–20, 538:1–24; *see also id.* at 492:21–500:19 (describing differences between Van Urk's yeast-based and Deeter's plant-based systems). The myriad differences Patent Owner

identifies reinforce our concern with the shortcomings in Petitioner's rationale for combining the references. Put differently, why would a POSA seek to apply guidance from a disparate yeast-based system to further purify Deeter's rice-derived rHSA when Deeter already teaches a purification process specific to its system that provides rHSA and shows that rHSA is effective for stimulating cell growth?

As explained above, Petitioner cannot rely on information in the '951 patent, but not present in the prior art, to answer this question because that would invite improper hindsight. *See supra* § III(E). And the other, more generalized evidence Petitioner cites is not persuasive, particularly when considered in context of the testimony Patent Owner cites from the ITC proceeding. *Id.*

Petitioner's argument that a POSA "would have [been] further motivated . . . to use the guidance of Van Urk to remove endotoxins from Deeter's rHSA" because Van Urk's process provides the "added benefit" of providing "rHSA beneficially containing up to 1% aggregated albumin" is also unpersuasive. *See* Pet. 53. First, this argument presumes that a POSA would be motivated to remove endotoxins from Deeter's rHSA, but Petitioner has not shown this to be the case. Second, even if a POSA were motivated to apply Van Urk's process for yeast to Deeter's rice-derived rHSA, Petitioner has not sufficiently shown that a POSA would have reasonably expected that this "added benefit" could be obtained given the myriad differences between these systems and their impurity profiles. *See* Ex. 2002, 495:8–20, 538:1–24. The brief explanation offered in the Petition does not address these issues. *See* Pet. 53, 55–56.

For these reasons, and based on the record before us, Petitioner has not demonstrated a sufficient rationale for combining Van Urk's purification guidance with Deeter's rHSA. Thus, Petitioner has not demonstrated a reasonable likelihood that it will succeed in showing that claim 1 is unpatentable over Deeter and Van Urk. Petitioner's showing for each of the other claims in grounds 3 and 4 relies on the showing for claim 1. Therefore, petitioner's showing for the other claims is deficient for the same reasons noted above.

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 burden for institution on the merits, we do not reach Patent Owner's arguments for discretionary denial under 35 U.S.C. §§ 314(a) and 325(b).

V. ORDER

Accordingly, it is:

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

IPR2022-00712
Patent 10,618,951 B1

For PETITIONER:

Maximilienne Giannelli
Timothy McAnulty
Ningling Wang
Jessica Roberts
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER LLP
maximilienne.giannelli@finnegan.com
timothy.mcanulty@finnegan.com
ningling.wang@finnegan.com
jessica.roberts@finnegan.com

For PATENT OWNER:

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