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 No. IPR2023-00684

Patent No. 11,492,389

Petition for *Inter Partes* Review

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1002	Prosecution History of U.S. Patent No. 11,492,389 (excerpted to exclude prior art publications included therein)
1003	Declaration of Douglas S. Clark, Ph.D.
1004	U.S. Patent Publication No. 2007/0166825 ("Hatsuyama")
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1007	U.S. Patent Publication No. 2006/0110399 ("Van Holten")
1008	U.S. Patent Publication No. 2006/0194300 A1 ("Schulz")
1009	U.S. Patent Publication No. 2006/0008792 A1 ("Viswanathan")
1010	Jayme et al., "Basal Medium Development for Serum-Free Culture: a Historical Perspective," *Cytotechnology*, 23:95-101 (1997) ("Jaymne")
1011	Castilho et al., "Animal Cell Technology: From Biopharmaceuticals to Gene Therapy," (Castilho, Moraes, Augusto, and Butler, Eds.) (New York, Taylor & Francis Group, 2008) ("Castilho")
1012	Glassy et al., "Serum-Free Media in Hybridoma Culture and Monoclonal Antibody Production," *Biotechnology and Bioengineering*, vol. 32, 1015-1028 (1988) ("Glassy")
1013	Peters, T., "All About Albumin [subtitled:] Biochemistry, Genetics, and Medical Applications," (Peters, T., Ed.) (New York, Academic Press, 1996) ("Peters")

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1014	Dockal et al., "The Three Recombinant Domains of Human Serum Albumin," *The Journal of Biological Chemistry*, vol. 274, no. 41, 29303-29310 (1999) ("Dockal")
1015	Simard et al., "Locating High-Affinity Fatty Acid-Binding Sites on Albumin by X-Ray Crystallography and NMR Spectroscopy," *Proceedings of the Nat'l Acad. of Sci.*, vol. 102, no. 50, 17958=17963 (2005) ("Simard")
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1018	K. Griebenow and A.M. Klibanov, "Lyophilization-Induced Reversible Changes in the Secondary Structure of Proteins," *Proc. Nat'l Acad. Sci. USA*, vol. 92, 10969-10976 (Nov. 1995) ("Griebenow and Klibanov")
1019	P. Matejtschuk, et al., "Production of Human Albumin Solution: a Continually Developing Colloid," *Br. J. Anaesth.*, vol. 85, 887-95 (2000) ("Matejtschuk")
1020	J. Brandt and L-O Anderson, "Heat Denaturation of Human Serum Albumin. Migration of Bound Fatty Acids," *Int. J. Peptide Protein Res.*, vol. 8, 33-37 (1976) ("Brandt and Anderson")
1021	F. Garcia-Gonzalo et a., "Albumin-Associated Lipids Regulate Human Embryonic Stem Cell Self-Renewal," *PLoS One*, (2008), Issue 1, e1384 ("Garcia-Gonzalo")
1022	Jurgens et al., "Investigation into the Interaction of Recombinant Human Serum Albumin with Re-lipopolysaccharide and Lipid A," *J. of Endotoxin Research*, vol. 8, no. 2, 115-126 (2002) ("Jurgens")

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1023	David et al., "Characterization of the Interaction of Lipid A and Lipopolysaccharide with Human Serum Albumin: Implications for an Endotoxin Carrier Function for Albumin," *J. of Endotoxin Research*, vol. 2, 99-106 (1995) ("David")
1024	U.S. Patent No. 7,304,208 titled "Expression of Human Serum Albumin (HSA) in Monocot Seeds"
1025	Schenerman et al., "Characterization of Alternatives to Animal-Derived Raw Materials [subtitle:] 'Animal-Free' May Not Mean 'Problem Free,'" *BioProcess Technical*, 42-47 (Sept. 2003) ("Schenerman")
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1033	Kusnadi et al., "Production of Recombinant Proteins in Transgenic Plants: Practical Considerations," *Biotechnology and Bioengineering*, vol. 56, no. 5, 473-484 (Dec. 5, 1997) ("Kusnadi")

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1034	Sijmons et al., "Production of Correctly Processed Human Serum Albumin in Transgenic Plants," *Biotechnology*, vol. 8, 217-221 (March 1990) ("Sijmons")
1035	Farran et al., "Targeted Expression of Human Serum Albumin in Potato Tubers," *Transgenic Res.*, vol. 11, 337-346 (2002) ("Farran")
1036	Huang et al., "Production of Human Serum Albumin by Sugar Starvation Induced Promoter and Rice Cell Culture," *Transgenic Res.*, vol. 14, 569-581 (2005) ("Huang")
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1039	Larrick et al., "Production of Secretory IgA Antibodies in Plants," *Biomolecular Eng'r*, vol. 18, 87-94 (2001) ("Larrick")
1040	Brereton et al., "Single Chain Antibody Fragments for Ocular Use Produced at High Levels in a Commercial Wheat Variety," *J. of Biotechnology*, vol. 129, 539-546 (2009) ("Brereton")
1041	Fujiwara et al., "Extraction and Purification of Human Interleukin-10 from Transgenic Rice Seeds," *Protein Expression and Purification*, vol. 72, 125-130 (2010) ("Fujiwara")
1042	Magalhaes et al., "Methods of Endotoxin Removal from Biological Preparations: a Review," *J. Pharm. Pharmaceut. Sci.*, 10(3): 388-404 (2007) ("Magalhaes")
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1045	Elsheikh et al., "Manipulated Mouse Embryos as Bioassay for Water Quality Control," *Reproduction in Domestic Animals*, 38(3), 204-208 (2003) ("Elsheikh")
1046	Reichelt et al., "Single Step Protocol to Purify Recombinant Proteins with Low Endotoxin Contents," *Protein Expression and Purification*, 46 (2006) 483-388 ("Reichelt")
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1053	Tanaka et al., "Isolation of Bovine Plasma Albumin by Liquid Chromatography and its Polymerization for Use in Immunohematology," *Brazilian J. of Medical and Biological Res.*, 34:977-983 (2001) ("Tanaka")
1054	Jachimska et al., "Characterization of Globular Protein Solutions by Dynamic Light Scattering, Electrophoretic Mobility, and Viscosity Measurements," *Langmuir*, 24:6866-6872 (2008) ("Jachimska")
1055	Brahma et al., "Characterization of a Dimeric Unfolding Intermediate of Bovine Serum Albumin under Mildly Acidic Conditions," *Biochimica et Biophysica Acta*, 1751 (2005) 159-169 ("Brahma")
1056	Gorin et al., "The Evolution of α-Feroprotein and Albumin," *J. Biological Chemistry*, vol. 256, no. 4, 1954-1959 (Feb. 25, 1981) ("Gorin")
1057	U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research, "Guidance for FDA Reviewers and Sponsors," April 2008 ("2008 FDA Guidance")
1058	*Certain Plant-Derived Recombinant Human Serum Albumins ("rHSA") and Products Containing Same*, Inv. No. 337-TA-1238, Transcript of Open Sessions (U.S.I.T.C. Nov. 21, 2021)
1059	U.S. Patent No. 5,094,960 ("Bonomo")
1060	U.S. Provisional Application No. 61/154,204

I. Introduction

Petitioner Wuhan Healthgen Biotechnology Corp. respectfully requests *inter partes* review of claims 1-29 of U.S. Patent No. 11,492,389 ("'389 patent") (EX1001) assigned to Ventria Bioscience Inc. ("Ventria" or "Patent Owner").

The '389 patent is related to cell culture media compositions comprising recombinant human serum albumin ("rHSA") produced in a transgenic plant such as rice, wherein the independent claims require that the albumin comprises less than 1 EU endotoxin/mg albumin (claims 1, 24, 26), less than 10 ppm detergent (claim 1), and a plant carbohydrate or lipid (claim 24).

Prior to the '389 patent, the use of albumin, including rHSA, in cell culture media was well known. Traditionally, the albumins in cell culture media were sourced from human plasma or serum (human serum albumin, "HSA" or "pHSA") and/or cows (bovine serum albumin, "BSA"). However, such albumins had several disadvantages, including the risk of contamination with animal-associated pathogens (e.g., viruses and/or prions associated with Mad Cow disease). Researchers thus developed safer alternatives, including rHSA and recombinant versions of other proteins traditionally used in cell culture media.

Recombinant proteins are expressed in hosts that would not naturally produce them. Such proteins serve the same function as their native counterparts. For

example, a primary function of HSA and rHSA in cell culture media is to solubilize and deliver of lipids that support cell growth.

U.S. Patent Publication No. 2007/0166825 ("Hatsuyama," EX1004), Petitioner's primary prior art reference, exemplifies the use of rHSA with sufficient purity in cell culture media. Hatsuyama teaches that its rHSA is preferably purified sufficiently to be used as a pharmaceutical—a standard that necessarily requires far less than 1 EU endotoxin/mg albumin—and thus prepared cell culture media comprising rHSA containing only 0.002 EU endotoxin/mg albumin. Hatsuyama exemplifies its invention with rHSA expressed in yeast, while teaching that the rHSA for use in its cell culture media may be expressed in transgenic plants.

WO 2007/002762 ("Deeter," EX1005), Petitioner's secondary prior art reference, discloses the expression of rHSA in transgenic rice at remarkably high levels—nearly 100 times greater than yields previously reported for other transgenic plants. Moreover, Deeter discloses that its plant-derived rHSA advantageously had physicochemical properties equivalent to pHSA and can replace animal-derived albumin for use in tissue culture. A skilled artisan would have expected that Deeter's rHSA comprised bound lipids from a plant (as recited in independent claim 24), as Deeter's rHSA promoted the growth of hybridoma cells, and lipids were known to be essential for growing such cells in culture media, and because Deeter discloses

that its rHSA was stable up to 65 °C—a hallmark of albumin stabilized by bound fatty acids (which are lipids).

A skilled artisan would have been motivated to modify Hatsuyama to include Deeter's rHSA given the widely reported advantages of plants as recombinant hosts for protein expression. When making this simple substitution, a skilled artisan would have been motivated to use common purification techniques to ensure that Deeter's rice-derived rHSA contained well below 1 EU endotoxin/mg albumin (as Hatsuyama's rHSA comprised only 0.002 EU endotoxin/mg albumin) and would have had a reasonable expectation of doing so by using, for example, a simple, fast, and effective two-phase extraction with a detergent such as Triton X-114—a technique that had been used to remove endotoxins from albumin and recombinant proteins expressed in *E-coli* that were contaminated with very high levels of endotoxins.

Of course, it was generally known that any endotoxin-removing detergent would need to be removed preferably to concentrations below 10 ppm or below 5 ppm, as such detergents were harmful to cells and tissue cultures, and this general knowledge is reflected in U.S. Patent Publication Nos. 2006/0110399 ("Van Holten," EX1007), 2006/0194300 ("Schulz," EX1008), and 2006/0008792 ("Viswanathan," EX1009) and U.S. Patent No. 5,094,960 ("Bonomo," EX1059). The prior art provided ample guidance on removing such detergents, including by

using hydrophobic interaction chromatography ("HIC") to remove detergents from plasma and blood proteins to achieve concentrations less than 10 ppm, less than 5 ppm, or even less than 1 ppm, without harming the target protein.

As such, the independent claims of the '389 patent would have been obvious over Hatsuyama in view of Deeter and the general knowledge of a skilled artisan. The dependent claims of the '389 patent would also have been obvious over Hatsuyama and Deeter, as they recite limitations that were known or at a minimum obvious in view of Hatsuyama and Deeter and the well-known properties of albumin.

As detailed below, there is at least a reasonable likelihood that Petitioner will establish that the challenged claims are unpatentable. Petitioner respectfully requests that the Board institute IPR and cancel claims 1-29 of the '389 patent.

II. Identification of Challenge

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). These publications qualify as prior art under pre-AIA 35 U.S.C. § 102(b) and § 103.

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

III. The '389 Patent

The '389 patent is related to cell culture media supplement compositions containing plant-produced heterologous proteins. *E.g.*, EX1001, 3:8-62. The '389 patent thus describes the production of recombinant proteins, including rHSA, in transgenic rice, as well as the purification of such proteins and their use in cell culture media. *Id.*, 62:59-96:44.

The '389 patent states that, in certain embodiments, the disclosed albumin contains less than about 1 EU endotoxin per mg albumin and less than about 10 ppm detergent. *Id.*, 45:43-60. The '389 patent also acknowledges that "other commercially available albumin products may have similar overall purity, endotoxin and detergent levels to rice derived recombinant albumin." *Id.*, 75:5-8.

In addition, the '389 patent acknowledges that known methods of preparing and purifying albumin "provide those skilled in the art reading this disclosure with significant possible methods for preparing and purifying albumin," citing several patents concerning the purification of albumin from various expression systems as examples. *Id.*, 50:1-12. Indeed, the '389 patent states that "[i]n one aspect, the

albumin for use in the present invention is purified using any of these art recognized processes listed above, and then mixed in aqueous solution with a heat shock protein." *Id.*, 50:1-12.

A. Claims

The '389 patent has three independent claims that are generally directed to a cell culture media supplement comprising recombinant albumin (e.g., rHSA) produced in a transgenic plant having less than 1 EU endotoxin per mg albumin, wherein claim 1 further requires less than 10 ppm detergent and claim 24 further requires a plant carbohydrate or plant lipid. EX1001, claims 1, 24, and 26.

The Independent Claims of the '389 Patent		
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	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 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:	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.

The Independent Claims of the '389 Patent		
recombinant human albumin comprising: i) less than 1 EU of endotoxin/mg of albumin; and ii) less than 10 ppm detergent.	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.	

B. Priority Date

The '389 patent is not entitled to rely on the filing date of Provisional Application No. 61/154,204 (filed February 20, 2009), as the Provisional Application lacks any written description of the recombinant albumin claimed in the '389 patent. For example, all claims of the '389 require "less than 1 EU endotoxin/mg albumin," yet the Provisional Application does not contain the word "endotoxin," much less describe recombinant albumin containing "less than 1 EU endotoxin/mg albumin." *See* EX1060 (Provisional Application). Nor does the Provisional Application describe how to prepare recombinant albumin comprising "less than 1 EU endotoxin/mg albumin." *Id.*

Moreover, the Provisional Application does not include any new disclosures regarding the production and purification of rHSA; the description of production and purification of rHSA in the Provisional Application was all disclosed two years earlier—nearly verbatim—in Deeter. *Compare* EX1060, [0113]-[0115] (expression of rHSA in Example 3 and Table 1) *with* EX1005, [0103]-[0105] (same expression

of rHSA in Example 3 and Table 1); *compare* EX1060, [0121]-[0122] (purification of rHSA in Example 5 and properties in Table 2) *with* EX1005, [0116]-[0117] (same purification of rHSA in Example 5 and properties in Table 2).

IV. Background

A. Cell Culture Media

It was well known that cells grown in culture media required several nutrients for growth, proliferation, and productivity (e.g., for producing biological products of interest). EX1003, ¶¶ 64-72; EX1010, 2-4. Indeed, a "vast amount of information was available to those seeking to develop and/or optimize cell culture media for the growth and/or productivity of various cell lines." EX1003, ¶ 72.

For example, it was understood that when serum is used in cell culture media, it provides numerous nutrients to cells, including albumin, transferrin, growth factors, insulin, growth hormones, and minerals such as iron, copper, selenium, and zinc. EX1003, ¶ 68; EX1011, 118 (Table 5.3).

Throughout the years, researchers sought to develop serum-free media comprising a more well-defined and less variable mixture of nutrients than serum. EX1003, ¶ 70; EX1028, 1-2. For example, serum-free media comprising a basal medium supplemented with animal-sourced proteins such as insulin, transferrin, and albumin combined with lipids and selenium "can promote growth of a number of different cell types ... from a number of different sources and species." EX1028, 4;

EX1012, 2 ("The major protein components in serum-free media are usually albumin, insulin, and transferrin.").

While such serum-free media provided promising results, those in the field recognized that it would be desirable to replace animal-derived proteins in cell culture media to reduce the risks of contamination with animal-associated pathogens. EX1003, ¶¶ 89-92; EX1005, [0006]-[0007]; EX1004, [0016]; EX1024, 1:32-35. Researchers thus sought to incorporate recombinant proteins into cell culture media (instead of their animal-sourced counterparts). *E.g.*, EX1005, [0006]-[0007]. Indeed, by 2003, it was reported that a recombinant protein could "often" be found that "meets or exceeds the desired functionality of the original animal component." EX1025, 1.

B. Human Serum Albumin

Human serum albumin ("HSA" or "pHSA") is a component of blood serum that is commonly used to supplement cell culture media. EX1003, ¶¶ 73-76; EX1014, 1. In cell culture, HSA functions as a carrier of essential nutrients to cells. EX1003, ¶ 70. For example, HSA serves as a carrier of fatty acids and other lipids that were reported to be essential for promoting the growth of a variety of cells, including hybridoma cells and stem cells. EX1003, ¶¶ 80-81; EX1011, 92 (discussing cell culture, wherein "the importance of serum albumin has been recognized as a carrier of supplemented fatty acids and lipids."); EX1021, Abstract

(explaining that lipid-rich albumin promotes embryonic stem cell renewal, while lipid-poor albumin does not); EX1012, 12 (explaining that albumin serves as a source of lipids that are important to hybridoma growth); EX1011, 132 (noting that certain fatty acids "have been shown to be essential for hybridomas in serum-free cultures"); EX1015, 1 "HSA is the primary transporter for delivering FA [fatty acids]…."; EX1019, 1 (noting the carrier function of albumin).

In addition to binding ligands, albumin may bind to other albumin molecules to form albumin aggregates, including albumin dimers and oligomers. EX1003, ¶ 82. Albumin aggregation was considered undesirable. EX1003, ¶ 84. For example, it was expected that aggregates would have a reduced capacity to deliver nutrients to cells. EX1003, ¶ 84. Certain processing steps, such as freeze-drying (lyophilization), were reported to promote the formation of albumin dimers and larger aggregates. *Id.*; EX1013, 75 ("S-S-linked dimers constitute the majority of the 5-10% of polymeric forms found in most albumin preparations that have been lyophilized during production."); EX1016, 6 (noting it had been observed that "the dimer content increased after freeze-drying."); EX1017, 11 ("The presence of oligomers in the freshly prepared solutions of different commercial BSA and HSA albumin preparations can be attributed to the preparation procedures including lyophilization."). However, the structural changes induced by lyophilization were reported to be reversible upon reconstitution of rHSA in water. EX1003, ¶ 86;

EX1018, 7 (noting that, for proteins including HSA, "*all* structural changes caused by lyophilization were reversible"). Moreover, albumin oligomers were reported to dissociate into albumin monomers and dimers over time in an aqueous solution at 8 °C. EX1003, ¶ 83; EX1017, 11 ("When the solutions of BSA and HSA were stored at 4 months at 8 °C, oligomers dissociated into dimer (17-23%) and monomer (17-83%) with no higher aggregates (Table 2)."); EX1017, 11 ("[I]isolated pure dimer and tetramer underwent dissociation into monomer, and monomer and dimer, respectively, within few hours of isolation, but no higher aggregates were detected.").

C. Transgenic Rice Was Known as a High-Yield, Well-Characterized System for Expressing rHSA

It was also well known that rHSA that was equivalent to pHSA had been expressed in transgenic rice at exceptionally high yields (up to 8.5 g/kg rice flour). EX1003, ¶ 93; EX1005, [0105], [0117]. Transgenic rice was understood to be among the most attractive hosts due to its high grain yield and the potential for producing large quantities of recombinant proteins. EX1031, 56. Indeed, transgenic plants were touted as "potentially one of the most economical systems for large-scale production of recombinant proteins for industrial and pharmaceutical uses." EX1033, 1; EX1003, ¶ 94; EX1031, 5 ("[P]lants have emerged as a convenient, safe and economical alternative to mainstream expression systems…."); EX1031, 206 (estimating that proteins could be produced in plants at 2-10% of the cost of

microbial fermentation systems (such as those used for yeast)); EX1039, 4 ("Cost benefits of plant production are enormous."). Indeed, in 2004 (prior to Deeter), the "major disadvantage" of rHSA was "the price," which was several times higher than "purified"/"pharmaceutical quality" HSA. EX1032, 5, 9; EX1058, 150:8-11.

While other plants such as tobacco and potato had been used to express rHSA, the yields were very low, e.g., producing only 0.01 g rHSA/kg plant material—orders of magnitude lower than the yields reported by Deeter. EX1003, ¶ 95; EX1034, 2; EX1035, 5 (noting that the highest level of rHSA expressed in potato tuber was 0.01 g/kg of tuber fresh weight). Transgenic tobacco had the additional problem of producing toxic secondary metabolites, while transgenic rice was "a well-characterized food crop that does not produce any toxic secondary metabolites." EX1036, 10. Moreover, transgenic seeds (e.g., rice seeds) provide a "better alternative" to plant leaves (e.g., tobacco leaves) as (1) seeds "contain a less complex mixture of proteins and lipids," which is "an advantage for purification," and (2) the stability of recombinant proteins was expected to be higher in seeds. EX1031, 297.

D. Endotoxins

Endotoxins are lipopolysaccharides ("LPS") that comprise part of the outer membrane of gram-negative bacteria such as *E-coli*. EX1023, 1. Endotoxins are everywhere, including in tap water, in sera, and on glassware and plasticware.

EX1003, ¶¶ 97-100; EX1027, 4-5 (listing common sources of endotoxin in cell culture media); EX1011, 114-15 (explaining that water is a source of endotoxin contamination). As such, endotoxins contaminate all materials and equipment, unless steps are taken to exclude or remove them. EX1003, ¶ 100; EX1030, 1 ("Unless they are removed by certain procedures described below, [endotoxins] are essentially ubiquitous contaminants[.]").

Additionally, HSA was "known to bind to endotoxin." EX1022, 1; EX1023, 5 ("serum albumin is a major LPS-binding factor"). As rHSA has the same structure as HSA (e.g., the same amino acid sequence and thus generally the same folding and ligand binding sites), rHSA also binds endotoxin. EX1003, ¶ 102; EX1022, 1, 7-10.

E. It Was Well Known that Endotoxins Should Be Removed from Proteins Prior to Using them in Cell Culture Media

The prior art clearly and repeatedly teaches that endotoxin contamination should be avoided in cell culture media, as endotoxins may contaminate a biological product of interest and/or otherwise complicate biological research. EX1003, ¶¶ 103-107; EX1026, 1 (noting "laboratory reagents used in cell culture" had been found to contain endotoxin, and the effect of endotoxin contamination on "scientific evaluation of biomaterials should [] not be ignored."); EX1029, 1-3 (detailing reasons to minimize endotoxin contamination in cell culture media); EX1027, 8 ("Endotoxins have also been shown in many cell culture experiments to affect cell growth and function as well as being a significant source of variability."). As such,

it was recognized the cell culture media supplements should have the lowest possible endotoxin contamination. EX1003, ¶¶ 103-108; EX1028, 2 (for serum-free media, the first "basic rule[]" is to use components "that have the lowest possible levels of bacterial endotoxin."); EX1013, 329 (albumin for use in cell culture should "optimally" be endotoxin free).

While it was well-known that cell culture media should be relatively free of endotoxins, it was recognized that cell culture media components were often contaminated. EX1003, ¶¶ 108-109; *see* EX1026, 1 ("[R]eagents used in cell culture ... have also been found to contain endotoxin"); EX1030, 2 (noting that significant concentrations of endotoxins were found in common reagents such as non-USP serum albumin and recombinant hormones); EX1037, 1 ("[C]ommercial albumin preparations contain significant amounts of endotoxins, and it is well known that endotoxins have profound biological effects.").

The prior art thus strongly urged researchers to verify that cell culture media supplements contain no or sufficiently low levels of endotoxin. EX1003, ¶¶ 110-111. For example:

- "Whenever possible, ask manufacturers to certify the endotoxin levels of their products; when in doubt test the media endotoxin levels both before and after adding any new components." EX1027, 4.

- "We advocate routine testing of endotoxin on biomaterials and reagents used in evaluation of biomaterials and this should be the responsibility of every scientist to ensure the validity of any biomaterial study." EX1026, abstract.

- "If the certificate of analysis of a reagent or buffer does not mention endotoxin level, one should assume that it is contaminated." *Id.*, 4.

- "The endotoxin content of processed biological materials should be stated by the supplier, or should be tested by the investigator before they are used in biological research." EX1037, 3.

- "If you purchase peptide X, query the manufacturer as to whether X has been manufactured under GMP conditions or at least tested for endotoxin by the Limulus test. If the manufacturer is not familiar with these terms, then you must assume that X has been produced under conditions that could lead to MCWP [endotoxin] contamination." EX1030, 3.

Thus, it was well known that, when the level of endotoxins in a cell culture media supplement was unknown, the supplement should be tested before it is used in biological research. EX1003, ¶¶ 110-111.

F. The Art Recognized that Endotoxins May Contaminate Recombinant Proteins Produced in Plants

Expressing recombinant proteins in transgenic plants avoids potential contamination from pathogens associated with animal and human hosts, but it does

not eliminate the risk of endotoxin contamination. EX1003, ¶¶ 112-113; EX1025, 1, 2, 4 (recommending testing new protein products for endotoxin); EX1031, 300 (recommending quantification of endotoxins after purification of plant-derived products).

For recombinant proteins extracted from transgenic plants grown in dirt (as opposed to plant cells in a bioreactor), the risk of endotoxin contamination was well known. EX1003, ¶ 114; EX1040, 7 ("[I]t is likely the residual endotoxin was derived from gram-negative bacteria resident on the wheat seed during growth and storage."); EX1038, 2 (plant cells in a bioreactor have "reduced potential for endotoxin" contamination "derived from the plant and soil source"). Indeed, by 2007, Ventria learned that its rHSA produced in transgenic rice (Cellastim) could not meet certain customers' requirements due to the amount of endotoxin present. EX1058, 151:20-152:12, 153:25-154:3.

Given the known risks of endotoxin contamination, techniques were employed to avoid introducing endotoxins during the purification of recombinant proteins expressed in transgenic plants, including transgenic wheat and transgenic rice. EX1003, ¶¶ 115-117. Such techniques included cleaning or treating equipment to remove or decompose endotoxins and using endotoxin-free water. *Id.*; EX1040, 3 ("Extracts were prepared to avoid the introduction of exogenous endotoxin. Equipment was cleaned ... and solutions were prepared using sterile, pyrogen-free

water."); EX1041, 2 (treating glassware to "decompose any endotoxins" and using Milli-Q (endotoxin-free) water when extracting and purifying a recombinant protein expressed in transgenic rice seeds); EX1045, 4-5 (noting that Milli-Q water had < 0.000 EU endotoxin/ml water); EX1041, 5 (reporting that a recombinant protein expressed in transgenic rice seeds comprised 0.024 EU endotoxin/mg protein after purification).

G. Techniques for Removing Endotoxins from Albumin Were Well Known

Techniques for removing endotoxins from numerous proteins were well known. EX1003, ¶¶ 118-126; EX1043, 7-20 (reviewing techniques for endotoxin removal from protein solutions); EX1042, 7-12 (same). For albumin in particular, the process proven most successful for removing endotoxins involved two-phase separation using a detergent, Triton X-114. EX1003, ¶ 121. This technique separates endotoxins from albumin, without altering the normal function of albumin. EX1003, ¶ 121; EX1043, 10 (explaining how two-phase separation removes endotoxin). For BSA, the first phase separation provided a 1000-fold reduction in endotoxin, and additional cycles result in "***[c]omplete removal of endotoxin***"[1] (EX1044, Abstract), meaning the residual endotoxins were "undetectable by the *Limulus* assay"

[1] ***Bold/italics*** indicates emphasis added.

(EX1044, 4). Given the sensitivity of the *Limulus* gel assay, the albumin purified using this technique would have been expected to contain at most 0.001 EU endotoxin/mg albumin. EX1003, ¶ 122; EX1027, 4 (sensitivity of the *Limulus* gel assay was 0.03 EU/ml); EX1026, 4 (same).

Not only was this process effective at removing endotoxin, it was simple to perform. EX1003, ¶ 123. Indeed, each phase separation could be "completed within 15 minutes." EX1044, abstract; EX1042, 11 (noting that "[i]n addition to its simplicity," endotoxin removal using Triton X-114 "is cost effective, especially at a large scale."). As such, phase separation using Triton X-114 had been used to purify recombinant proteins expressed in *E-coli*—proteins expectedly contaminated with very high loads of endotoxin (as each *E-coli* contains about 2 million endotoxins). EX1042, 10-11; EX1003, ¶ 124; *see also* EX1046, 4 (disclosing a modified technique using Triton X-114 to remove endotoxins from tagged recombinant proteins expressed in *E-coli* from levels of 2,500 EU endotoxin/mg protein to as low as 0.4 to 0.2 EU/mg protein).

H. It Was Well Known that Endotoxin-Removing Detergents Should Be Removed from Protein Preparations

It was well known that detergents used to purify proteins must be removed. EX1003, ¶ 127. For example, it was known residual detergent used in protein purification could be harmful to cells, even at very low concentrations. *Id.*; EX1044, 4 (residual Triton X-114 at 0.018% was harmful to cellular activity); EX1047, 4-6

(discussing cytotoxicity of common nonionic surfactants, including Triton X-114); EX1048, 4-5 (comparing techniques for the evaluating cytotoxicity using Triton X-100). The prior art thus teaches that the detergents used for protein purification must be removed. EX1003, ¶ 127; EX1042, 10 (explaining that residual detergent "needs to be removed"); *see infra*, § VIII.C.

I. Techniques for Removing Detergents Were Well Known

Techniques for removing detergents from protein solutions were well known in the art. EX1003, ¶¶ 128-139. For example, it was well known in the art that hydrophobic interaction chromatography ("HIC") effectively removed detergents without harming the target protein(s). *Id.*; EX1049, 1; EX1059, 3:31-33 ("Hydrophobic interaction chromatography (HIC) is a commonly used tool in the biochemists' arsenal of molecular separation techniques."). The advantage of this technique was that it was "fast and it induces minimal impact on the protein composition." EX1049, 1.

As such, HIC had been widely adopted for detergent removal from plasma and blood proteins. EX1003, ¶¶ 128-139. For example, an HIC sorbent ("Bulk C-18 media") reduced the concentrations of Triton X-100 in plasma preparations to 1.5 ppm to 8.0 ppm. EX1059, Example 1 and Table 1 (column 9). A similar technique reduced concentration of the detergent octoxynol 9 to less than 5 ppm. EX1050, 4.

A different HIC sorbent (SDR HyperD) was identified as the "first and most preferable adsorbent" for removing Triton X-100 from blood proteins. EX1007, 17:10-11. The SDR HyperD sorbent was also expected to be useful for removing detergent from albumin solutions, as it would allow for the recovery of more than 99% HSA after detergent removal. EX1003, ¶ 132; EX1051, 5 (reporting recovery of HSA from SDR HyperD sorbent). HIC sorbents were also understood to be suitable for recombinant proteins. EX1003, ¶ 134; EX1008, [0032]; EX1007, [0036].

By 2009, C18 and SDR HyperD were the "HIC sorbents most often used for removal of S/D [solvent/detergent] agents from therapeutic protein products." EX1049, 2. Both sorbents performed comparably in the removal of Triton X-45 (to be below 2 ppm), while SDR HyperD was superior for removing Triton X-100 (achieving levels as low as 7 ppm). EX1049, 4 (Table 2). And both C18 and SDR HyperD provided nearly complete recovery of the target protein. EX1049, 4-5.

A POSA would have expected the efficiency of HIC in the removal of Triton X-114 (the Triton used to remove endotoxins from albumin) would fall between Triton X-45 and Triton X-100, as the Tritons have the same basic structure, and Triton X-114 has properties that fall between those of Triton X-45 and Triton X-100, as summarized below. EX1003, ¶¶ 136-137; EX1052, 2.

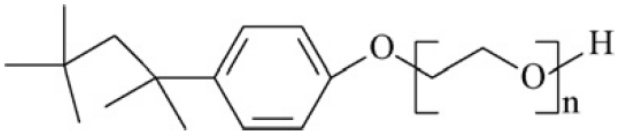

Fig. 1. Basic structure of Triton X series.

Table 1
Basic parameters of Triton X series

Trade name	Average ethylene unit	Cloud point[a] (°C)	CMC (ppm)	HLB
Triton X-45	4.5	Dispersible	57	9.8
Triton X-114	7.5	25	100	12.3
Triton X-100	9.5	66	130	13.4

[a] Aqueous solution containing 1% (v/v) nonionic surfactant.

Figure 1. EX1052, 2 (highlighting added).

Other HIC sorbents would have also been expected to be effective at removing detergents from protein solutions. EX1003, ¶ 138. For example, SEPABEADS® had been used to remove Triton X-100 to concentrations of about 5 ppm and 6.16 ppm. EX1009, [0070], [0073]-[0074], Tables 1-2. The conditions of detergent removal were optimized to reduce the concentration of Triton X-100 to less than 1 ppm. *Id.*, [0075]-[0076], Table 3.

The prior art thus discloses that suitable techniques exist for removing detergents to levels well below 10 ppm from blood proteins and plasma, that HIC sorbents are suitable for purifying HSA, and that such techniques also work for recombinant proteins. EX1003, ¶¶ 128-139.

J. Purifying Proteins from Different Sources

In general, the same techniques that successfully purify native proteins from non-host-specific contaminants (e.g., endotoxins and detergents) can be used to purify recombinant proteins with similar or identical physicochemical properties. EX1003, ¶ 140; EX1031, 233 ("[T]here are more common steps than operations addressing expression system-specific problems or requirements" and "the intrinsic features used for purification (affinity, hydrophobicity, etc.) are the same."); *see also* EX1008, [0032] (technique for purifying a protein obtained from plasma reported to be suitable for purifying its recombinantly counterpart); EX1007, [0036] (explaining that the disclosed purification technique can be used to purify, e.g., blood proteins and "transgenic derived products and recombinant proteins.").

Protein purification involves three phases: (1) capture, (2) intermediate purification, and (3) polishing. EX1003, ¶ 144; EX1031, 234-243. The capture phase "generally aims to concentrate the highly dilute starting material and remove bulk impurities, rather than achieving a high degree of purity by high resolution and selectivity." EX1031, 240. While the "capture" step may be optimized for a specific host (e.g., to remove the bulk plant impurities), the intermediate and polishing steps "will not significantly differ from established biotechnological processes." EX1031, 243.

Thus, it was generally known that after the initial "capture" phase of purification, proteins expressed in various systems may be purified using the same techniques, provided the proteins have similar physicochemical properties, regardless of any differences in the transgenic hosts themselves. EX1003, ¶¶ 140-154.

K. rHSA, pHSA, and BSA Were Well Known to Share Similar and/or Equivalent Physicochemical Properties

BSA and pHSA were well known to have very similar (often equivalent) physicochemical properties. EX1003, ¶¶ 145-151; EX1053, 1 (BSA is "very similar to human albumin in terms of structure and physicochemical properties"); EX1054, 1-2 (comparing BSA and HSA). Notably, BSA and pHSA have domains that are either identical or differ only in one amino acid, meaning that they have strikingly similar structures. EX1003, ¶ 146; EX1056, 4, Fig. 4 (showing the similarities in amino acid sequences and domains in pHSA, BSA, α-fetoprotein); EX1055, abstract (BSA is "a structural analog of human serum albumin."). As such, the surfaces of BSA and pHSA were known to be strikingly similar, as reflected in the locations of their negatively charged amino acid residues (shown in red below) and positively charged residues (shown in blue). EX1055, 8-9 (a "remarkable feature of these structures is most of the surface residues were polar supporting their high solubility in aqueous solvents.").

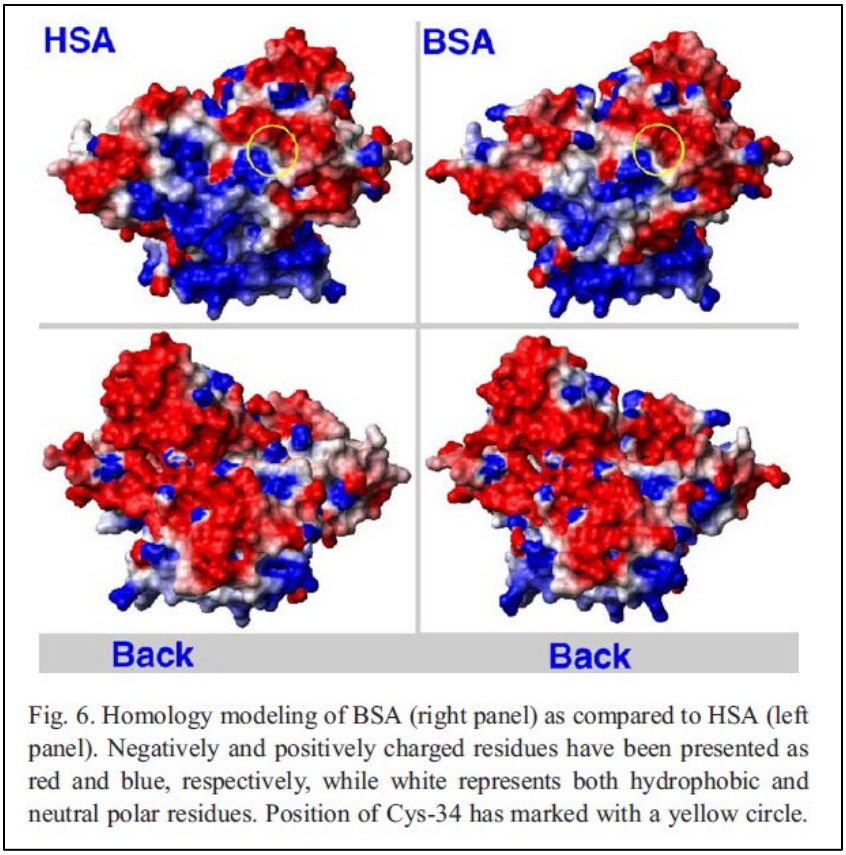

Fig. 6. Homology modeling of BSA (right panel) as compared to HSA (left panel). Negatively and positively charged residues have been presented as red and blue, respectively, while white represents both hydrophobic and neutral polar residues. Position of Cys-34 has marked with a yellow circle.

Figure 2. EX1055 (Brahma), Fig. 6.

Moreover, Deeter discloses that its rHSA has physicochemical properties "equivalent" to those of pHSA. EX1005, Table 3; *see also* EX1032, 9 (noting that different rHSA "is structurally identical to HSA."). Deeter's rHSA would thus have been understood to have properties strikingly similar to BSA, just as pHSA is strikingly similar to BSA. EX1003, ¶¶ 140-154. As Dr. Clark explains, there is no indication that Deeter's rHSA and pHSA have any structural differences that would impact purification or function. EX1003, ¶ 152. Thus, BSA, pHSA, and equivalent rHSA would have all been understood to share strikingly similar structures and,

relatedly, properties, and the purification techniques that work for one of these albumins would also be expected to work for another. EX1003, ¶¶ 145-151.

V. Level of Skill in the Art

A POSA as of February 18, 2010, would have had a Ph.D. in chemistry, biochemistry, chemical engineering, or a related discipline and at least two years of experience involving the production and/or and purification of proteins, such as rHSA. EX1003, ¶ 52. A POSA would have been familiar with common laboratory techniques and strategies for characterizing and purifying proteins and the use of proteins, including albumin and rHSA, in cell culture media. *Id.*, ¶ 53. A POSA would also have been knowledgeable of common uses of cell culture media, including the use of cell culture media in biological research and for the production of biological products. The level of skill in the art would have been the same as of 2009. EX1003, ¶ 54.

VI. Claim Construction

Healthgen does not expect that the construction of any term is required for institution. Nevertheless, the ’389 patent provides definitions for certain claim terms, which are summarized below.

Claim Term Definitions in the '389 Patent	
Claim Term (claims)	**'389 Patent**
"cell culture media" (all claims)	"The terms 'cell culture medium,' 'cell culture media,' and 'culture medium' refer to the solutions used for growing, storing, handling and maintaining cells and cell lines." '389 patent, 16:46-48.
"cell culture media supplement" (all claims)	"The term 'cell culture media supplement' refers to a combination of one or multiple cell culture media components, with or without other ingredients, for addition to cell culture media." *Id.*, 17:16-19.
"heterologous protein" (claims 1, 24) "recombinant" protein (all claims)	"The term 'heterologous protein' or 'recombinant protein' refers to a protein encoded in all or part by heterologous DNA, or a protein that is expressed from expression control sequences (such as a promoter, or enhancer) created in whole or part by the heterologous DNA which activates the expression of an endogenous gene." *Id.*, 19:50-56.
"homologous" (claim 8)	"The term 'homologous' refers to the relationship between two proteins that possess a "common evolutionary origin', including proteins from superfamilies (e.g., the immunoglobulin superfamily) in the same species of animal, as well as homologous proteins from different species of animal (for example, myosin light chain polypeptide, etc.; see Reeck et al., Cell, 50:667, 1987). Such proteins (and their encoding nucleic acids) have sequence homology, as reflected by their sequence similarity, whether in terms of percent identity or by the presence of specific residues or motifs and conserved positions." *Id.*, 20:13-23.
"identical" (claim 10)	Not explicitly defined; however: "As used herein, 'identity' means the percentage of identical nucleotide or amino acid residues at corresponding positions in two or more sequences when the sequences are aligned to maximize sequence matching, i.e., taking into account gaps and insertions." *Id.*, 21:1-5.

Claim Term Definitions in the '389 Patent	
Claim Term (claims)	**'389 Patent**
"monocot seed component" (claims 14, 15, 24)	"'Monocot seed components' refers to carbohydrate, protein, and lipid components extractable from monocot seeds, typically mature monocot seeds." *Id.*, 23:18-20.
"produced in a transgenic plant" (claim 26)	Not explicitly defined, however: "With respect to recombinant proteins, the term 'produced in a plant' means that the recombinant protein has been expressed within a plant cell, and then purified from host cells proteins and lipids." '*Id.*, 26:28-31.

The '389 patent also provides a detailed description of the term "albumin." EX1001, 37:23-39:3. In particular, the specification describes certain biologically active fragments, variants, derivatives, and fusion proteins of albumin (*id.*, 37:23-39:3), noting (as tabulated above) the term "fragment" includes fragments of albumin "provided that the fragment retains the biological or therapeutically beneficial activity of the whole molecule" (*id.*, 37:26-28). The specification further explains that "[a]ll such variants, derivatives, fusion proteins, or fragments of albumin are included, may be used in any of the methods disclosed herein, and are subsumed under the term 'albumin.'" *Id.*, 39:3-7. The specification also explains that the claimed albumin "preferably" comprises "at least 40, 50, 60, 70, 75, 80, 85, 90, 95, 98, or 99% identity" with the amino acid sequence of a native albumin such as HSA, meaning a preferred albumin may be missing up to 60% of the amino acids in HSA. *Id.*, 38:20-23, 36:60 (Table D1). Additionally, claim 10 requires rHSA "has

an amino acid sequence that is at least 80% identical" to HSA, i.e., rHSA that may be missing up to 20% of the amino acids of HSA. EX1001, claim 10; EX1003, ¶ 57. This claimed rHSA would be expected to retain some, but perhaps not all, of the beneficial activity of HSA. EX1003, ¶ 57. Healthgen thus submits that the terms "recombinant human albumin" in claims 1 and 24 and "recombinant mammalian albumin" in claim 26 should be construed as:

- "recombinant albumin (i.e., albumin heterologous or foreign to the transgenic plant producing it), [1] which has the amino acid sequence of a native [human or mammalian] albumin or [2] which is a variant, derivative, fusion protein, or fragment of native [human or mammalian] albumin (provided the fragment retains biological or therapeutically beneficial activity associated with the native [human or mammalian] albumin."

This is proposed construction clarifies Healthgen's proposed construction of the term "recombinant [] albumin" in a prior proceeding. *See Wuhan Healthgen Biotechnology Corp. v. Ventria Bioscience Inc.*, IPR2022-00712, Paper No. 2, 15.

Next, claim 5 of the '389 patent recites "albumin and fragments thereof provided that the fragments retain the biological or therapeutically beneficial activity of said albumin." EX1001, claim 5. This claim term must be read in connection with the term "recombinant [] albumin" above, which includes fragments that retain the beneficial biological activity associated with a native albumin such as HSA. The

added limitation of claim 5 would be understood to have a similar meaning, specifically:

- "albumin and fragments thereof provided that the fragments retain the biological or therapeutically beneficial activity associated with native albumin."

EX1003, ¶¶ 58-59.

This proposed construction encompasses preferred embodiments of the invention, including albumin having "preferably at least 40, 50, 60, 70, 75, 80, 85, 90, 95, 98, or 99% identity with" a native albumin such as HSA that would be expected to retain some, but perhaps not all, of the beneficial biological activity to native albumin. *See Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, (Fed. Cir. 1996) (noting that a claim construction that excludes a preferred embodiment "is rarely, if ever correct and would require highly persuasive evidentiary support").

Finally, the independent claims' preambles recite "improving growth, viability, and/or productivity of cultured cells as compared to cells grown without said supplement or complete media composition" (claims 1 and 24) or "improving the growth of a cell in cell culture" (claim 26). Healthgen submits that these phrases in the claim preambles are not limiting, as they do not provide antecedent support for any term in the claim body and were not relied on to establish patentability. *Symantec Corp. v. Computer Assocs. Int'l, Inc.*, 522 F.3d 1279, 1288 (Fed. Cir.

2008) ("Absent clear reliance on the preamble in the prosecution history, or in situations where it is necessary to provide antecedent basis for the body of the claim, the preamble 'generally is not limiting.'") (quoting *Catalina Mktg. Int'l v. Coolsavings.com, Inc.*, 289 F.3d 801, 809 (Fed. Cir. 2002)). However, even if limiting, the prior art discloses the claimed improvement in activity. EX1003, ¶¶ 60, 195.

All other terms have been afforded their plain and ordinary meaning as they would have been understood in the context of the '389 patent. All constructions discussed above have been applied throughout this petition.

VII. Asserted Prior Art

A. Hatsuyama

Hatsuyama discloses serum-free cell culture media comprising rHSA for hematopoietic stem cells and hematopoietic progenitor cells. EX1004, Abstract; EX1003, ¶ 156.

Hatsuyama exemplified its cell culture media composition with rHSA expressed in yeast having less than 0.5 EU endotoxin/250 mg rHSA, which is less than 0.002 EU endotoxin/mg albumin. EX1003, ¶ 157; EX1004, [0076], Table 1. 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 (injection)" (*id.*, [0024]), which

necessarily requires far less than 1 EU endotoxin/mg albumin. EX1003, ¶ 160; EX1057, 22; EX1043, 5-6. Hatsuyama explains that its rHSA may be collected and purified using known techniques for separation and purification. EX1004, [0024], [0225]. For example, Hatsuyama notes that rHSA expressed in yeast may be purified by "cation exchange treatment, hydrophobicity chromatography, and anion exchange treatment," and the rHSA may be further purified by a "chelate resin treatment or boric acid/salt treatment." EX1004, [0030].

Hatsuyama teaches that the rHSA used in its cell culture compositions may be obtained from any recombinant host, including transgenic plants, noting that hosts developed in the future "can also be utilized as appropriate." EX1004, [0026].

B. Deeter

Deeter discloses the use of recombinant proteins expressed in transgenic rice to improve the growth and productivity of cells in cell culture media. EX1005, [0009], [0019]. Deeter also discloses that its invention comprises cell culture media with "at least one plant-produced heterologous protein as a cell culture media component." *Id.*, [0010].

Deeter describes expressing rHSA in transgenic rice, yielding up to 8.5 grams rHSA/kg rice flour. *Id.*, [103]-[105]. In addition, Deeter teaches that its rHSA was "equivalent" to HSA (identified as "pHSA" in Deeter). *Id.*, [0117]; *see also id.*, Table 3 (above [0118]). Deeter's rHSA had approximately the same molecular

weight, the same isoelectric focusing point (5.3), and the same thermal stability (midpoint: 65 °C) as pHSA. *Id.*, Table 3 (above [0118]).

Deeter also discloses purifying the rHSA to achieve a purity of 90%, as observed by SDS-PAGE, after extraction, filtration, and an initial chromatography step (akin to the initial "capture" phase of protein purification). *Id.*, [0116]; EX1003, ¶ 165. Deeter further discloses that the purity of the rHSA may be increased from 90% to 98% by performing an additional chromatography step (akin to the "intermediate" purification phase). EX1005, [0116]; EX1003, ¶ 165. Notably, Deeter does not disclose any "polishing" steps, e.g., the final phase of protein purification. EX1003, ¶ 165. Indeed, Deeter defines the term "purifying" to include any step that enriches the component of interest and acknowledges that other components may remain after purification. EX1005, [0063]. A POSA would thus have understood that impurities may remain in Deeter's "purified" rHSA. EX1003, ¶¶ 167-168.

In Examples 8 and 9, Deeter evaluates the effectiveness of rHSA in stimulating the growth of hybridoma AE1 cells and concludes that rHSA from rice was "functionally equivalent" or "better than" pHSA in enhancing hybridoma cell growth in reduced-serum media and serum-free media. EX1005, [0118]-[0120], Figs. 23, 24.

C. General Knowledge that Purified Proteins Should Comprise Less than 10 ppm of Detergents Employed in During Purification

The general principle that detergents used to purify proteins must be removed to concentrations of less than 10 ppm was well known to ordinarily skilled artisans. EX1003, ¶¶ 170-171. For example:

- Van Holten acknowledges that it was "important to be able to determine that the residual amount of the S/D [solvent/detergent] post removal is ***less than about 10 ppm***" in blood proteins. EX1007, 16:43-45.

- Schulz states that for "medical preparations," concentrations of Triton X-100 (a common detergent used in protein purification) ***above 10 ppm should preferably be avoided***, and "***it is generally desirable to reduce the detergent contents as much as possible***." EX1008, [0012].

- Viswanathan notes that "detergents may readily destroy or damage living cells," and further notes that "***to ensure living cells*** and proteins ***are not damaged ... removal of detergents is imperative***" (EX1009, [0010]); that the British pharmacopeia limits the level of Triton X-100 to ***less than 5 ppm*** in virus-inactivated plasma products (*id.*, [0069], [0101], Table 7); and that plasma preparations comprising 44 ppm, 25 ppm, 15 ppm, and 13.7 ppm Triton were unacceptable, and preparations comprising 5 ppm and 6.16 ppm were acceptable (*id.*, [0071], Table 1, [0073]-[0074], Table 2).

- Bonomo notes that residual detergents should be removed if a purified biological product will be used "in tissue culture." EX1059, 2:9-14. Bonomo reports reducing Triton concentrations to 1.5 to 8.0 ppm. *Id.*, 9:50-67 (Table 1).

As Dr. Clark explains, these publications reflect the general knowledge of a skilled artisan that proteins should comprise less than 10 ppm of any detergent used during protein purification, particularly when one intends to purify a protein to a sufficient degree for use as a pharmaceutical and/or when the protein is intended for use in tissue or cell culture media. EX1003, ¶ 171. Indeed, detergents used in protein purification (e.g. Triton detergents) were known to be cytotoxic (harmful to cells). *Id.* Thus, a POSA would have generally known that detergents used in protein purification must be removed to the greatest extent possible—and certainly to below 10 ppm—before using a purified protein in cell culture media. *Id.*

VIII. Claims 1-29 Would Have Been Obvious over Hatsuyama and Deeter and a POSA's General Knowledge

All claims of the '389 patent would have been obvious over Hatsuyama in view of Deeter and the general knowledge of a POSA that purified proteins intended for use in cell culture media should comprise less than 10 ppm detergent. EX1003, § X. A determination of obviousness requires finding that a POSA (1) would have been motivated to combine or modify the teachings in the prior art and (2) would have had a reasonable expectation of success in doing so. *Adapt Pharma Operations*

Ltd. v. Teva Pharms. USA, Inc., 25 F.4th 1354, 1365 (Fed. Cir. 2022). As detailed below, both requirements are met here.

A. Motivation to Combine

A POSA would have been motivated to modify Hatsuyama's cell culture media to include Deeter's rice-derived rHSA. EX1003, ¶¶ 172-181. *First*, both Hatsuyama and Deeter seek to avoid contaminating cell culture media with animal-associated pathogens, and Hatsuyama and Deeter both teach the use of rHSA as a replacement of pHSA. EX1003, ¶ 175. Consistent with Federal Circuit precedent, these facts alone provide a motivation to combine Hatsuyama and Deeter. *Intel Corp. v. PACT XPP Schweiz AG*, 61 F.4th 1373, 1380 (Fed. Cir. 2023) (where two prior art publications "address the same problem" and each discloses "a known way to address that problem," "there's a motivation to combine under *KSR* and our precedent."); *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740 (2007); *Adapt Pharma*, 25 F.4th at 1368 ("Here, the 'interrelated teachings' of the prior art references support the district court's finding that a skilled artisan would have been motivated to combine the references.").

Second, Hatsuyama specifically suggests using plant-derived rHSA, providing a skilled artisan with further motivation to replace Hatsuyama's exemplary rHSA (expressed in yeast) with Deeter's rHSA (expressed in transgenic rice). EX1004, [0025]; EX1003, ¶ 176. A skilled artisan would have considered this

a simple substitution, well within the ordinary level of skill. *See KSR*, 127 S. Ct. at 1740 ("If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability.").

Third, a POSA would have appreciated that Deeter's rHSA was an advantageous replacement for yeast-derived rHSA in Hatsuyama's cell culture media. EX1003, ¶ 176. For example, Deeter discloses the expression of rHSA in remarkably high yields from transgenic rice, and Deeter's system would thus have been expected to provide a more cost-effective option than yeast-derived rHSA. *Id.*; *see Everstar Merch. Co. v. Willis Elec. Co.*, No. 2021-1882, 2022 WL 1089909, *3 (Fed. Cir. Apr. 12, 2022) (*unpub'd*) (concluding that the Board "abused its discretion when it refused to consider cost reduction as a potential motivation to combine.").

Fourth, based on the successful results of Hatsuyama (with stem cells) and Deeter (with hybridoma cells), a POSA would have recognized that Hatsuyama's cell culture media comprising Deeter's plant-derived rHSA could be further developed and/or optimized to promote the growth of a wide range of cell types. EX1003, ¶¶ 177, 180.

As such, a skilled artisan would have had ample motivation to modify Hatsuyama in view of Deeter. Additional considerations regarding a POSA's motivation to combine are addressed below in the context of specific claim limitations.

B. Reasonable Expectation of Success

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. EX1003, ¶ 182; EX1004, [0025]; *see Almirall LLC v. Amneal Pharms. LLC*, 28 F. 4th 265, 275 (Fed. Cir. 2022) ("A finding of a reasonable expectation of success does not require absolute predictability of success.") (citation omitted).

A POSA would have considered this a simple substitution, as Deeter enabled the production of rHSA in transgenic rice (using the same method copied into the '389 patent). *Compare* EX1005, [0103]-[0104] *with* EX1001, 64:5-60. Additional considerations regarding a POSA's reasonable expectation of success are detailed below in the context of specific claim limitations.

C. Claim by Claim Analysis

1. Claim 1

Claim 1 recites a (a) cell culture media supplement or complete media composition comprising (b) plant-produced recombinant human albumin, (c) less than 1 EU of endotoxin/mg albumin, and (d) less than 10 ppm detergent. EX1001, claim 1.

a. Claim Preamble: "cell culture media supplement or complete media composition *for improving the growth, viability, and/or productivity of cultured cells as compared to cells growth without said supplement or media composition*"

Hatsuyama and Deeter each independently disclose cell culture media (i.e., "solutions used for growing, storing, handling and maintaining cell lines") comprising rHSA that improves the growth, viability, and/or productivity of cultured cells compared to media without said rHSA, e.g., when compared to media comprising serum or pHSA (as in Hatsuyama) or media without rHSA (as in Deeter). EX1003, ¶ 195; EX1004, [0016]; EX1005, [0118]-[0120], Figs. 23, 24.

b. "plant-produced heterologous protein [that] ... is recombinant human albumin"

Hatsuyama's cell culture media composition, as modified in view of Deeter, contains rHSA expressed in transgenic rice, where the rHSA is "plant-produced heterologous protein [that] … is recombinant human albumin" satisfying the definitions of a "recombinant" protein and a "heterologous protein" provided in the '389 patent. EX1003, ¶ 196.

c. "less than 1 EU endotoxin/mg albumin"

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]).

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.

A POSA would have reasonably expected to achieve rice-derived rHSA with far less than 1 EU endotoxin per mg rHSA. EX1003, ¶¶ 121-126, 140-154, 185-186, 202. Indeed, a POSA would have been knowledgeable about the use of endotoxin-free water and other methods to avoid high levels of endotoxin contamination during recombinant protein purification. EX1003, ¶ 202.

To the extent that residual endotoxin contamination remained above acceptable levels (e.g., substantially above Hatsuyama's 0.002 EU endotoxin/mg albumin), a POSA would have reasonably expected to remove such endotoxins using routine purification processes, e.g., by using a simple phase-separation using Triton

X-114 that had proven extremely successful for BSA. EX1003, ¶¶ 121-126, 140-154.

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. EX1003, ¶¶ 140-154. Moreover, in the context of a simple phase separation using Triton X-114, pHSA, rHSA, and BSA would have been reasonably expected to behave in the same way, as these proteins all have largely hydrophilic surfaces, meaning that they would be expected to preferentially separate into the water-rich, micelle-poor/endotoxin-poor phase. EX1003, ¶ 150.

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.

d. "less than 10 ppm detergent"

To the extent that detergents were employed to sufficiently deplete endotoxin contamination in rHSA, a POSA would have been motivated to further purify the rHSA to remove any such detergents to be below 10 ppm and would have had a reasonable expectation of success in doing so. EX1003, ¶¶ 203-207.

As Dr. Clark explains, it was generally known to a POSA that detergents used for protein purification should be subsequently removed to concentrations of less than 10 ppm or even less than 5 ppm, particularly where the protein would be used in cell culture media. EX1003, ¶¶ 170-171, 187-189, 204; *supra*, VIII.C; *see Koninklijke Philips N.V. v. Google LLC*, 948 F.3d 1330 (Fed. Cir. 2020) (affirming the Board's obviousness determination based in part on the general knowledge of a POSA, as evidenced by one prior art publication).

Indeed, detergent removal to less than 10 ppm or less than 5 ppm was characterized as "necessary," "important," and "imperative." EX1059, 2:9-14 (removal of detergents "is ***necessary***" if the biological product will be used "in tissue culture"); EX1007, [0112] (it is "***important t***o be able to determine that the residual amount of [detergent] is less than about 10 ppm"); EX1009, [0010] ("removal of detergents is ***imperative***" to "ensure that living cells and proteins are not damaged"); *see also* EX1008, [0012] (detergent concentrations should "preferably" be below 10 ppm, and "it is generally desirable to reduce the detergent contents as much as possible."). This general knowledge is directly applicable to Hatsuyama, as a POSA would have been motivated to avoid introducing agents (e.g., Triton detergents) at concentrations that could harm the living cells that the cell culture media are intended to support. EX1003, ¶ 189.

A POSA would have reasonably expected to achieve less than 10 ppm detergent using routine purification techniques. EX1003, ¶¶ 128-139, 190-191. Indeed, HIC sorbents successfully removed a variety of detergents to levels below 10 ppm (and at times below 5 ppm and even below 1 ppm) from plasma and blood proteins, including immunoglobulins, and the art specifically taught that HIC sorbents did not harm the target protein and were suitable for purifying albumin and recombinant proteins. *Id.*; *supra*, § V.I. As Dr. Clark explains, techniques reported to be suitable for blood proteins (including pHSA), recombinant proteins, and plasma would have expectedly also worked for Deeter's rHSA. EX1003, ¶ 190.

A POSA would have reasonably expected that rHSA comprising less than 10 ppm detergent would not adversely impact Hatsuyama's cell culture media, rHSA preferably comprises at most 10% of the media, such that the detergent would preferably be present as, at most, 1 ppm in the cell culture media. EX1003, ¶ 205 n. 12.

A POSA would have been able to modify the known techniques in the art to achieve far less than 10 ppm detergent for rice-derived rHSA, if desired, using routine optimization. EX1003, ¶ 206. Indeed, the prior art indicates that under optimized conditions, levels of less than 1 ppm detergent could be achieved. EX1009, [0075]-[0076], Table 3.

Thus, claim 1 would have been obvious over Hatsuyama in view of Deeter and a POSA's general knowledge that detergents used to purify proteins should be removed to concentrations of less than 10 ppm.

2. Claim 2

Claim 2 depends from claim 1 and further requires that the "recombinant human albumin is a sterile liquid or powder." EX1001, claim 2.

Hatsuyama teaches that its rHSA may be prepared as a sterile liquid or powder composition. EX1003, ¶¶ 209-212; EX1004, [0031], [0041]. Hatsuyama explains that sterilization may be achieved "by filtration sterilization through a bacterial retention filter, combining with a bactericidal agent, or irradiation." EX1004, [0043]. Thus, claim 2 would have been obvious to a POSA.

3. Claim 3

Claim 3 depends from claim 1 and further requires that the recombinant human albumin "has a molecular weight of 65-75 kDa." EX1001, claim 3.

Hatsuyama's cell culture media modified in view of Deeter would contain rHSA having a molecular weight of 66.9 to 68.1 kDa, as disclosed in Deeter. EX1005, Table 3 (page 31). Thus, claim 3 would have been obvious to a POSA. EX1003, ¶ 214.

4. Claim 4

Claim 4 depends from claim 1 and further requires that the recombinant human albumin "has an isoelectric focusing point of 5.3." EX1001, claim 4.

Hatsuyama's cell culture media modified in view of Deeter would contain rHSA having an isoelectric focusing point of 5.3, as disclosed in Deeter. EX1005, Table 3. Thus, claim 4 would have been obvious to a POSA. EX1003, ¶ 216.

5. Claim 5

Claim 5 depends from claim 1 and further requires that the recombinant human albumin comprises "albumin and fragments thereof provided that the fragments retain the biological or therapeutically beneficial activity of said albumin," i.e., "albumin and fragments thereof provided that the fragments retain the biological or therapeutically beneficial activity associated with native albumin." EX1001, claim 5.

Hatsuyama's cell culture media modified in view of Deeter would contain rHSA and fragments thereof, as Deeter discloses that its recombinant proteins include "albumin ... and fractions thereof." EX1005, [0061]; EX1005, [0081] (stating that the disclosed plant produced heterologous proteins are "preferably human" and include "growth factors, lactoferrin, transferrin, ***serum albumin***, insulin, growth hormone, ***and fractions thereof*** ...."); EX1003, ¶¶ 218-222.

As Dr. Clark explains, a POSA would have expected a fragment (or fraction) of Deeter's rice-derived rHSA to retain the activity associated with native albumin, as albumin by nature has three homologous domains, each of which has beneficial biological activity. EX1003, ¶ 221. Indeed, even if albumin lost an entire domain or

subdomain, a POSA would have expected that the fragment would retain the beneficial activity associated with native albumin. *Id.* Thus, claim 5 would have been obvious to a POSA.

6. Claim 6

Claim 6 depends from claim 1 and further requires that the recombinant human albumin comprises "albumin dimers having a molecular weight of about 130 kDa as detected by SDS-PAGE." EX1001, claim 6.

Hatsuyama's cell culture media in view of Deeter would have been reasonably expected to comprise albumin dimers, particularly when processed following the guidance in Hatsuyama. EX1003, ¶ 1003. Hatsuyama teaches that its rHSA may be subject to lyophilization—a technique commonly performed on research chemicals—and a POSA would have reasonably expected that lyophilization would induce the formation of albumin dimers. EX1003, ¶ 224; EX1004, [0031].

A POSA would have also understood that the dimers present in and/or formed during processing of Deeter's rHSA would have had "a molecular weight of about 130 kDa as detected by SDS-PAGE," as recited in claim 6, because Deeter's rHSA had a molecular weight of 66 kDa as observed by SDS-PAGE, and a POSA would have expected to observe dimers by SDS-PAGE at around 130 kDa (twice the molecular weight of one rHSA—66 kDa + 66 kDa = 132 kDa). EX1003, ¶ 225.

Thus, claim 6 would have been obvious to a POSA.

7. Claim 7

Claim 7 depends from claim 1 and further requires that the recombinant human albumin comprises "less than 2% aggregates at around 250 kDa as detected by SDS-PAGE." EX1001, claim 7.

A POSA would have been motivated to eliminate albumin oligomers (if present[2]) when purifying rHSA for use in Hatsuyama's cell culture media, as such higher aggregates would not have been expected to provide the same beneficial delivery of cell nutrients as non-aggregated rHSA. EX1003, ¶ 228.

A POSA would have reasonably expected to remove albumin oligomers from the rHSA preparation using routine processing steps such as gel filtration. EX1003, ¶ 229. A POSA would have also understood that omitting Hatsuyama's optional step of lyophilizing rHSA would maximize the amount of monomeric rHSA. *Id.* Alternatively, a POSA would have reasonably expected that any albumin oligomers formed during lyophilization would be converted to monomeric and dimeric albumin when the lyophilized protein was reconstituted in water. *Id.*

Thus, claim 7 would have been obvious to a POSA.

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[2] While the data in the '389 patent indicate that prior batches of rHSA/Cellastim comprised more than 2% albumin aggregates around 250 kDa, those data do not reflect the content of *Deeter's* rHSA. EX1003, ¶¶ 231-233.

8. Claim 8

Claim 8 depends from claim 1 and further requires that the recombinant human albumin has "an amino acid sequence that is homologous to native human albumin," i.e., recombinant human albumin and native human albumin that "have sequence homology, as reflected by their sequence similarity, whether in terms of percent identity or by the presence of specific residues or motifs and conserved positions." EX1001, claim 8; *supra*, 26.

Hatsuyama's cell culture media modified in view of Deeter would comprise rHSA having an amino acid sequence that is homologous to native human albumin. EX1003, ¶ 235; EX1005, [0103]-[0104], Fig. 17. Indeed, Deeter's rHSA would be expected to include 100% of the amino acid sequence of native human albumin. EX1003, ¶ 239. For example, Deeter discloses codon-optimizing the "consensus sequence" of P02768 (Swiss-Prot) for "suitable expression of human serum albumin in rice grain." EX1005, [0103]; EX1003, ¶ 235 (explaining that codon optimization optimizes protein expression but does not alter the amino acid sequence of the protein). Deeter further discloses confirming the "correct DNA and protein sequences," and using the optimized gene to express rHSA. EX1005, [0103]-[0105], Table 2, Fig. 17. Thus, claim 8 would have been obvious to a POSA.

9. Claim 9

Claim 9 depends from claim 1 and further requires that the recombinant human albumin is "recombinant human serum albumin." EX1001, claim 9. Hatsuyama's cell culture media modified in view of Deeter would comprise recombinant human serum albumin (rHSA). EX1003, ¶ 237; EX1005, [0103]. Thus, claim 9 would have been obvious to a POSA.

10. Claim 10

Claim 10 depends from claim 9 and further requires that the rHSA "has an amino acid sequence that is at least 80% identical to secreted human serum albumin comprising the amino acid sequence of SEQ ID NO: 1." EX1001, claim 10. SEQ ID No. 1 is the sequence of amino acids naturally present in mature secreted HSA identified as "Swiss-Prot P02768." *Id.*, 38:24-53.

Hatsuyama's cell culture media modified in view of Deeter satisfies the limitation of claim 10. Deeter's rHSA was expressed using a codon optimized HSA sequence "based on the native protein sequence derived from P02768 (Swiss-Prot)." EX1003, ¶ 239; EX1003, ¶ 235 (explaining that codon optimization optimizes protein expression but does not alter the amino acid sequence of the protein); EX1005, [0039]; *see also* EX1005, [0103], Fig. 17. Thus, claim 10 would have been obvious to a POSA.

11. Claim 11

Claim 11 depends from claim 1 and further requires that the rHSA has "the amino acid sequence of SEQ ID NO: 12." EX1001, 11. "SEQ ID NO 12" is listed in columns 121-124 of the '389 patent, where it is identified using standard three-letter codes. EX1003, ¶ 241.

Hatsuyama's cell culture media modified in view of Deeter satisfies the limitation of claim 11, as the same sequence is disclosed in Deeter. As Dr. Clark explains, SEQ ID NO. 12 also appears in Figure 5A of the '389 patent and Figure 17 of Deeter, where the sequence is listed using one-letter codes. EX1003, ¶¶ 242-243 (showing that converting Deeter's one-letter code to three-letter code results in the same sequence disclosed in the '389 patent); EX1001, Fig. 5A; EX1005, Fig. 17.

Thus, claim 11 would have been obvious to a POSA.

12. Claim 12

Claim 12 depends from claim 1 and further requires that the recombinant human albumin comprises "one or more bound lipids from a plant." EX1001, claim 12.

Hatsuyama's cell culture media modified in view of Deeter satisfies the limitation of claim 12, as a POSA would have reasonably believed that Deeter's rHSA contained one or more lipids from a plant. EX1003, ¶ 246. First, Deeter's rHSA had a thermal stability around 65 °C, which is consistent with the heat stability

of albumin bound to fatty acids (which are lipids). *Id.*, ¶ 247; EX1005, Table 3; EX1020, 1-2. A POSA would have understood that lipids such as fatty acids bound to Deeter's rHSA were "from a plant" (as recited in claim 12), as there is no other apparent source of fatty acids. EX1003, ¶ 247.

A POSA's expectation that Deeter's rHSA comprised bound plant lipids and/or plant fatty acids would have been bolstered by the results of Deeter's rHSA in culture. EX1003, ¶ 248; EX1005, [0118]-[0200], Figs. 23-24. As Dr. Clark explains, the ability of Deeter's rHSA to promote the growth of hybridoma cells would have been attributed, at least in part, to the presence of fatty acids bound to albumin, as fatty acids were essential for hybridoma growth in culture. EX1003, ¶ 248.

A POSA would have reasonably expected Deeter's rHSA would retain bound lipids/fatty acids, even if such rHSA were treated with a detergent to remove endotoxins and subjected to detergent removal using an HIC sorbent. EX1003, ¶ 249. The prior art taught that bound fatty acids should be released from albumin by treatment with acid (e.g., at pH 3.0) to allow for their removal by a hydrophobic resin, and the known, common techniques for removing endotoxins and detergents discussed above do not involve treatment with acid or otherwise lowering the pH to 3.0. *Id.*; EX1013 (Peters), 337. Additionally, treatment with an HIC sorbent did not

alter the function of albumin, and a POSA would not have expected albumin to retain its normal function if ***all*** the bound fatty acids had been removed. EX1003, ¶ 249.

Thus, claim 12 would have been obvious to a POSA.

Moreover, the '389 patent does not expressly state that its rHSA comprised bound lipids from a plant. *Id.*, ¶ 252. It appears that the inventors expected that a POSA would understand that the rHSA of the '389 patent comprised bound lipids from a plant, even after the purification process disclosed therein, and even if the presence of bound lipids was not explicitly stated. *Id.*, ¶¶ 251-256. As Dr. Clark notes, the same understanding would have applied to Deeter and been reinforced by the thermal stability of Deeter's rHSA and the ability of Deeter's rHSA to promote the growth of hybridoma cells in culture. *Id.*, ¶ 256.

13. Claim 13

Claim 13 depends from claim 1 and further requires that the recombinant human albumin "is a protein extract of a transgenic monocot plant." EX1001, claim 13. Hatsuyama's cell culture media modified in view of Deeter would comprise a protein extract of a transgenic monocot plant, as Deeter discloses that its rHSA is an extract from transgenic rice grains, and rice is a monocot. EX1003, ¶ 257; EX1005, [0103], claim 3 (page 34). Thus, claim 13 would have been obvious to a POSA.

14. Claim 14

Claim 14 depends from claim 13 and further requires that the recombinant human albumin comprises "a monocot seed component," i.e., EX1001, claim 14. As noted above, monocot seed components are defined as "carbohydrate, protein, and lipid components extractable from monocot seeds, typically mature monocot seeds." EX1001, 23:18-20. The identical definition is disclosed in Deeter. EX1005, [0056].

Hatsuyama's cell culture media modified in view of Deeter would contain rHSA comprising "a monocot seed component," as POSA would have reasonably expected that Deeter's rHSA comprised bound lipids from a plant, which are "monocot seed components," as required by claim 14. EX1003, ¶¶ 259-260. Thus, claim 14 would have been obvious to a POSA.

15. Claim 15

Claim 15 depends from claim 14 and further requires that the monocot seed component "is a plant carbohydrate or plant lipid." EX1001, claim 15. This claim would have been obvious for all the reasons discussed above for claims 12 and 14, as Hatsuyama's cell culture media modified in view of Deeter would comprise rHSA expectedly bound to plant lipids. *Supra*, § IX.C.12, 14. Thus, claim 15 would have been obvious to a POSA.

16. Claims 16 and 17

Claims 16 and 17 depends from claim 13 and further requires that the recombinant human albumin "is a protein extract of a transgenic seed" (claim 16) or

"a protein extract of a transgenic rice seed" (claim 17). EX1001, claims 16, 17. Hatsuyama's cell culture media modified in view of Deeter would comprise rHSA that is a protein extract of a transgenic seed, specifically, a transgenic rice seed. EX1003, ¶¶ 262-263; EX1005, [0105]. Thus, claims 16 and 17 would have been obvious to a POSA.

17. Claim 18

Claim 18 depends from claim 17 and further requires that the "rice is *Oryza sativa*." EX1001, claim 18.

A POSA modifying Hatsuyama's cell culture media modified in view of Deeter would have been motivated to use extract rHSA from transgenic *Oryza sativa* rice seeds, as that was the only expression host employed in Deeter. EX1003, ¶ 265. For example, Deeter identifies using *Oryza sativa* (Taipei 309) to produce recombinant human epidermal growth factor (rhEGF), recombinant human insulin-like growth factor I (rhIGF), recombinant human intestinal trefoil factor (rhITF), and recombinant human lactoferrin (rhLF). EX1005, [0026], [0030], [0034], [0037], [0099]-[0100] (rhLF). A POSA would have reasonably expected that *Oryza sativa* was used to express rHSA, or at a minimum would have been motivated to select *Oryza sativa* as an appropriate host for such expression. EX1003, ¶ 266.

Thus, claim 18 would have been obvious to a POSA.

18. Claim 19

Claim 19 depends from claim 1 and further requires that the cell culture media supplement or complete media composition "is free of serum derived albumin and yeast derived albumin." EX1001, claim 19.

Hatsuyama's cell culture media modified in view of Deeter would have contained rHSA expressed in transgenic rice as the only albumin, i.e., it would be "free of serum derived albumin and yeast derived albumin," as required by claim 19. EX1003, ¶ 268.

Thus, claim 19 would have been obvious to a POSA.

19. Claims 20 and 21

Claim 20 depends from claim 1 and further requires that the composition comprise "at least one additional protein," and claim 21 depends from claim 20 and further requires that the additional protein "is selected from the group consisting of growth factors, lactoferrin, ***transferrin***, ***insulin***, growth hormone...." EX1001, claims 20, 21.

Both Hatsuyama and Deeter teach cell culture media comprising rHSA and at least one additional protein, e.g., transferrin and insulin. EX1003, ¶ 271; EX1004, [0078], [0079] (cell culture media comprising rHSA, insulin, and holotransferrin); EX1005, [0118], [0119] (cell culture media comprising rHSA, insulin, and transferrin).

Thus, claims 20 and 21 would have been obvious to a POSA.

20. Claim 22

Claim 22 depends from claim 20 and further requires that the additional protein "is a heterologous plant-produced protein." EX1001, claim 22.

A POSA modifying Hatsuyama's cell culture media in view of Deeter would have been motivated to replace Hatsuyama's transferrin with Deeter's heterologous plant-produced recombinant lactoferrin to avoid the known disadvantages of using proteins sourced from animals. EX1003, ¶¶ 276-279.

First, Deeter suggests using "***at least*** one plant-produced heterologous protein as a cell culture component." EX1005, [0081]. A POSA would have thus been motivated to combine Deeter's plant-produced rHSA with other plant-produced proteins. EX1003, ¶ 276. Next, Deeter explains that plant-produced recombinant human lactoferrin "can replace animal-derived transferrin in cell culture media for hybridoma growth." *Id.*, [0113]; *see also id.*, [0114]-[0115], Table 2.

A POSA would have reasonably expected Deeter's recombinant human lactoferrin would serve as an advantageous replacement for transferrin in other systems, including Hatsuyama's. EX1003, ¶ 279. Indeed, Deeter indicates that its method of combining plant-produced recombinant proteins applies to cell culture media generally (e.g., it was not limited to hybridoma cells), and specifically notes

that cell culture media includes media for stem cells (e.g., Hatsuyama's cells). *See* EX1005, [0002], claim 12.

Thus, claim 22 would have been obvious to a POSA.

21. Claim 23

Claim 23 depends from claim 20 and further requires that the cell culture media comprise "selenium and ethanolamine." EX1001, claim 23.

A POSA would have been motivated to try well-known cell culture media supplements components such as selenium and ethanolamine when modifying Hatsuyama's cell culture media in view of Deeter. EX1003, ¶ 283; *Adapt Pharma*, 25 F.4th at 1367 (determining that it would have been obvious to include a "commonly used" ingredient).

First, Deeter discloses combining rHSA with sodium selenite and ethanolamine to promote the growth of hybridoma cells in cell culture media. EX1005, [0118], [0119]. That is, Deeter discloses ethanolamine, and a POSA would have understood that sodium selenite was a source of selenium, a common nutrient in cell culture media. EX1003, ¶¶ 282-283.

Next, a POSA would have understood that selenium and ethanolamine promoted the serum-free cultivation of many cell types and would have been motivated to include such well-known, beneficial components in Hatsuyama's cell culture media. EX1003, ¶ 284. A POSA would have had a reasonable expectation of

success in doing so, as selenium and ethanolamine were common cell culture media supplements used to promote the growth of a variety of cells in serum-free media. *Id.*

Thus, claim 23 would have been obvious to a POSA.

22. Claim 24

Claim 24 is an independent claim that recites a cell culture media supplement or complete media composition comprising plant-produced recombinant human albumin, where the recombinant human albumin comprises "i) less than 1 EU endotoxin/mg of albumin; and ii) a monocot seed component, wherein said monocot seed component is a plant carbohydrate or plant lipid." EX1001, claim 24.

The limitations of claim 24 are also required by claim 1 (e.g., recombinant human albumin comprising less than 1 EU endotoxin/mg albumin) and claims 12, 14, and 15 (a monocot seed component that is a plant carbohydrate or plant lipid).

Thus, claim 24 would have been obvious to a POSA for all the reasons set forth above for claims 1, 12, 14, and 15. EX1003, ¶ 286.

23. Claim 25

Claim 25 depends from claim 24 and further requires that said recombinant human albumin has a purity of greater than 95%. EX1001, claim 25.

Hatsuyama's cell culture media modified in view of Deeter would comprise rHSA having a purity of greater than 95%, as Deeter discloses that its rHSA may be

purified "to approximately 98% based on scanning analysis by SDS-PAGE gels." EX1005, [0116]; EX1003, ¶ 288. As explained in the '389 patent, protein purity may be evaluated by SDS-PAGE. EX1001, 22:31-34.

Thus, claim 25 would have been obvious to a POSA. EX1003, ¶¶ 287-288.

24. Claim 26

Claim 26 is an independent claim that recites a cell culture media supplement or complete media composition containing recombinant mammalian albumin (e.g., recombinant human albumin) that is "i) produced in a transgenic plant; and ii) has less than 1 EU endotoxin/mg albumin." EX1001, claim 26.

The limitations of claim 26 are also required by claim 1. As such, claim 26 would have been obvious for all the reasons discussed above for claim 1. EX1003, ¶ 289.

25. Claims 27-29

Claims 27, 28, and 29 depend from claim 26 and further require that the albumin is rHSA (claim 27), that the transgenic plant is a transgenic grain (claim 28), specifically, transgenic rice (claim 29). Hatsuyama's cell culture media modified in view of Deeter would satisfy the limitations of claims 27-29, as Deeter discloses rHSA expressed in a transgenic grain, specifically, rice. EX1003, ¶ 290; EX1005, [00103]-[0105]. Thus, claims 27-29 would have been obvious to a POSA.

IX. Secondary Considerations

Petitioner is unaware of any secondary considerations that support the patentability of the claims of the ’389 patent. As Dr. Clark explains, the ’389 patent does not describe any results that would have been surprising or unexpected to a person of ordinary skill in the art familiar with the closest prior art that existed in February 2010 (or even 2009), e.g., Hatsuyama and Deeter.

A. Achieving “less than 1 EU endotoxin/mg albumin” Was Not Unexpected

As Dr. Clark explains, a POSA would not have considered it unexpected to achieve rHSA comprising less than 1 EU endotoxin/mg albumin. EX1003, ¶ 299. Indeed, the prior art discloses a technique that provided complete removal of endotoxin from BSA, and a POSA would have reasonably expected that a technique that removed endotoxins from BSA would also work for Deeter’s rHSA. EX1003, ¶¶ 299-301; *supra*, § IV.G. Indeed, the inventors of the ’389 patent recognized that techniques for purifying one albumin would work for another. EX1001, 50:1-12 (explaining that known methods of purifying albumin may be used to purify the “albumin of the present invention.”). And, notably, claim 26 broadly recites “recombinant mammalian albumin” comprising “less than 1 EU endotoxin/mg of albumin,” indicating that the inventors appreciated that a technique that worked for rHSA would also work for other mammalian albumins, e.g., recombinant BSA.

B. rHSA Comprising "less than 10 ppm detergent" Was Not Unexpected

As Dr. Clark explains, there is no evidence that achieving rHSA comprising "less than 10 ppm detergent" was unexpected. EX1003, ¶¶ 305-306; EX1006, 700 (asserting that removing endotoxins was surprising while not asserting that removing detergent was surprising). For example, the prior art contains numerous teachings regarding removing detergents using a hydrophobic detergent-binding resin (an HIC sorbent). EX1003, ¶¶ 305-306.

C. The '389 Patent Does Not Describe Any Unexpected Results in Cell Culture Media

As Dr. Clark explains, the '389 patent does not provide any surprising results in cell culture media, despite its repeated references to "surprising" activity. EX1003, ¶¶ 307-310; EX1001, 31:50-56, 92:57-60, 94:33-37.

For example, the '389 patent purports to describe unexpected synergy with rHSA and recombinant lactoferrin, yet it provides no data showing the effect of combining HSA and lactoferrin for comparison. EX1003, ¶ 309; EX1001, 85:1-87:38. Thus, the purported synergy may simply be the natural result of combining the native forms of such proteins. EX1003, ¶ 308.

At most, the '389 patent includes comparative data for rHSA versus pHSA in combination with recombinant transferrin (rTF), where the combination of rHSA and rTF had a greater than additive effect, while pHSA and rTF did not. EX1003,

¶ 309; EX1001, 92:62-95:13. However, the claims of the '389 patent are not limited to combinations of rHSA and rTF. For example, claim 21 requires recombinant albumin combined with an additional protein selected from a list that includes transferrin but does not require that the additional protein be produced in a plant, and claim 22 requires recombinant albumin in combination with *any* plant-produced heterologous protein (not limited to transferrin). EX1001, claims 20-22.

Next, the '389 patent asserts that "[s]urprisingly, despite the increased product purity [of new versus old batches of rHSA], these changes in processing also resulted in enhanced co-purification of heat shock proteins, (see below) with the recombinant albumin." EX1001, 73:45-53. As Dr. Clark explains, the '389 patent does not provide any data to support this assertion—and the data in Tables E3 and E4 tend to undermine the presence of more heat shock proteins in the purportedly new rHSA. EX1003, ¶ 310.

X. Discretionary Denial of Institution Is Not Warranted

The Board should institute review of the '389 patent. First, there are no related matters involving the '389 patent, making denial under § 314(d) inappropriate. *Infra*, § XII.B.

Next, this IPR should be instituted because the evidence identified in this Petition was neither before the Office nor fully considered during prosecution. *See*

Advanced Bionics, LLC v. MED-EL Elektromedizinische Gerate GmbH, IPR2019-01469, Paper 6, at 6–11 (Pat. Tr. & App. Bd. Feb. 13, 2020) (precedential).

First, Hatsuyama was not cited or disclosed during prosecution. Nor is Hatsuyama cumulative over the art of record during prosecution. 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, and where the cell culture media comprising such rHSA provided superior results compared to comparable media comprising pHSA. EX1004, [0016], [0024]-[0026], Table 1. *See Thorne Research, Inc. v. Tr. of Dartmouth Coll.*, IPR2021-00491, Paper 18, at 8–9 (Pat. Tr. & App. Bd. Aug. 12, 2021) (using a reference that discloses new or additional subject matter may prevent the Board from finding the art to be substantially the same).

Next, while Deeter was considered during prosecution, the Examiner made two material errors when discussing Deeter. EX1003, ¶¶ 32-36. First, the Examiner erroneously concluded that "the levels of endotoxin in the cell culture medium were not appreciated at the time of Deeter's invention." EX1002, 281. But the Applicant's Declaration submitted during prosecution indicates that endotoxin contamination in Deeter's rHSA was "observed"—it was simply not reported. EX1006, 698. Further, a POSA would have appreciated that Deeter's rHSA was contaminated with

endotoxin. EX1003, ¶ 33. Endotoxins would have expectedly contaminated recombinant proteins expressed in plants grown in dirt (like Deeter's transgenic rice), as noted by Larrick (EX1039, 4), McDonald (EX1036, 2), Brereton (EX1040, 3, 7), and Fujiwara (EX1041, 2, 5)—none of which were of record during prosecution.[3] EX1003, ¶¶ 112-117.

Second, the Examiner erroneously concluded that Deeter's rHSA was "incapable" of achieving "less than 1 EU endotoxin/mg albumin [see Table E3 and Table E4]." EX1002, 281. As an initial matter, neither Table E3 nor Table E4 (cited by the Examiner) concern ***Deeter's*** rHSA. EX1003, ¶¶ 38-41. Moreover, there is nothing about Deeter's rHSA that renders it "incapable" of purification using successful techniques repeatedly disclosed in the prior art. EX1003, ¶ 34. In this regard, it is notable that, prior to June 10, 2022, no art of record described a simple, cost-effective technique for removing endotoxins from albumin solutions, as initially disclosed in Aida (EX1044, 1-5) and discussed by Magalhaes (EX1042, 10-11). EX1003, ¶ 36. On June 10, 2022, the Applicant submitted Aida among over 100 documents for the Examiner's consideration. EX1002, 179-219. Aida's disclosures suggest the Examiner did not appreciate Aida's teachings, including the ease of

[3] The full titles of the publications cited herein are provided in Petitioner's Exhibit List.

purifying albumin to remove endotoxin, which contradicts the assertion that "the compositions of Deeter et al. are ***incapable*** of achieving less than 1 EU of endotoxin/mg albumin." *See* EX1002, 323. At a minimum, the Examiner did not have the benefit of Magalhaes's discussion of Aida's technique and its application to recombinant proteins. EX1042, 10-11.

Further, apart from Aida (submitted in 2022), it does not appear that the prosecution record includes any publications explaining the importance of removing detergent from proteins intended for use in cell culture media, e.g., Van Holten (EX1007), Schulz (EX1008), Viswanathan (EX1009), and Bonomo (EX1059). EX1003, ¶¶ 37. Nor does the record appear to contain any publications detailing the routine removal of detergents from protein solutions, e.g., Burnouf (EX1049), Piquet (EX10050), Guerrier (EX1051), Bonomo (EX1059); the applicability of that technique to HSA (Guerrier, EX1051) and recombinant proteins (Van Holten, EX1007); and the striking similarity of BSA to pHSA that supports a POSA's reasonable expectation of success in purifying equivalent albumins such as Deeter's rHSA, e.g., Atmeh (EX1017), Tanaka (EX1053), Jachimska (EX1054), Brahma (EX1055), and Gorin (EX1056).

Healthgen notes that it previously submitted a petition for IPR of the '951 patent. *See Wuhan Healthgen Biotechnology Corp. v. Ventria Bioscience Inc.*, IPR2022-00712. The Board denied institution in that matter. *Id.*, Paper No. 8.

Healthgen submits the claims of the ’389 patent are much broader and rendered unpatentable by the prior art identified here, and the prior art and arguments presented herein have addressed any pertinent issues identified by the Board in denying institution against the ’951 patent.

Accordingly, any argument for non-institution under § 325(d) is misplaced.

XI. Grounds for Standing

Petitioner certifies that the ’389 patent is available for an IPR and that Petitioner is not barred or estopped from requesting institution of an IPR on the grounds presented herein.

XII. Mandatory Notices Under 37 C.F.R. § 42.8

A. Real Parties-in-Interest

Petitioner Wuhan Healthgen Biotechnology Corporation is the real party-in-interest.

B. Related Matters

Healthgen notices the following related U.S. patents and applications related to the ’389 patent:

- Application No. 17/212,403, filed on Mar. 25, 2021;
- U.S. Patent No. 10,981,974, which issued from Application No. 16/847,337, filed on Apr. 13, 2020;
- U.S. Patent No. 10,618,951, which issued from Application No. 15/188,478, filed on Jun. 21, 2016;

- Application No. 12/708,462, filed on Feb. 18, 2010, now abandoned; and

- Provisional Application No. 61/154,204, filed on Feb. 20, 2009.

Healthgen is not presently involved in any other matters involving the ’389 patent. Healthgen is identified in the following matters related to the ’951 patent (listed above), which issued from an application in the chain of priority to the ’389 patent:

- *Ventria Bioscience Inc. v. Wuhan Healthgen Biotechnology Corp.* DKS-5-21-cv-04008 (D. Kan.) (complaint filed Feb. 5, 2021) (“Kansas Litigation”). This district court action was stayed pursuant to 28 U.S.C. § 1659 on March 4, 2021.

- *Wuhan Healthgen Biotechnology Corp. v. Int’l Trade Comm’n*, No. 2023-1389 (Fed. Cir.), which is an appeal from: *Certain Plant-Derived Recombinant Human Serum Albumins (“rHSA”) and Products Containing Same*, U.S.I.T.C. Inv. No. 337-TA-1238 (instituted Jan. 25, 2021) (“ITC Investigation”).

C. Lead and Backup Counsel

Lead Counsel	Backup Counsel
Maximilienne Giannelli Reg. No. 57,286 Finnegan, Henderson, Farabow, Garrett & Dunner, LLP 1875 Explorer St., Suite 800 Reston, VA 20190-6023 (571) 203-2432 Maximilienne.Giannelli@finngan.com	Joshua Goldberg (Reg. No. 59,369) Finnegan, Henderson, Farabow, Garrett & Dunner, LLP 901 New York Avenue, N.W. Washington, DC 20001 (202) 408-6092 Joshua.Goldberg@finnegan.com Ningling Wang Reg. No. 52,412 Finnegan, Henderson, Farabow, Garrett & Dunner, LLP Mirae Asset Tower, Units 28A-B Shanghai, 200120 PRC +86-21-6194-2000 Ningling.Wang@finnegan.com Jessica L. Roberts Reg. No. 73,656 Finnegan, Henderson, Farabow, Garrett & Dunner, LLP 901 New York Avenue, NW Washington, DC 20001 (202) 408-4323 Jessica.Roberts@finnegan.com

D. Service Information

Please send all correspondence to lead and backup counsel at the address shown above. Petitioner consents to service by e-mail sent to the following e-mail addresses:

Maximilienne.Giannelli@finngan.com

Joshua.Goldberg@finnegan.com

Ningling.Wang@finnegan.com

Jessica.Roberts@finnegan.com

HealthgenIPR@finnegan.com

XIII. Payment of Fees

The required fees are submitted herewith in accordance with 37 C.F.R. §§ 42.103(a) and 42.15(a). If any additional fees are due during this proceeding, the Office is authorized to charge Deposit Account No. 06-0916.

XIV. Conclusion

Healthgen respectfully requests that the Board grant this Petition for IPR, institute trial, and find all challenged claims unpatentable.

Respectfully submitted,

Dated: March 31, 2023

By: */s/ Maximilienne Giannelli*

Maximilienne Giannelli, Lead Counsel
Reg. No. 57,286

Counsel for Wuhan Healthgen Biotechnology Corp.

CERTIFICATE OF COMPLIANCE WITH WORD COUNT

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that this Petition complies with the type-volume limits of 37 C.F.R. § 42.24(a)(1)(i), because it contains 13,724 words, according to the word-processing system used to prepare this Petition, excluding the words in the Table of Contents, Table of Authorities, Mandatory Notices, Certification Under § 42.24(d), and Certificate of Service, as set forth in 37 C.F.R. § 42.24(a)(1).

Respectfully submitted,

Dated: March 31, 2023

By: */s/ Maximilienne Giannelli*

Maximilienne Giannelli, Lead Counsel
Reg. No. 57,286

Counsel for Wuhan Healthgen Biotechnology Corp.

CERTIFICATE OF SERVICE

The undersigned certifies that, in accordance with 37 C.F.R. § 42.6(e) and 37 C.F.R. § 42.105, **Petition for *Inter Partes* Review; Petitioner's, Wuhan Healthgen Biotechnology Corp., Power of Attorney; Petitioner's, Wuhan Healthgen Biotechnology Corp., Exhibit List, and the associated Healthgen Exhibits 1001-1060 are being served via FedEx on the 31 day of March 2023**, the same day as the filing of the above-identified documents in the United States Patent and Trademark Office/Patent Trial and Appeal Board, upon the Patent Owner by serving the correspondence address of record with the USPTO as follows:

Crissa A. Seymour Cook
Hovey Williams LLP
10801 Mastin Blvd., Suite 1000
84 Corporate Woods
Overland Park, Kansas 66210
Telephone: (913) 647-9050
Email: cac@hoveywilliams.com

Dated: March 31, 2023

By: */Lauren K. Young/*
Lauren K. Young
Litigation Legal Assistant
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.