Filed on behalf of: Ventria Bioscience Inc.

Filed: July 14, 2023

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Wuhan Healthgen Biotechnology Corp.,
Petitioner,

v.

Ventria Bioscience Inc.,
Patent Owner.

Case IPR2023-00684
Patent No. 11,492,389

PATENT OWNER'S PRELIMINARY RESPONSE

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I. Introduction.

Healthgen's Petition should be denied under 35 U.S.C. § 325(d). Healthgen presents the same or substantially the same prior art and arguments that were previously presented to and rejected by: (1) the Patent Office during original prosecution of the present patent and its parent patents before the same Examiner, (2) the Board in a related IPR proceeding involving the parent patent, which it denied on the merits, and (3) the International Trade Commission ("ITC") and ALJ in an Investigation involving the parent patent. Notably, Healthgen elected **not** to appeal to the Federal Circuit the ITC's final determination that the parent patent is valid.

Multiple tribunals have been down this road before and reached the same conclusion—the subject matter at issue is inventive and patentable, and a person of ordinary skill in the art ("POSA") would have no motivation or reason to combine yeast-based expression systems with the plant-based expression system of Deeter, much less a reasonable expectation of success at arriving at the claimed subject matter.

In its Petition, Healthgen glosses over this history, saving it for the last handful of pages of its Petition. Further, Healthgen tries to reframe and re-characterize the references and substance considered by the Examiner, and all but ignores that the Board has already given ***thorough*** consideration to one of the ***same main***

references, Deeter, with respect to the ***same claim limitation(s)***, in denying its previous Petition on the parent patent. Healthgen also does not address the fact that the "new" prior art reference, Hatsuyama is at best ***cumulative*** in substance to the previously-considered Van Urk reference (or other yeast-based references in the record, including Berezenko). Moreover, Healthgen fails to meet its burden under *Advanced Bionics* to explain how the Office or the Board erred in a manner material to the consideration of the art and patentability of the claims.

Healthgen has had more than enough "bites at the apple" but continues to fall short of demonstrating that cell culture media or media supplements comprising ***plant-produced recombinant albumin*** having ***less than 1 EU of endotoxin/mg of albumin*** were known or obvious in the art. As discussed in more detail below, with respect to recombinantly-produced albumin, and the purification thereof to reduce endotoxin to levels of less than 1 EU of endotoxin/mg albumin, the only prior art that Healthgen presents relates to recombinant albumin produced in completely different systems, such as yeast or bacteria, or to purification systems for purifying albumin from completely different sources (such as yeast or bacteria culture, lab-created albumin solutions, blood, or plasma).

On the merits, Healthgen fails to demonstrate that a POSA would have any "apparent reason" to combine Hatsuyama and Deeter, and then rely on the purported "prior general knowledge" to further modify this proposed combination to achieve

the features of the claims in contravention to well-settled law. *E.g.*, *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418, 82 U.S.P.Q.2d 1385, 1396 (2007). Moreover, ***even if*** the person of skill in the art had a reason to combine these references, Healthgen's own references as well as prior testimony by its President and Founder, demonstrates that there could be no reasonable expectation of success in achieving the recited features of the claims, most notably, the recited level of less than 1 EU endotoxin/mg albumin. Accordingly, even though Healthgen now makes a ***third*** attempt to invalidate the inventive subject matter, Healthgen does not demonstrate a reasonable likelihood that any of the challenged claims of the '389 Patent are unpatentable on the merits, let alone the higher burden of demonstrating material error on behalf of the Examiner or the Board.

This is true despite the fact that Healthgen, in its repetitive Petition, has clearly attempted to use the "prior Board decision[] as a roadmap to correct past deficiencies." *In re Vivint Inc.*, 14 F.4th 1342, 1350 (Fed. Cir. 2021). The present Petition must fail.

II. Pertinent Factual History.

U.S. Patent No. 11,492,389 (the "'389 Patent") was filed on June 7, 2022. It is part of a family of patents with a shared priority chain, and is a continuation of parent patents U.S. Patent No. 10,981,974 (the "'974 Patent"), which issued from Serial No. 16/847,337, filed April 13, 2020, and U.S. Patent No. 10,618,951 (the

"'951 Patent"), which issued from Serial No. 15/188,478, filed June 21, 2016. The '951 Patent is a continuation of the original U.S. Serial No. 12/708,462, which was abandoned in favor of the '951 Patent filing. Notably, the '951 Patent is the subject of the following ongoing matters between Ventria and Wuhan Healthgen:

- *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"), on appeal to the Federal Circuit (*Wuhan Healthgen Biotechnology Corp. v. ITC, et al.* (Appeal No. 2023-1389).

At the ITC, Healthgen's invalidity arguments were premised, in part, on WO 2007/002762 to Deeter (EX1005, same reference cited here) and WO 2000/044772 to Van Urk (yeast-based system) on asserted grounds of both anticipation and/or obviousness[1]. (EX2011) Healthgen also relied upon expert testimony from its first expert, Dr. DeFilippi, as well as numerous other secondary and tertiary references relating to albumin and endotoxin. The ITC proceeding involved a five-day long evidentiary hearing on November 4-5, 2021, and November 8-10, 2021. (EX2001,

[1] Healthgen also relied on U.S. Patent No. 6,034,221 to Berezenko (EX2012), another yeast-based reference.

Page 15). The publicly available portion of the transcript recording the evidence of the evidentiary hearing is more than 700 pages, but the entire record of the evidentiary hearing constitutes more than 1400 pages. (*See, generally,* EX2002). Following that hearing, Judge McNamara concluded in her Final Initial Determination ("FID") that Healthgen failed to prove **any** asserted claims of the '951 invalid. (EX2001, Page 2).

Independent claim 1 of the '951 patent recites:

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:

iii) produced in a **transgenic plant**;

ii) has **less than 1 EU of endotoxin/mg of albumin**; and

iii) less than 2% aggregated albumin.

(EX2004, Page 85).

Dissatisfied with the FID's finding of infringement and no invalidity, on April 19, 2022, Healthgen sought review of the decision. (EX2003). On October 11, 2022, the Commission issued its public version of its opinion in which the validity of the '951 Patent was upheld in its entirety. (EX2005). Healthgen elected not to appeal the ITC's determination that the '951 Patent is valid over the same subject matter and certain references asserted here. (EX2013, Page 17).

The '951 Patent was also the subject of an IPR Petition filed by Healthgen (IPR2022-00712) on March 17, 2022. (EX2014). Healthgen's Petition challenged the validity of claims 1-8, and 11-13 of the '951 Patent on obviousness grounds premised upon combinations of Deeter and Van Urk as well as Deeter and Tanaka (which relates to purifying albumin from plasma). (*Id.* at 4). And for claim 9, Healthgen added the Meng reference to those combinations. (*Id.*). The Petition also relied upon a declaration by its new expert, Dr. Douglas S. Clark, and numerous tertiary references related to albumin and endotoxin.

In the meantime, Ventria filed a continuation application, which issued as the now-challenged '389 Patent. In its Information Disclosure Statement (IDS), Ventria provided the Examiner with copies of all of the prior art that had been cited against the '951 Patent, ***including the expert declaration of Dr. Douglas Clark***, which Healthgen had relied upon to support its Petition against the '951 Patent. Ventria also notified the Examiner of the pending IPR matter against the parent application. The IDS also included copies of the prior office actions in the parent matters as well as in related foreign matters. (EX1002, Pages 294-324). All of the applications in this family have been examined by the same two Examiners, involving numerous office actions and thorough consideration of the prior art, *infra*.

On August 19, 2022, the Board denied Wuhan Healthgen's petition ***on the merits***. (EX2015) ("Because we determine Petitioner has not met the burden for

institution of the merits, we do not reach Patent Owner's arguments for discretionary denial under 35 U.S.C. §§ 314(a) and 325(b).") Notably, the Board's discussion of the merits and decision focused on the **endotoxin level** recited in the '951 Patent claims as compared to the cited references, and provided only a minor comment related to the "aggregated albumin" limitation in one brief paragraph of the decision. (*Id.* at Page 21) In other words, the validity analysis did **not** depend on that feature of the '951 Patent claims, but rested on the demonstrated patentability of a recombinant albumin produced in a transgenic plant and having less than 1 EU endotoxin/mg albumin.

Ventria amended the present application to include an additional set of claims nearly identical to the '951 Patent claims, but without the "aggregated albumin" limitation. These claims correspond to claims 26-29 of the '389 Patent. (EX1002, EX2004).

III. Challenged Claims

The Petition challenges claims 1-29. Claims 1, 24, and 26 are the independent claims. Claim 1 reads as follows:

> 1. 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 supplement 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.

Claim 24 reads as follows:

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 supplement 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.

Claim 26 reads as follows:

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**.

IV. Asserted Ground of Unpatentability

In its Petition, Healthgen only identifies one ground of alleged unpatentability:

Ground	Combination	Basis	Claim(s)
1	Hatsuyama and Deeter and the General Knowledge of a POSA that Purified Proteins Should Contain Less than 10 ppm Detergent	35 U.S.C. § 103	1-29

(Paper 2, Page 5).

Specifically, Healthgen states:

> Petitioner challenges claims 1-29 of the '389 patent and requests that these claims be found unpatentable under 35 U.S.C. § 103 over Hatsuyama (EX1004) in view of Deeter (EX1005) and the prior general knowledge of a person of ordinary skill in the art ("POSA" or "skilled artisan") that purified proteins should preferably contain no more than 10 ppm detergent, as exemplified by Van Holten (EX1007), Schulz (EX1008), Viswanathan (EX1009), and Bonomo (EX1059).

(Paper 2, Page 4).

In its Introduction, it also expressly calls out that Hatsuyama is "Petitioner's primary prior art reference" while Deeter is "Petitioner's secondary prior art reference." (Paper 2, Page 2).

Healthgen's Petition must fail, because it again presents substantially the **same arguments** as those presented at the ITC and in the prior IPR Petition, relying on the **same substantive teachings** in the prior art including many of the exact **same references**. These are also the **same arguments and substantive teachings** in the prior art that were **before the Examiner** in ***numerous*** rounds of examination in the parent applications.

The issues at hand are not "new" merely because Healthgen has moved Deeter from the primary reference to the secondary reference. Further, as discussed in detail, *infra*, Healthgen's "new" primary reference, Hatsuyama, concerns a **yeast-based system** and presents **no** new substantive prior art information than what has ***already*** been considered by the Examiner (numerous times), the Board in the failed IPR, the ALJ during the ITC hearing, *and* by the Commission. Moreover, Healthgen appears to attempt to hide this fact by highlighting the "Less than 10 ppm Detergent" feature in their Identification of Challenge, since this feature is not recited in the '951 Patent claims. However, this overlooks the fact that neither independent claim 24 nor independent claim 26 recite a detergent limitation, even though they are included in the challenged claims.

Moreover, Healthgen attempts to obscure the ***actual shared features*** of each of the independent claims which have been found to be patentable over the prior art repeatedly by numerous tribunals, including the art and subject matter asserted here. Namely, that each of independent claims 1, 24, and 26 share the feature of recombinant mammalian or human albumin that is plant-produced or produced in a transgenic plant, and has less than 1 EU of endotoxin/mg of albumin.

As discussed in more detail below, the references cited by Healthgen are not new, substantively overlap with, and are at best cumulative of the issues already considered both by the Office, the ITC, and the Board, and fail to establish unpatentability of any of the challenged claims.

V. The Board Should Exercise its Discretion to Deny the Petition Under §325(d).

The institution of an *inter partes* review is a matter of the Board's discretion. "[T]he PTO is permitted, but never compelled, to institute an IPR proceeding." *Harmonic Inc. v. Avid Tech, Inc.*, 815 F.3d 1356, 1367 (Fed. Cir. 2016). Here, the Board should exercise its discretion under 35 U.S.C. § 325(d) to deny Healthgen's Petition because it simply recycles art, subject matter, and arguments from the prior prosecutions and failed Petition against the '951 Patent. All of Healthgen's prior art was either directly before the Examiner and/or the Board or is cumulative of the information already presented to and given due consideration by the Examiner

and/or the Board. Section 325(d) states that the Board should "take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. § 325(d)

Specifically, "under § 325(d), the Board uses the following two-part framework: (1) whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and (2) if either condition of first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims." *Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 8 (PTAB Feb. 13, 2020) (precedential).

Whether the same or substantially the same asserted art or argument was "previously presented to the Office" covers a broad range of proceedings, including examination of the underlying patent application, reexamination of the challenged patent, a reissue application for the challenged patent, and other AIA post-grant proceedings. *Advanced Bionics*, Paper 6 at 7-8, 10. The Board may also look at applications directly related to the challenged patent, such as a parent application. *Id.* at 10. Previously presented art also includes art cited by the Examiner and art provided to the Office by the Applicant (e.g., in an Information Disclosure

Statement). *Id. see also Weatherford U.S. v. Enventure Global Technology Inc.*, IPR2020-01661, Paper 19 (PTAB April 15, 2021).

A. The same or substantially the same asserted art or argument was previously presented to the Office.

According to *Advanced Bionics*, whether previously presented art or argument is "substantially the same" as that asserted in the Petition can be determined using factors (a), (b) and (d) set forth in *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (Dec. 15, 2017) (precedential as to § III.C.5, first paragraph). These factors are: (a) the similarities and material differences between the asserted art and the prior art involved during examination 1; (b) the cumulative nature of the asserted art and the prior art evaluated during examination; and (d) the extent of the overlap between the arguments made during examination and the manner in which petitioner relies on the prior art.

In the present case, Healthgen's only asserted ground of unpatentability rests on the combination of Hatsuyama and Deeter. As discussed in more detail below, Hatsuyama concerns yeast-derived rHSA, while Deeter concerns rice-derived rHSA. The ITC and the Board have ***already*** found that there would be no basis to combine yeast-based techniques with those of Deeter, and more specifically no basis to further purify the already purified rice-derived rHSA of Deeter using yeast-based techniques of Van Urk or Berezenko. "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?" (EX2015, Page 21) (Emphasis added).

i. Deeter Has Been Presented and Considered by the Office Numerous Times.

Deeter was considered by the Examiner in each of the parent cases through numerous office actions and in the present application[2]. Deeter is expressly

[2] Deeter has been considered over the course of **seven** office actions by two different Examiners. Deeter and Berezenko were first cited in the first office action, dated February 19, 2013, in the abandoned parent application Serial No. 12/708,462. (EX2006, Pages 1-12). The rejections were maintained in the second office action dated September 18, 2013. (EX2006, Pages 13-33). In the third office action, dated June 3, 2015, new grounds of rejection were raised involving Deeter and Berezenko with several new references and reference combinations, totaling four different grounds of rejection. (EX2006, Pages 34-55). The rejections were maintained in the fourth office action, dated December 21, 2015. (EX2006, Pages 56-81). These same four grounds of rejection were raised in the first office action in the prosecution history of the '951 patent. (EX2007, Pages 1-16). In the second office action, dated June 17, 2019, Berezenko was overcome, but Deeter was still asserted in combination with three other references. (EX2007, Pages 17-29). In the first office action for the '974 Patent, dated September 1, 2020, Deeter was asserted in combination with three references. (EX2008, Pages 1-12).

addressed by the Examiner in the Notice of Allowance for the '389 Patent, and is stated by the Examiner as the "closest prior art of record." (EX1002, Page 281). Deeter was also asserted by Healthgen in the ITC proceedings and likewise in its failed IPR Petition against the '951 Patent. As noted by the Board in its denial decision, "Deeter [is] a reference Petitioner relies upon in each of the four grounds in this proceeding." (EX2015, Page 4). The Board's denial decision also includes a thorough summary of Deeter on Pages 7-9. (*Id.*). On Pages 11-22, the Board analyzes the combination of Deeter with previously-asserted references Tanaka (purifying albumin from plasma) or Van Urk (purifying recombinant albumin from yeast). (EX2016, Pages 11-22) As noted by the Board on Page 13:

> 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 have been motivated to apply a different purification process or to add additional purification steps to Deeter's existing process.

(EX2015, Page 13).

Further, even after considering Dr. Clark's testimony, the Board found on Page 17:

> 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.

(*Id.*, at page 17).

The end of the above passage includes a footnote 10, which states:

> 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 [to reach the desired endotoxin levels].

(*Id*.).

With regard to combining Deeter with Van Urk, the Board's prior decision includes a likewise thorough analysis, concluding with:

> 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.

(*Id*. at Page 22).

In this Petition, Healthgen attempts to circumvent the matter by repackaging Deeter as the "secondary reference." However, this is unpersuasive as the ***substance***

for which Deeter is relied upon is ***identical*** to the substance asserted in the prior proceedings (namely that it teaches plant-produced recombinant albumin for use in cell culture). *See In re Mouttet*, 686 F.3d 1322, 1333 (Fed. Cir. 2012) (explaining that "where the relevant factual inquiries underlying an obviousness determination are otherwise clear, characterization by the examiner of prior art as 'primary' and 'secondary' is merely a matter of presentation with no legal significance."). In that regard, the Board has already determined combining yeast-based references like Hatsuyama with Deeter is unviable. (EX2015, Pages 20-21). This is now the ***third*** proceeding in which Healthgen has presented Deeter as a basis to invalidate claimed subject matter related to plant-produced recombinant albumin, in combination with non-plant-based references.

ii. Hatsuyama is Cumulative to the Previously Presented Van Urk, Tanaka, Berezenko, and Others

The fact that Deeter is relegated to "secondary" reference status, now combined with an allegedly "new" primary reference does not save Healthgen's Petition. Hatsuyama is "substantially the same" as art and arguments previously presented to the Office. *Advanced Bionics*, Paper 6 at 8. In particular, Hatsuyama concerns cell culture systems containing recombinant human serum albumin derived from a yeast-based expression system. Healthgen specifically asserts that "Hatsuyama exemplifies its invention with rHSA expressed ***in yeast***." (Paper 2, Page

2 (emphasis added)). Elsewhere in their Petition, Healthgen misleadingly refers to Hatsuyama in a way that suggests that it ***broadly*** teaches recombinant albumin from plants. However, it neglects to point out that the **only** mention of "plants" in Hatsuyama is in paragraph [0025], which is copied below in its entirety for context as follows:

> The rHSA is not subject to limitation, as long as it is an HSA produced by an ***HSA-producing host prepared via gene manipulation***, and it is preferably one substantially free from impurity components derived from the HSA-producing host (for example, proteins, polysaccharides and the like), more 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. **Transgenic animals and transgenic *plants* can also be utilized** (Japanese Patent Kohyo Publication Nos. HEI-9-509565 and HEI-10-504289). Specifically, the following methods can be mentioned.

(EX1004 (emphasis added)).

Again, this is the **only** mention of "plants" in the entire reference. Notably, the "mentioned" methods that are subsequently described in paragraphs [0026] et

seq. refer to various *in vitro* recombinant protein production techniques that involve host ***cells***, which are ***cultured*** *in vitro* to produce the recombinant protein into the cell culture media in which the engineered host ***cell*** is being grown (i.e., under controlled laboratory conditions or in closed bioreactor systems).

In particular, Hatsuyama refers to "microorganisms (for example, *Escherichia coli*, yeasts, *Bacillus subtilis* and the like), animal ***cells*** and the like that have been rendered rHSA-producing." (EX1004, Paragraph [0026] (emphasis added)). The subsequent paragraph explains that "Preparation of these rHSA-producing hosts, production of rHSA by ***culturing the hosts***, and separation and ***collection of rHSA from cultures*** can be performed by employing known methods or methods based thereon." (EX1004, Paragraph [0027]). What follows is a proposal of the process including description of media components and "culture conditions" (Paragraph [0028]), as well as "examples of the method of ***culturing an rHSA-producing host***" (Paragraph [0029]), and "how to isolate and purify the ***rHSA produced by culturing treatment*** from components derived from host ***cells***, culture components and the like" Paragraph [0030]. Thus, **just like Van Urk**, the detailed information all relates to *in vitro* expression systems and the working examples only exemplify **yeast-derived rHSA**, which the Board found to be a critical "shortcoming" of the teachings of Van Urk:

> 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.

(EX2015, Pages 20-21) (emphasis added).

Moreover, despite how Healthgen characterizes it, Hatsuyama is **not** actually concerned with purification *per se*. Rather, it only generally describes "conventionally used methods" for purifying rHSA expressed in cell culture (EX 1004, Paragraph [0030]), and makes mention of "Pyrogen" content in the rHSA **once** in Table 1 (Paragraph [0076]). In fact, Hatsuyama does **not** actually refer to "endotoxin" (or "toxin") anywhere in the reference, and all other references to "contaminants" are with respect to viruses and prions. (Paragraphs [0005], [0016], [0032], [0066], and [0132]).

Importantly, **at no point** does Hatsuyama describe methods relating to animals or plants themselves (as multicellular organisms) that have been rendered "rHSA-producing" or any techniques or methods for extracting, isolating, and then purifying rHSA ***from an animal or plant***.

In fact, this reference is arguably *worse* than the Van Urk reference the Board already considered. Specifically, the Board summarized Van Urk as follows:

> 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.

(EX2015, Page 10)(footnote omitted).

In other words, unlike Hatsuyama, Van Urk ***was*** expressly concerned with processes for "the preparation of a highly pure albumin." Van Urk actually included slightly "more" disclosure related to other expression systems, with five generic mentions of "plants" (as compared to Hatsuyama's single mention).

The relevant ***teachings*** of Van Urk are otherwise the ***same*** as Hatsuyama, as is Healthgen's ***purpose*** for reliance on these references. In its prior Petition,

Healthgen relied upon Van Urk as teaching use of rHSA ***in cell culture***, specifically stating at the top of Page 46 of their failed Petition:

> Van Urk similarly teaches that rHSA may be used "in cell culture." EX1004, 23:26-24:4 (disclosing that the "albumin of the present invention" may be used "in cell culture"); *id.*, 1:8-9 (disclosing that the term "albumin" refers to HAS and/or rHSA). Van Urk also acknowledges that albumin and rHSA are "used to supplement media used for growing higher eukaryotic cells." EX1004, 1:13-15.

(EX2014, Page 46).

Furthermore, the argument regarding the combination of Deeter and Hatsuyama is also the same as in the previous proceedings. In particular, in its failed Petition, Healthgen previously argued:

> A POSA would have reasonably expected that Deeter's rHSA when purified using the guidance of Van Urk would continue to be a cell culture media component, as removing endotoxins from Deeter's rHSA would have been expected to improve (or at a minimum not reduce) the effectiveness of Deeter's rHSA in cell culture given the toxic nature of endotoxins.

(*Id.,* at Page 46).

In particular, regarding the endotoxin limitation, Healthgen argued:

> Deeter's rHSA, as purified using the guidance of Van Urk, would have reasonably been expected to contain less than 1 EU endotoxin/mg albumin, as recited in claim 1 of the '951 patent.

(*Id.,* at Page 47).

> 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.

(*Id.,* at Page 52).

> A POSA would have reasonably expected that techniques to purify rHSA produced in transgenic yeast (the preferred embodiment of Van Urk) would also work to purify rHSA produced in transgenic rice (the rHSA of Deeter).

(*Id.,* at Page 53).

In its **present** Petition, Healthgen similarly argues:

> A POSA would have been motivated to modify Hatsuyama's cell culture media to include Deeter's rice-derived rHSA.

(Paper 2, Page 35).

> A POSA would have reasonably expected to successfully substitute Hatsuyama's rHSA (exemplified by yeast-derived rHSA) with Deeter's rice-derived rHSA, as Hatsuyama taught that its serum-free media could comprise rHSA from any host, including transgenic plants.

(*Id.,* at Page 37).

> Hatsuyama's cell culture media composition, as modified in view of Deeter, comprises "less than 1 EU endotoxin/mg albumin." EX1003, ¶¶ 197-202. In fact, Hatsuyama teaches the use of rHSA comprising only 0.002 EU endotoxin/mg albumin and further recommends that the rHSA for use in its cell culture media be "purified to a sufficient extent to permit its use a pharmaceutical (injection)," which necessarily requires far less than 1 EU endotoxin/mg albumin. EX1003, ¶¶ 159, 198-199; EX1004, [0024], Table 1 (below [0076]).\

(*Id.,* at Pages 38-39).

> Based on Hatsuyama's teachings, 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. EX1003, ¶¶ 199-200; EX1004, [0025]. 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 Page 39).

> As such, a POSA would have been motivated to modify Hatsuyama's cell culture media to comprise rHSA produced in transgenic rice that contained less than 1 EU endotoxin/mg albumin and would have had a reasonable expectation of success in doing so. EX1003, ¶ 202.

(*Id.,* at Page 40).

Thus, it is clear, ***from a comparison of Healthgen's own words***, that its current arguments about Hatsuyama are substantively identical to the failed arguments about Van Urk, and Hatsuyama does **not** offer anything new to the analysis, as the relevant teachings of Hatsuyama relating to yeast-derived rHSA, use in cell culture, and purification thereof to remove endotoxins, provide nothing more than (and in fact provides less than) what was taught in the previously-presented Van Urk reference. *See Dropworks, Inc. v. The University of Chicago*, IPR2021-00100, Paper 9 at 13-14 (PTAB May 14, 2021) (The teachings do not need to "be identical or entirely cumulative, only [] substantially same" and "relied on for the same proposition" as previously considered art, to satisfy the first prong of the A*dvanced Bionics* framework).

iii. Healthgen Uses Repeat and Cumulative Tertiary References for the Identical Purposes Previously Used In the Denied Petition

Healthgen has attempted to "pad" its Petition with numerous additional tertiary references couched as presenting "new" issues (and attempting to blatantly address deficiencies the Board highlighted in its prior decision). Healthgen's prior Petition employed the same, misguided approach they take here—i.e., relying on additional tertiary references, as well as Dr. Clark's testimony, to support alleged "well-established and routine" techniques for purifying rHSA that could be further applied to the cited references (Deeter, Van Urk, Tanaka) to achieve low endotoxin, if needed. (EX2014, Pages 53-58). Indeed, Healthgen's prior Petition already contained a lengthy explanation of techniques that were allegedly "widely used to remove endotoxins from proteins." (Id. at Pages 7-8). More specifically, Healthgen's prior Petition and Dr. Clark's prior testimony included ***express citation to and discussion of*** one of the main tertiary references also used in the present Petition, Aida:

> As another example, Aida discloses a simple process for removing endotoxin from bovine serum albumin (BSA). Aida explains that endotoxins may be removed by treating proteins with a detergent such as Triton X-114. Aida reported that the purified BSA had no detectable

> endotoxin. Aida explains that a "major advantage of the procedure was that it appeared not to harm the proteins." Aida suggests this process for removal of endotoxin from recombinant products and albumin.

(Id at Page 8)(citation omitted).

It is clear that the present Petition contains nothing more than recycled arguments and art Healthgen used unsuccessfully at the ITC and previously before the Board, namely that Deeter's rice-based rHSA expression system could be combined with non-rice-based rHSA systems (e.g., yeast) and purification methods to arrive at the claimed invention. This is underscored by the Board's own characterization of the Van Urk analysis in its prior decision denying institution:

> 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.

(EX2015, Page 18).

The ***same*** characterization could be made here, namely, that Healthgen's current ground is effectively identical to grounds 1-4 of its prior Petition, but instead of Tanaka or Van Urk, this ground relies on the combination of Hatsuyama's purified yeast-derived rHSA with Deeter's rice-derived rHSA.

As noted in the prior proceedings, the substance of Van Urk (along with numerous other yeast- or bacteria-based expression systems) was also before the

Examiner in the prosecution of the '951 Patent (and '974 Patent and abandoned parent application, Serial No. 12/708,462 (EX2006, EX2007, EX2008)), and was cited on the IDS in the present application (EX1002, Pages 294-324). Moreover, the IDS and references submitted for the Examiner's consideration ***in the present application*** also contained Aida along with Dr. Clark's original declaration (EX1002, Pages 321, 332).

In each of the prior proceedings, the Office (and the ITC) has determined that Deeter's rice-based expression system is **not** properly combinable with purification techniques for yeast-based systems (or other systems). Most recently, the Board concluded in its denial of the '951 petition:

> 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***….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?

(EX2015, Page 20-21)(emphasis added).

Hatsuyama is "new" in name only. It discloses the ***same relevant features*** and is being used for the ***same purpose*** as Van Urk and the other previously-considered yeast-based systems. Moreover, the additional references Healthgen now cites regarding purification of albumin from various non-plant sources add nothing more beyond what has already been considered, for example in Tanaka, or Aida. The "new" references also do not add anything or address the shortcomings expressly in the prior art identified by the Board, copied above.

Thus, the first prong of the *Advanced Bionics* framework is clearly met, because Healthgen has not shown any "significant and material differences between the prior art asserted in this Petition and the prior art evaluated during prosecution" or in the prior IPR proceeding. (*Advanced Bionics*, Page 16).

B. Healthgen Has Failed to Demonstrate the Office Made A Material Error In Its Prior Consideration of the Art and Arguments Presented Again.

Under *Advanced Bionics*, once it is determined that the same or substantially the same art or arguments were previously presented to the Office, then "factors (c),

(e), and (f) [of *Becton, Dickinson*] relate to whether the petitioner has demonstrated a material error by the Office." (*Id*. at Page 10).

Given the lengths Healthgen goes to in its Petition to obscure the overlap of the references and reframe the prior art arguments, it appears to recognize its difficult position. However, it fails to meet its burden to demonstrate that the Office made a "material error" in its prior consideration of the art or arguments.[3] In this scenario, the burden on the Petitioner is significant—simply presenting a different interpretation of previously presented art or repackaging the art as "primary" or "secondary" references is insufficient. Indeed, the Board in *Advanced Bionics* instructed that "[i]f 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." *Advanced Bionics*, Paper 6 at 9.

i. Healthgen fails to distinguish or explain material error in the Office's prior consideration of Van Urk.

Healthgen has failed to meet its burden to show a material error on the part of either the Examiner or the Board where the same or analogous/cumulative prior art was considered by the Examiner and the Board and found to be lacking. As an initial

[3] *Advanced Bionics*, Page 8 ("If the petitioner fails to show that the Office erred, the Director may exercise his discretion not to institute *inter partes* review.").

matter, Healthgen all but ignores the Board's prior decision and consideration of the prior art in the parent patent. With regard to errors by the Examiner, on Page 62, Healthgen makes the conclusory assertion that "Nor is Hatsuyama cumulative over the art of record during prosecution." (Paper 2, Page 62). It follows this statement with the disingenuous assertion:

> For example, Healthgen is unaware of any publication of record during prosecution of the '389 patent that teaches cell culture media comprising rHSA that may be expressed in a transgenic plant, where the rHSA used in the examples comprised 0.002 EU endotoxin/mg albumin,[4] and where the cell culture media comprising such rHSA provided superior results compared to comparable media comprising pHSA.

(*Id*.)

[4] Ventria also disagrees that Hatsuyama actually teaches "cell culture media comprising rHSA that may be expressed in a transgenic plant, where the rHSA used in the examples comprised 0.002 EU endotoxin/mg albumin." Rather, this characterization is based upon the purported ***combination*** of Deeter with Hatsuyama ***further*** modified using one of the tertiary references to reduce endotoxin levels.

Healthgen relies on Hatsuyama's yeast-based system but makes **no attempt** to distinguish Van Urk (also yeast-based system), which is conspicuously absent from its current Petition. And the above statement is, in spirit, entirely at odds with Healthgen's own prior characterization of Van Urk from its failed Petition, copied verbatim *supra* at Pages 22-23, which essentially asserts that "rHSA when purified using the guidance of Van Urk… would have been expected to improve… Deeter's rHSA in cell culture" (EX2014, Page 46) and "Van Urk details a process for purifying rHSA, including rHSA produced in transgenic plants, to achieve a product with no detectable endotoxins (*Id.* at Page 52)."

ii. Healthgen fails to explain material error in the Office's prior consideration of Deeter or the tertiary references.

Healthgen does acknowledge that Deeter was considered by the Examiner, but merely attempts to offer a different interpretation of the reference, which does not amount to "material error." *Advanced Bionics*, Paper 6 at 9. Healthgen also acknowledges that Aida was submitted for the Examiner's consideration, but argues that "the Examiner did not appreciate Aida's teachings." Page 63. Healthgen also attempts to assert that that "the Examiner did not have the benefit of Magalhaes's discussion of Aida's technique." Page 64. However, Healthgen omits that the Examiner **did** have the benefit of the declaration from its expert, Dr. Clark, and his

"discussion of Aida's technique," which was also submitted to the Examiner for consideration. (EX1002, Pages 321).

Finally, Healthgen attempts to confuse the issue by focusing on *additional* patentable claim limitations, such as arguing that the prosecution record did not include "any publications explaining the importance of removing detergent from proteins intended for use in cell culture media." Page 64. As discussed in more detail below, the record **did** include Aida and Dr. Clark's declaration, both of which addressed detergent to remove endotoxin and techniques for removing detergent (albeit in a context distinguishable from the claimed invention). Nonetheless, the detergent limitation provides an *additional* basis for patentability of claim 1, which the Board need not ever reach if patentability of the other limitations is acknowledged, as detergent is not even recited in independent claims 24 and 26.

Finally, Healthgen offers the conclusory assertion, without support, that "the claims of the '389 patent are much broader and rendered unpatentable by the prior art identified here" and then even expressly acknowledges "the prior art and arguments presented herein have addressed ***any pertinent issues identified by the Board in denying institution against the '951 patent***." (Paper 2, Page 65).

Thus, despite expressly using the prior Board decision as a roadmap to correct past deficiencies in the redundant presentation of the instant Petition, and despite the benefit of the voluminous record in the various proceedings, Healthgen is still unable

to identify anything but cumulative references and even further, fails to demonstrate that the Office made a material error in its prior consideration of the recycled art and arguments. Such gamesmanship should doom the petition. See *In re Vivint Inc.*, 14 F.4th 1342, 1350 (Fed. Cir. 2021).

Thus, the Board should exercise its discretion to deny the Petition under §325(d).

VI. Institution Should be Denied on the Merits.

A. Claim Construction

Validity of the '389 Patent does not hinge on claim construction. That is, regardless of which constructions are applied, the prior art fails to disclose each claim limitation individually or in the manner or combination claimed, and further Healthgen fails to establish that a POSA would be motivated to combine the references with a reasonable expectation of success in achieving the claimed invention.

B. Healthgen Fails to Establish Deeter's Rice-Based Expression System is Combinable with Non-Plant Based Systems.

To succeed on its invalidity claim based upon the combination of Deeter and Hatsuyama, Healthgen must establish that a person of ordinary skill in the art would have been motivated to combine these references and reasonably expect success in

achieving the claimed invention. *Personal Web Techs. LLC v. Apple, Inc.*, 848 F.3d 987, 993 (Fed. Cir. 2017). Healthgen cannot meet this burden.

As noted above, Healthgen clearly uses the Board's previous denial to craft their current Petition. The first thirty pages are devoted almost exclusively to attempting to establish the state of the art and explain how or why the POSA would "know" to reduce the endotoxin (or detergent levels) in Deeter to the recited levels. This appears to be in direct response to comments by the Board, including "Petitioner has not articulated persuasive reasoning with rational underpinning to explain why a POSA would have sought to further purify Deeter's rHSA." (EX2015, Page 13).

Nevertheless, Healthgen still fails to establish a critical missing link that was fatal to its previous Petition and is fatal here—Healthgen's Petition fails to address and overcome the findings in various proceedings that Deeter's rice-based expression system is **not** properly combinable with yeast-based systems (or other non-plant systems). "In view of these disclosures, Petitioner has not sufficiently explained why a POSA would be[*sic*] have been motivated to apply a different purification process or to add additional purification steps to Deeter's existing process." (EX2015, Page13). In the present Petition, Healthgen still fails to sufficiently explain why a POSA would have been motivated to apply a different

purification process or to add additional purification steps to Deeter's existing process, because the prior art simply does not support such an assertion.

D. Healthgen Fails to Establish Why a POSA Would Be Motivated to Combine Hatsuyama and Deeter or a Reasonable Expectation of Success in Doing So.

Deeter is directed to a *plant*-derived rHSA, whereas Hatsuyama concerns purification of *yeast*-derived rHSA (i.e., not a transgenic *plant*). (EX1004). Hatsuyama exemplifies rHSA produced in yeast which is reported to have low "pyrogen" content. EX1004, [0076], Table 1. In its Petition, Healthgen tries to reframe the combination of Deeter with the yeast-based system from Hatsuyama (instead of Van Urk) by arguing that it would be obvious to modify Hatsuyama's cell culture media to include Deeter's rice-derived rHSA in place of Hatsuyama's yeast-derived rHSA. (Paper 2, Page 35). Healthgen argues that the POSA would be motivated to make this modification because it would have been a "simple substitution, well within the ordinary level of skill." (*Id.* at Page 36). Healthgen proposes that Deeter's rice-derived rHSA would be an "advantageous replacement for yeast-derived rHSA" for example because it would be a more "cost-effective option" due to high yields from rice, and that "Deeter's plant-derived rHSA could be further developed and/or optimized to promote the growth of a wide range of cell types." (*Id.* at Page 36). Healthgen argues that there would be a reasonable

expectation of success in making this substitution because it would be a "simple substitution, as Deeter enabled the production of rHSA in transgenic rice." (*Id.* at Page 37).

However, Healthgen's assertion of unpatentability must fail with respect to each of independent claims 1, 24, and 26 for several reasons.

i. Healthgen Fails to Establish How or Why a POSA Would be Motivated to Reduce Endotoxin Levels in Deeter Based on Hatsuyama.

Each of independent claims 1, 24, and 26 recite a cell culture media supplement or complete media composition. Each of independent claims 1, 24, and 26 also share the feature of recombinant mammalian or human albumin that is plant-produced or produced in a transgenic plant, and has less than 1 EU of endotoxin/mg of albumin.

While Deeter itself concerns a ***purified*** rHSA from rice, Ventria has submitted evidence, data, and expert testimony, both during prosecution and during the ITC proceedings, to establish that the purified plant-derived rHSA disclosed in Deeter did **not** have less than 1 EU of endotoxin/mg of albumin. Indeed, the '389 patent includes directly comparative data (e.g., Tables E3 and E4 (EX1001, at 60)) complete with Batch Numbers and ***dates*** comparing the rHSA from the time of Deeter with the improved, inventive, and purified rHSA developed via the '389

patent (and showing unequivocally that ***plant-derived rHSA at the time of Deeter did not come close to the recited levels of endotoxin***).

This data was explained by way of a technical declaration by Dr. Lorne Jordan, one of Ventria's scientists. (EX2010). This "old process" represented the best product specifications that Ventria was able to achieve at the time of Deeter in plant-derived albumin and, as explained by Dr. Jordan, was used for comparison testing in the '389 Patent[5].

Given Ventria's expertise specifically with plant-produced proteins, its own **actual** data, **complete with Batch Numbers and dates**, which is part of the ***intrinsic record***, is strong evidence of what would have been actually "reasonably expected" at the time of the invention. It does **not** suffer the biases inherent in Healthgen's hindsight-inspired outcomes proffered by their hired expert for the purposes of the dispute.

[5] The predecessor rice-derived rHSA of Deeter and the rice-derived rHSA that is exemplified in the '951 patent fall under Ventria's brand name "Cellastim." For clarity, the previous versions of this product are sometimes referred to in the ITC record as "old" Cellastim and the improved versions of the product are referred to as "new" Cellastim.

Despite this, Healthgen argues on Page 39 that "[b]ased on Hatsuyama's teachings, 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."

ii. Hatsuyama Does Not Teach Less than 1 EU endotoxin/mg albumin of Albumin for Cell Culture Media.

Healthgen cannot point to any particular teachings in Hatsuyama that would teach a POSA ***how*** to reduce endotoxin levels ***from a plant-derived rHSA*** below 1 EU/mg albumin.

As an initial matter, it's not clear whether Hatsuyama's Table 1 (which merely reports pyrogen levels for its yeast-derived rHSA) would, in fact, motivate the POSA to further reduce endotoxin levels in ***Deeter's*** plant-derived rHSA, especially given that Deeter ***already*** teaches that its rHSA outperforms other albumins in cell culture. (EX2015, Page 15 ("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.")). This is further underscored by the fact that 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.[6] It merely reports the pyrogen levels in Table 1:

TABLE 1

Properties of Recombinant HSA (-comprising Composition)

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)

(EX1004, Page 8).

The only "teaching" Healthgen cites to in Hatsuyama to support its alleged motivation to reduce endotoxin is paragraph [0024]. In particular, Healthgen asserts:

> Consistent with this low level of endotoxin contamination, Hatsuyama teaches that rHSA included in cell culture media should preferably be "purified to a sufficient extent to permit its use as a pharmaceutical

[6] Indeed, in the numerous general references that Healthgen relies on in Section E, beginning on page 13, to argue it was known to remove endotoxins specifically in cell culture, nowhere can Healthgen point to any particular thresholds or endpoints, only that endotoxins should be "minimized" or at the "lowest possible levels". (Paper 2, Pages 13-15, cited to a handful of references).

> (injection)" (id., [0024]), which necessarily requires far less than 1 EU endotoxin/mg albumin. EX1003, ¶ 160; EX1057, 22; EX1043, 5-6.

(Paper 2, Pages 30-31).

However, a review of Paragraph [0024] reveals that this is a mischaracterization of what Hatsuyama actually "teaches." That is, Hatsuyama does **not** teach that rHSA to be used "in cell culture" should be purified to such levels. For clarity and context, the entirety of Paragraph [0024] is copied below:

> 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.

(EX1004) (emphasis added).

In other words, 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.

At no point does Hatsuyama teach or imply that rHSA ***to be used in cell culture media*** should have ***any*** particular pyrogen thresholds. And, as noted above, Hatsuyama contains far more mentions of concerns about virus or prion

contamination, than other components (and again, seemingly only in the context of embodiments it plans to use as injections).

iii. A Person of Skill in the Art Would Not be Motivated to Further Purify Deeter's rHSA for use in Hatsuyama.

As the Board previously questioned, "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?" (EX2015, Page 21). Healthgen has not explained, nor (as explained above) does Hatsuyama provide any details or guidance for how or why any particular purification process should be applied to Deeter's rice-derived rHSA. As noted above, 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 1 EU/mg albumin.

Moreover, the POSA would immediately recognize that subjecting Deeter's rice-derived rHSA to ***additional*** purification directly undercuts Healthgen's arguments about it being a "cost-effective" alternative to yeast-derived rHSA, as the

additional processing will necessarily increase the time and cost to produce, as evidenced by Healthgen's own reference[7].

Even if, **after** making the hypothetical "substitution" of Deeter's rHSA in Hatsuyama's cell culture, a POSA wanted to further reduce the endotoxin levels to the levels reported in Hatsuyama, Healthgen can point to **no** pertinent references that relate to purifying albumin (which has particular nuanced properties) ***from a plant expression system*** to remove endotoxins. The best Healthgen can point to are conclusory assertions about "routine purification processes" and an alleged general knowledge or desire to reduce endotoxins. (Paper 2, Page 39).

Again, myriad general references about endotoxin removal were ***already*** in front of and given due consideration by the Examiner and the Board previously. (EX2015, Pages 14-15, referring to Healthgen's prior "string-cite of exhibits" that "evidence a desire to minimize endotoxins in biological products generally or discuss methods for detecting them."). For example, Healthgen's prior Petition pointed to Matejtschuk (EX1019, also cited here), which is an article surveying the

[7] See Fischer, Molecular Farming (EX1031, Page 300 ("The costs for these measures can easily double production costs and should be included in the cost calculations of molecular farming when compared with classical fermentation.")).

state of the art in albumin purification and endotoxin removal. Healthgen's position here fares no better.

Healthgen's explanation of routine processing is misplaced. That is, its arguments rely almost exclusively on Dr. Clark's testimony, which in turn relies on a variety of references containing conflicting teachings. For example, with respect to trying to tie various protein processes to ***plant-based systems***, Dr. Clark's testimony relies heavily on Fischer, Molecular Farming (EX1031). However, a brief review of this reference for its teachings related to purifying proteins from plant systems and in particular, obtaining ***low endotoxin levels***, reveals a **fatal flaw** in the overall technical arguments premised on this reference. In particular, Page 206 of Fischer states:

> All plant expression platforms, including ***whole plants*** and cell/tissue culture systems, also have ***safety benefits over microbial and animal cells***. This is because they ***lack the endotoxins*** produced by bacterial cells and they do not harbor human pathogens.

(EX2031) (emphasis added).

Notably, this is the ***only*** mention of "endotoxin" as it relates to plant-produced proteins in the entire 300+ Page reference. This reference does **not** otherwise propose any particular measures that are needed or should be taken to reduce

endotoxins in plant-produced proteins, as it seems to assume endotoxins are a low risk in plant-based systems.

On its face, this teaching directly contradicts Dr. Clark's own current and prior testimony about the "ubiquitous" nature of endotoxins. EX1003, Pages 43, 46. It also directly contradicts his testimony of the "known" and "expected" contamination by endotoxin when dealing with proteins produced in plants. EX1003, Page 49. For example, in paragraph 114 on Page 49, Dr. Clark expressly states, "I note that while aseptic suspension cultures of plant cells in a bioreactor had a relatively low risk of endotoxin contamination, it was understood that the same was not true for plants grown in dirt." (EX1003). Likewise, Dr. Clark's declaration includes an ***entire section*** entitled "Endotoxin Contamination of rHSA Expressed in Transgenic Rice (as in Deeter) Was Not Unexpected." EX1003, Page 119. On its face, Dr. Clark's testimony is directly contradictory to the teachings about endotoxins and plant-based protein production systems from Healthgen's own main reference related to plant-based systems.

The arguments by Healthgen in terms of what the POSA would "know" or "expect" with respect to plant-produced proteins and endotoxins cannot be reconciled with the references and testimony it proffers. Healthgen's arguments suffer the same deficiencies outlined by the Board in its prior denial on Pages 15-16. (EX2015).

iv. Healthgen Has Failed to Establish a Reasonable Expectation of Success in Achieving Less than 1 EU Endotoxin/mg Albumin in the Proposed Combination of Hatsuyama and Deeter.

In sections J and K on Pages 22-25 of its Petition, Healthgen tries to overcome the deficiencies and conflicting information in the cited references by arguing that the underlying proteins from the various albumin sources are the same, and thus, the "purification techniques that work for one of these albumins would also be expected to work for another." (Paper 2, Page 25).

Indeed, Healthgen's argument for "expectation of success" hinges on the alleged similarities in the ***protein*** itself. In doing so, Healthgen appears to argue that the expression system or source does **not** matter, but what matters is the protein itself. Again, despite citing to Fischer, such a position directly contradicts nearly the entirety of the Fischer reference, which spends most of its 300 Pages highlighting why plant-based expression systems are different and better from other systems. Nevertheless, Healthgen asserts that what matters are the similarities of the protein itself, stating on Page 40:

> A POSA would have reasonably expected that a technique that worked for BSA would also work for Deeter's rHSA, as Deeter's rHSA had physicochemical properties equivalent to pHSA, and pHSA has strikingly similar properties to BSA.

(Paper 2, at 40).

This is because the references submitted by Healthgen that provide any specific teachings on purification processes to remove endotoxin, all relate to purifying albumin (or other proteins) from a variety of different sources or systems, ***none of which relate to plant expression systems***. In particular, the main references relied upon by Dr. Clark in his discussion are Aida (EX1044) and Magalhães (EX1042).

Again, Healthgen's reliance on Aida is misleading. In its arguments, it refers generically to Aida's teaching with regard to "albumin" in an attempt to equate it with recombinant albumin, and fails to accurately characterize what's described in this reference, namely that it concerns ***commercially-available bovine serum albumin*** (BSA) from a chemical supplier, Sigma. (EX1044, Page 1). Aida teaches that the BSA (or other tested commercially-available proteins) are then dissolved in a standard buffer solution, phosphate buffered saline (PBS). (EX1044, Page 2). Thus, Aida does **not** concern removal of endotoxin from a complex mixture of proteins extracted from a transgenic plant source (or any transgenic expression system for that matter). Instead, it concerns a laboratory-created mixture of BSA in PBS. Thus, while Healthgen may assert that Aida's process using Triton X-114 was "simple to perform" (Paper 2, Page 18), the underlying solution on which the extraction was performed was likewise a simple solution of BSA dissolved in PBS.

As such, Aida provides limited insight to the POSA regarding purifying recombinant protein from transgenic expression systems, such as plants.

Further, while Healthgen later argues that the Examiner did not appreciate Aida because he "did not have the benefit of Magalhaes's discussion of Aida's technique," (Page 64), Healthgen fails to appreciate the entirety of the context of the discussion of Aida in Magalhães, and further also fails to appreciate the entirety of Aida itself, not just the section cherry-picked for its argument.

Again, Aida concerns experiments run on a lab-created solution of commercial BSA in PBS (and not recombinant albumin produced in a plant). While Aida does relate to exploring detergent to remove endotoxin from this simple solution, in the lower righthand corner of Page 4, Aida reports information that a POSA would find directly relevant to the use of such purified albumin in cell culture: "The major disadvantage of the procedure reported here is that a small amount of detergent (0.018%) persisted in the aqueous phase. Because of this residual detergent, ***the aqueous phase [containing the albumin] could be harmful to living cells***." (EX1044 (emphasis added)).

Aida then goes on to expressly state on Page 5 that "Residual detergent could be removed by absorption on Bio-Beads SM-4 or by gel filtration on Bio-Gel P-300. However, a substantial amount of protein might be absorbed on the SM-4 beads, and dilution of proteins unavoidably occurred in the gel filtration method." (EX1044).

In fact, earlier, with respect to the BSA tested, Aida expressly states that "15%" of the BSA "was also absorbed by the treatment with SM-4." Page 5. Magalhães itself directly discusses the shortcomings of Aida, noting that their "process leads to 15-20% product loss." (EX1042, Page 10). Again, these outcomes cut directly against all the "motivation" proffered by Healthgen that a POSA would substitute Hatsuyama's yeast-derived rHSA with Deeter's rice-derived rHSA for "cost" purposes, and then ***further*** subject the rice-derived rHSA to additional processing. Healthgen's own reference demonstrates that this is **not** what a POSA would be motivated to do.

More importantly, the POSA would not have a reasonable expectation of success in this modified combination of Hatsuyama and Deeter. In particular, Magalhães states in its Abstract that "it is essential to remove endotoxins ***from drugs, injectables, and other biological and pharmaceutical products***." (EX1042 Abstract). Again, like Hatsuyama itself, the main concern in Magalhães related to endotoxins relates to their presence in "drugs" or "injectables" to be used in patients, and not on their impact in cell culture media.

Healthgen and Dr. Clark cite to this reference (and Aida) to argue that a "POSA would have considered the removal of endotoxin from a solution of rHSA routine based on the teachings of at least Aida (EX1044) and Magalhaes (EX1042)." (EX1003, Page 117). Even if that statement were taken as true, it still does **not**

establish that a POSA would have considered removal of endotoxin from ***recombinantly*** produced albumin, produced in a transgenic ***plant***, related to cell culture media or supplements, to have been routine (or even needed[8]). Nor does it teach the POSA how to apply this information to a complex expression system to remove endotoxin from recombinant albumin produced in a plant. Neither Aida (which relates to BSA in PBS) nor Magalhães changes that conclusion.

Magalhães is a review of various approaches for removal of endotoxins. Notably, this reference makes **no** mention of plant-based systems. Further, its discussion of "recombinant" proteins is limited to those produced in ***bacterial*** systems. It doesn't even describe yeast systems, like Hatsuyama. Moreover, the particular micellar system given "special attention" in Magalhães and highlighted by Dr. Clark, concerns "using Triton X-114 to remove endotoxins present ***in fermented culture of E. coli cells*** during the production of protein." As Magalhães explains, "Many recombinant proteins are produced by the Gram-negative bacteria *Escherichia coli*. These products are always contaminated with endotoxins [because it's a component of Gram-negative cell membranes]." (EX1042, Page 2).

In his declaration, Dr. Clark relies on Aida and Magalhães to show various "known" ways to use detergent to achieve various "x-fold" reductions in endotoxin (include "1000-fold" reduction). However, this is **not** useful information unless you

[8] See Fischer *supra* teaching that plant expression systems "lack endotoxins."

know the starting point of endotoxin and also the various other components of the composition from which it is being removed. Again, removing endotoxin from Aida's lab-created mixture of a commercially-obtained BSA mixed in PBS provides little instruction to the POSA trying to extract, isolate, and purify recombinantly produced mammalian albumin from a transgenic plant.

This is underscored by the other teachings in Magalhães which are overlooked by Healthgen and Dr. Clark. Indeed, the rest of Magalhães describes various purification methods using the exemplified Triton X-114 on Pages 10 and 11 with final endotoxin contents falling in a wide range. For example, Magalhães teaches "[u]sing Triton X-114, Adam et al. (1995) (108) showed a ***100-fold*** endotoxin reduction in two steps with a **final endotoxin content of 30 EU mg^{-1}** and 50% loss in bioactivity of the exopolysaccharide." (EX1042, Page 10 (emphasis added)). Likewise, other studies are disclosed in Magalhães that result in "reducing endotoxin content by 98-99% with remaining amounts of 1.5-25 EU mg^{-1}, depending on the protein." (EX1042, Page 10 (emphasis added)). Elsewhere on Page 11, Magalhães discusses a study where "purified recombinant proteins treated with Triton X-114 contained concentrations as low as 0.2 to 4 EU mg^{-1}." (EX1042). Again, none of the "recombinant" systems mentioned by Magalhães relate to plant-based expression systems (or even yeast), but are specific to ***bacterial*** expression systems.

This variety of outcomes reported by Magalhães, if nothing else, suggests that while there may have been a desire to reduce endotoxin levels as a general concept, the reasonable expectation of being able to reach specific thresholds for any particular type of protein and from a variety of sources was anything but "expected." In fact, Magalhães draws this for its "CONCLUSIONS":

> Efficient and cost-effective removal of endotoxins from pharmaceutical and biotechnology preparations is challenging. Despite development of novel methods, such as the two-phase aqueous micellar systems, in recent years, more research is needed in this field.

(EX1042, Page 1).

Notably, for its Summary of the "two-phase aqueous micellar systems" which was highlighted in paragraph 125 of Dr. Clark's testimony (EX1003), Magalhães states these are "valuable tools for endotoxin removal from ***pharmaceutical proteins on a small scale***." (EX1042, Page 1). Again, the POSA recognizes that reference to pharmaceutical proteins refers to pharmaceutical products, which are not equated to products for cell culture media or supplements.

Thus, this "overview" provided by the various tertiary references relied upon by Healthgen actually ***supports*** the conclusion that it cannot be said there'd be any reasonable ***expectation*** of success in achieving less than 1 EU endotoxin/mg

albumin in Deeter's rice-derived rHSA, ***even if*** applying "routine" purification processes.

Again, because it cannot find any prior art on point, Healthgen's position tries to obscure that the difficulty in purifying a protein is extracting and separating it ***from the underlying source***. Thus, the source in which the protein is contained is of paramount importance. As established by the experts in the ITC and acknowledged previously by the Board, this was recognized in the industry and is further underscored by the survey and overview articles cited above which unequivocally show disparate outcomes depending on the protein being purified and the source from which it is being purified. "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.'" (EX2015, Pages 19-20).

In fact, Daichang Yang, *Healthgen's President*, authored a book chapter "discussing the challenges associated with developing downstream processing techniques (e.g., purification) for the recovery of rHSA." (EX2001, at 95). Mr. Yang's own book chapter is consistent with Ventria's position that there "is no 'one-size-fits all approach' for developing downstream processes (e.g., purification

methods) for recombinant proteins." (EX2001, at 95 (citing EX2002, at 523-24, 1056:6-1057:2)). Since 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 skill in the art "would have understood that plant and yeast-derived rHSA are not interchangeable, and that **any given finding or technique used with yeast would <u>not</u> inform or read upon plants**." (EX2001, at 95, citing EX2002, at 538, 1071:1-24 (emphasis added)); *see also id.* at 112-15, 151:22-154:23).

Healthgen has to resort to its tenuous arguments because it simply cannot demonstrate by evidence or testimony that it was known to or that there would be a reasonable expectation of success for reducing endotoxin to less than 1 EU/mg albumin from a ***plant-derived rHSA***.

Again, Healthgen's "evidence" purporting to show the obviousness of further purifying Deeter to meet Hatsuyama's endotoxin levels all relate to albumin from other sources, including entirely artificially-created lab solutions, or relate to other types of proteins. The extreme dissimilarity of the source from which the albumin is extracted and purified cannot be ignored. It is appropriate for the Board to find, once again, that "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." (EX2015, Page 15).

Thus, Deeter's plant-based system is not combinable or informed by the likes of Hatsuyama's yeast-based purification process and Healthgen's obviousness grounds based upon the combination of Deeter and Hatsuyama must fail.

iv. "Less than 10 ppm detergent"

Regarding detergent, as noted above, the '389 Patent contains comparative data demonstrating that the improved rHSA has reduced levels of endotoxin, without undue detergent levels (e.g., Tables E3 and E4 (EX1001, at 60-61)). The data and development process was described by Dr. Jordan in his technical declaration submitted during prosecution. This comparative data, complete with dates and Batch numbers, has been directly considered by the Examiner in the parent '974 and '951 patents and also mentioned by the Examiner in the Notice of Allowance of the '389 Patent. (EX1002, Page 281). Hindsight interpretation cannot override this plain direct comparative data showing the product properties Ventria achieved at the time of Deeter, as compared to those endotoxin and detergent levels it achieved via the invention of the '389 Patent. Moreover, as noted above, Aida itself teaches that while detergent is useful for removing endotoxin, it introduces a new variable that is detrimental to cells (residual detergent). (EX1044, Page 4). Thus, while the detergent limitation in claim 1 provides an ***additional*** basis for patentability, the patentability of claim 1 does not hinge on this feature.

Healthgen's focus on the recited detergent levels and "new" prior art related thereto is meant to distract from the analysis, especially since neither of independent claims 24 and 26 recite detergent levels.

v. "a monocot seed component, wherein said monocot seed component is a plant carbohydrate or plant lipid"

Independent claim 24 is similar to claim 1, but instead of reciting a detergent limitation, it recites "a monocot seed component, wherein said monocot seed component is a plant carbohydrate or plant lipid." The premise of Healthgen's proposed combination is to substitute Deeter's rice-derived rHSA for Hatsuyama's yeast-derived rHSA, but also then ***further*** subject the product to purification to reduce endotoxin levels to the pyrogen levels disclosed in Hatsuyama. Since it cannot find a prior art reference describing purification from plant systems, Healthgen has no reasonable basis for asserting that such ***additional*** processing would **not** impact other factors of the extracted material, which are unique to plant-expressions systems, such as the monocot seed components, carbohydrates and lipids. In its Petition, Healthgen relies on an odd line of reasoning from Dr. Clark's testimony set forth in paragraph 249, essentially arguing because the "prior art" (allegedly) teaches that proteins "retain their normal function" after phase separation and detergent removal, "POSA would not have expected albumin to retain its normal functions if all bound fatty acids had been removed." In other words, Dr. Clark seems

to assert that Deeter's albumin allegedly retains its normal function and thus must retain bound fatty acids.

However, this line of reasoning ignores that the hypothetical combination proposed by Healthgen is **not** merely Deeter and Hatsuyama. Rather, the hypothetical combination relied on by Healthgen is Deeter and Hatsuyama, as ***further*** modified to reduce the endotoxin levels in Deeter. Thus, whether Deeter teaches that its albumin retains its normal function is irrelevant, because that does not necessarily mean a ***further*** purified or modified version of Deeter's albumin using a purification process other than that of Deeter (as required by Healthgen's combination) would likewise retain such function. Moreover, neither Dr. Clark nor the prior art provide any support to draw any reasonable conclusions about the fate of monocot seed components after subjecting Deeter's albumin to further purification to significantly decrease the endotoxin levels to the levels claimed.

Dr. Clark relies heavily on Peters (EX1013), which is a lengthy Book "All about Albumin." Notably, Peters' discussion of recombinant technology focuses on yeast and bacteria, and in particular on the Delta Biotechnologies yeast technology (the Assignee of Van Urk and Berezenko). (EX1013, Pages 317-319). Regarding plants, Peters only states briefly that prior attempts to express albumin in plants "carried the same burden" of the protein needing to be "extracted under denaturing conditions." (EX1013, Page 317). It otherwise focuses on albumin from human or

animal sources through the rest of its several hundred Pages. Peters provides no information whatsoever about plant carbohydrates or plant lipids, or any other monocot seed components. Moreover, the lengthy discussion cited by Dr. Clark related to fatty acids is specific to those that "circulate in plasma." Page 100. Thus, again, as with the endotoxin removal, Healthgen's position relies on entirely in apropos references that do **not** provide the POSA with any pertinent teachings related to extraction or purification of recombinant albumin from a plant to yield an rHSA with low endotoxin, while, for example, retaining other plant-related components. While the "monocot seed component" in claim 24 provides an ***additional*** basis for patentability, the patentability of claim 24 does not hinge on this feature.

vi. Claims 26-29

As a final matter, Ventria notes that claims 26-29 are identical to the previously-challenged claims from the '951 Patent, except omitting the "aggregated albumin" limitation. A review of the Board's decision (along with the prior ITC decisions, EX2001, EX2005) shows that this feature was not necessary for Ventria to establish patentability of these claims (EX2015).

VII. Conclusion

For at least the reasons set forth above, the Board should deny institution of Healthgen's Petition. The Petition fails on the merits, as Healthgen does not establish

a reasonable likelihood of prevailing as to any challenged claims. Further, the Board should exercise its discretion to deny institution because the cited art, subject matter, and arguments are substantially the same as already given due consideration in prior proceedings.

Respectfully submitted,

Dated: July 14, 2023

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Certificate of Word Count Compliance

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that this *Patent Owner Preliminary Response* complies with the type-volume limits of 37 C.F.R. § 42.24(a)(1)(i) by virtue of 37 C.F.R.§ 42.24(b)(1), because it contains 12,200 words, according to the word-processing system used to prepare this paper, excluding the words in the Table of Contents, Table of Authorities, Certification Under § 42.24(d), and Certificate of Service, as set forth in 37 C.F.R. § 42.24(a)(1).

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I certify that on this 14th day of July, 2023, a true and correct copy of the foregoing **Patent Owner's Preliminary Response** was served by electronic mail on Petitioner's lead and backup counsel at the following email addresses:

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