PUBLIC VERSION

UNITED STATES INTERNATIONAL TRADE COMMISSION
WASHINGTON, D.C.

In the Matter of **CERTAIN PLANT-DERIVED RECOMBINANT HUMAN SERUM ALBUMINS ("rHSA") AND PRODUCTS CONTAINING SAME**	**Investigation No. 337-TA-1238**

RESPONDENT HEALTHGEN'S PETITION FOR REVIEW OF THE FINAL INITIAL DETERMINATION

Wuhan Healthgen Biotechnology Corp. v. Ventria Bioscience Inc.
IPR2023-00684
Ventria Exhibit 2003

TABLE OF CONTENTS

I. INTRODUCTION 1

II. SUMMARY OF ISSUES REQUIRING COMMISSION REVIEW 3

III. STANDARD OF REVIEW 4

IV. THE COMMISSION SHOULD REVIEW AND REVERSE THE FID'S FINDINGS ON INFRINGEMENT 5

A. Introduction 5

B. The FID Erroneously Concluded that Healthgen's Medium Grade Products Infringe Claims 1 and 11-13 of the '951 Patent 5

1. The FID Failed to Address Ventria's Testing Establishing Healthgen's Medium Grade Products Do Not Infringe 5

a. Detailed Analysis of Ventria's Native-PAGE Data 7

2. The FID Erroneously Relied on Healthgen's Customer Communications to Show Infringement 11

3. The FID Erroneously Concludes Healthgen's Medium Grade Products Are the Same as the Clinical Grade Products 19

a. Healthgen's Medium Grade Products Are Different from the Clinical Grade Products 19

b. The FID's findings based on Mr. Shi's testimony and the flow chart are clearly erroneous. 20

C. The FID Erroneously Concluded that Healthgen's Clinical Grade Liquid Product Infringes Claims 1 and 11-13 of the '951 Patent 27

1. The FID Erroneously Relied on Data Collected in China 27

2. The FID Erroneously Relied on Reducing SDS-PAGE Data 31

a. Reducing SDS-PAGE Breaks Up Certain Albumin Aggregates 31

b. Reducing SDS-PAGE Artificially Decreased the Percent of Aggregated Albumin in Healthgen's Clinical Grade Products 36

3. The FID Erroneously Concluded that Reducing SDS-PAGE Is an Appropriate Test for Quantifying *Total* Aggreged Albumin 38

a. The '951 Patent Does Not Quantify *Total* Aggregated Albumin Using Reducing SDS-PAGE 38

b. The Peer-Reviewed Literature Confirms *Reducing* SDS-PAGE Is Not a Suitable Method for Quantifying *Total* Aggregates in an *Unaltered* Sample 39

c. The FID's Criticism of Dr. DeFilippi's Testimony Is Misplaced. 41

d. Dr. Wilken's Testimony Regarding SDS-PAGE Does Not Support the FID's Conclusion Regarding *Reducing* SDS-PAGE 43

e. Statements that Agents Like "SDS" Do Not Increase Monomer Content Say Nothing about the Impact of *Reducing* Agents 43

f. Healthgen's Internal Documents [redacted] 44

D. The FID Does Not Address Arguments Presented by Healthgen 45

V. THE COMMISSION SHOULD REVIEW AND REVERSE THE FID'S FINDINGS ON DOMESTIC INDUSTRY – TECHNICAL PRONG 47

A. The FID Improperly Relied on Reducing SDS-PAGE for Technical ID 47

B. The FID's Interpretation of the Data Is Based on an Error of Law 48

VI. THE COMMISSION SHOULD REVIEW AND REVERSE THE FID'S FINDINGS ON VALIDITY 53

A. The FID's Conclusion that Van Urk or Berezenko Do Not Anticipate Claims 1 and 11 Is Based on an Incorrect Legal Standard and Clearly Erroneous Factual Findings 53

1. "a cell culture media supplement or complete media composition" 54

2. "produced in a transgenic plant" 54

3. "less than 1 EU of endotoxin/mg of albumin" 55

4. "less than 2% aggregated albumin" 56

5. The FID's Misapplied the "At Once Envisage" Precedent 57

6. The FID's Finding that the PTO Considered the "Substance" of Van Urk is Clearly Erroneous 58

B. The Commission Should Reverse FID's Finding that Van Urk Does Not Anticipate Claim 12 59

C. The FID's Analysis of Prior Art Enablement Is Based on Legal Error and Clearly Erroneous Findings 59

1. The FID's Finding that Van Urk and Berezenko "are specific to yeast-derived rHSA" and would not "read on" the recited plant-derived rHSA is Clearly Erroneous 59

2. The FID's Finding that Van Urk and Berezenko Are not Enabling is Based on a Wrong Legal Standard and Clearly Erroneous 61

D. The FID's Conclusion that The Asserted Claims Are Nonobvious is Based on Legal Errors and Clearly Erroneous Factual Findings 66

1. The FID's Conclusion that a POSA Would Not Have Been Motivated to Combine Deeter with Van Urk or Berezenko Is Clearly Erroneous 66

2. The FID Applied the Wrong Analysis for Reasonable Expectation of Success 70

3. The FID's Finding that Healthgen Waived its Argument Regarding "DEAE-Sepharose" Chromatography is Clearly Erroneous 73

4. The FID's Failure to Address Two of Healthgen's Obviousness Grounds Against Claims 12 and 13 Warrants Review and Remand/Reversal 76

E. Ventria Failed to Overcome a Strong Prima Facie Case of Obviousness 79

VII. THE COMMISSION SHOULD REVIEW AND REVERSE THE FID'S FINDINGS ON DOMESTIC INDUSTRY – ECONOMIC PRONG 79

A. The FID Improperly Included Investments in Non-Domestic Industry Products in Ventria's Domestic Industry Total 80

B. Ventria's Alleged Domestic Industry Investments Are Neither Significant Nor Substantial by Any Appropriate Quantitative Measure 82

C. Ventria Fails to Demonstrate a Nexus between Its Alleged R&D Investments and the Alleged Domestic Industry Products 87

VIII. THE COMMISSION SHOULD REVIEW AND REVERSE THE FID'S FINDING OF A VIOLATION BASED ON THE LANHAM ACT BY THE DEFAULTING RESPONDENTS 87

IX. REMEDY & BOND 88

X. PUBLIC INTEREST 89

XI. CONCLUSION 89

TABLE OF AUTHORITIES

Page(s)

Cases

Allergan, Inc. v. Apotex Inc.,
754 F.3d 952 (Fed. Cir. 2014).....70

Amgen Inc. v. Hoechst Marion Roussel, Inc.,
314 F.3d 1313 (Fed. Cir. 2003).....59

Apple Inc. v. Corephotonics, Ltd.,
861 F. App'x 443 (Fed. Cir. 2021).....59

Atlantic Thermoplastics Co., Inc. v. Faytex Corp.,
5 F.3d 1477 (Fed. Cir. 1993).....78

Bristol-Myers Squibb Co. v. Ben Venue Labs, Inc.,
246 F.3d 1368 (Fed. Cir. 2001)..... *passim*

Broadcom Corp. v. ITC,
No. 20-2008, slip op. (Fed. Cir. Mar. 8, 2022).....66, 67

Certain Acid-Washed Denim Garments and Accessories,
Inv. No. 337-TA-324, Comm'n Op., 1992 ITC LEXIS 697 (Nov. 1992).....4

Certain Automated Teller Machines, ATM Products, Components Thereof, and Products Containing the Same,
Inv. No. 337-TA-972, Order No. 34, 2016 WL 5076114 (Aug. 26, 2016) ..... *passim*

Certain Computer Forensic Devices & Products Containing Same,
Inv. No. 337-TA-799, ID (Oct. 26, 2012).....79

Certain Electronic Stud Finders, Metal Detectors and Electrical Scanners,
Inv. No. 337-TA-1221, Comm'n Op. (March 14, 2022).....85, 86

Certain EPROM, EEPROM, Flash Memory, and Flash Microcontroller Semiconductor Devices and Products,
Inv. No. 337-TA-395, Comm'n Notice, 2000 ITC LEXIS 318 (Oct. 16, 2000).....4, 6

Certain Integrated Circuit Chips and Products Containing the Same,
Inv. No. 337-TA-859, Comm'n Op. (Aug. 22, 2014).....86

Certain Printing and Imaging Devices and Components Thereof,
Inv. No. 337-TA-690, Comm'n Op. (Nov. 1, 2011).....83

Certain Stringed Musical Instruments and Components Thereof,
Inv. No. 337-TA-586, Comm'n Op. (May 16, 2008) 83

Conoco, Inc. v. Energy & Env't Int'l, L.C.,
460 F.3d 1349 (Fed. Cir. 2006).....28

Ecolab, Inc. v. FMC Corp.,
569 F.3d 1335 (Fed. Cir. 2009), *amended on reh'g in part*, 366 F. App'x 154
(Fed. Cir. 2009).....77

Gemtron Corp. v. Saint-Gobain Corp.,
572 F.3d 1371 (Fed. Cir. 2009).....44

In re Gleave,
560 F.3d 1331 (Fed. Cir. 2009).....52

Golden Blount, Inc. v. Robert H. Peterson Co.,
365 F.3d 1054 (Fed. Cir. 2004).....78

In re Gosteli,
872 F.2d 1008 (Fed. Cir. 1989).....58

Harris Corp. v. Ericsson Inc.,
417 F.3d 1241 (Fed. Cir. 2005).....75, 76

Hybritech Inc. v. Monoclonal Antibodies, Inc.,
802 F.2d 1367 (Fed. Cir. 1986).....67

In re Inland Steel Co.,
265 F.3d 1354 (Fed. Cir. 2001).....68

InterDigital Commc'ns, LLC v. Int'l Trade Comm'n,
707 F.3d 1295 (Fed. Cir. 2013).....79

In re Keller,
642 F.2d 413 (CCPA 1981) 70

Kennametal, Inc. v. Ingersoll Cutting Tool Co.,
780 F.3d 1376 (Fed. Cir. 2015).....57

In re Merck & Co., Inc.,
800 F.2d 1091 (Fed. Cir. 1986).....70, 77

Merck & Co. v. Biocraft Labs., Inc.,
874 F.2d 804 (Fed. Cir. 1989).....68

Novartis Pharms. Corp. v. W.-Ward Pharms. Int'l Ltd.,
923 F.3d 1051 (Fed. Cir. 2019).....68

Novo Nordisk Pharms., Inc. v. Bio-Tech. Gen. Corp.,
424 F.3d 1347 (Fed. Cir. 2005).....61

In re O'Farrell,
853 F.2d 894 (Fed. Cir. 1988).....70

Pfizer, Inc. v. Apotex, Inc.,
480 F.3d 1348 (Fed. Cir. 2007).....77

Schering Corp. v. Geneva Pharms.,
339 F.3d 1373 (Fed. Cir. 2003).....52

Sciele Pharma Inc. v. Lupin Ltd.,
684 F.3d 1253 (Fed. Cir. 2012).....57

Tris Pharma, Inc. v. Actavis Lab'ys FL, Inc.,
755 F. App'x 983 (Fed. Cir. 2019).....77

Upsher-Smith Labs., Inc. v. Pamlab, L.L.C.,
412 F.3d 1319 (Fed. Cir. 2005).....55

Statutes

19 U.S.C. § 1337(a)(1)(A).....87

19 U.S.C. §§ 1337(a)(1)(A), (d)(1).....88

19 U.S.C. § 1337(a)(2).....80

19 U.S.C. § 1337(a)(3).....79, 81

19 U.S.C. § 1337(d)(1).....87

19 U.S.C. § 1337(g)(1).....87

19 U.S.C. § 1337 (g)(1)(E).....88

35 U.S.C. § 102(b).....78

Lanham Act.....87, 88

Other Authorities

19 C.F.R. § 210.10(b)(2).....88

19 C.F.R. § 210.43.....1, 88

19 C.F.R. § 210.43(b)(1).....4

19 C.F.R. § 210.43(d)(2).....4

19 C.F.R. § 210.45(c).....4

19 C.F.R. § 210.50.....89

86 Fed. Reg. 6916-17.....88

TABLE OF ABBREVIATIONS

Abbreviation	Title
'951 patent	U.S. Patent 10,618,951 (JX-0001)
FID	Final Initial Determination (EDIS Doc ID ###)
CPreHB	Complainant's Pre-Hearing Brief (EDIS Doc ID ###)
RPreHB	Respondents' Pre-Hearing Brief (EDIS Doc ID ###)
SPreHB	Staff's Pre-Hearing Brief (EDIS Doc ID ###)
CPostHB	Complainant's Post-Hearing Brief (EDIS Doc ID ###)
RPostHB	Respondents' Post-Hearing Brief (EDIS Doc ID ###)
SPostBH	Staff's Post-Hearing Brief (EDIS Doc ID ###)
CRPostHB	Complainant's Reply Post-Hearing Brief (EDIS Doc ID ###)
RRPostHB	Respondents' Reply Post-Hearing Brief (EDIS Doc ID ###)
SRPostHB	Staff's Reply Post-Hearing Brief (EDIS Doc ID ###)
bold italics	emphasis added
rHSA	recombinant human serum albumin
pHSA	plasma human serum albumin
PAGE	polyacrylamide gel electrophoresis
SDS-PAGE	sodium dodecyl sulfate-polyacrylamide gel electrophoresis
SEC-HPLC	size exclusion chromatography high pressure liquid chromatography
Van Urk	WO 00/44772 ("Van Urk") (JX-0030)
Berezenko	U.S. Patent No. 6,034,221 ("Berezenko") (JX-0027)
Deeter	WO 2007/002762 A2 ("Deeter") (RX-0030)
Huang	Huang et al., *Production of human serum albumin by sugar starvation induced promoter and rice cell culture*, Transgenic Research (2005) 14:569-581 ("Huang") (JX-0028)

I. INTRODUCTION

Respondent Wuhan Healthgen Biotechnology Corporation ("Healthgen") petitions for review of the Final Initial Determination ("FID") finding a Section 337 violation. 19 C.F.R. § 210.43. This petition is accompanied by a summary of the petition.

The asserted patent, U.S. Patent No. 10,618,951 (the '951 patent), claims a cell culture media supplement or complete media composition comprising recombinant mammalian albumin, such as recombinant human serum albumin ("rHSA") produced in a transgenic plant such as rice that contains low levels of endotoxins (a ubiquitous contaminant) and ***less than 2% aggregated albumin***, which was construed to mean "***less than 2% non-monomeric albumin by weight***."[1] Order No. 14, Chart A, 1; JX-0001, claims 1 and 11-13. The term "aggregated albumin" was construed to mean "non-monomeric albumin (e.g., albumin dimers)." *Id.*

The FID's analysis of whether the products at issue contain less than 2% aggregated albumin is based on clearly erroneous factual findings and (for technical domestic industry) legal error. *Infra*, Sections IV and V.

For example, when analyzing Healthgen's ***medium*** grade products, the FID disregards reliable data establishing non-infringement—data generated by Ventria pre-litigation—relying instead on mischaracterizations of product "purity" and the demonstrably incorrect "recollection" of Ventria's technical expert. *Infra*, Section IV.B. The FID's findings are clearly erroneous and conflict with the documentary evidence.

When assessing Healthgen's ***clinical*** grade products, the FID erroneously relies on (1) data collected in China one day after manufacture and (2) data collected after treating samples with a

[1] All instances of ***bold italics*** herein represent emphases added unless otherwise noted.

bond-breaking agent to reduce the level of aggregated albumin—which is wholly improper for evaluating whether the accused product contains "less than 2% aggregated albumin." Neither type of data relied on in the FID reflects the properties of the product as imported into the United States. *Infra*, Section IV.C.

In the context of technical domestic industry, the FID again relies on data collected after the samples were treated with a bond-breaking agent to reduce the level of aggregated albumin. *Infra*, Section V. Then—because the level of aggregated albumin remained above 2%—the FID redlines the data to disregard certain aggregates, in effect altering the operative claim constructions. This is clearly erroneous and legal error.

Turning to invalidity, the FID improperly raises the bar for both anticipation and obviousness.[2] *Infra*, Section VI. For example, the FID requires "actual" performance of suggested disclosures, in direct conflict with Federal Circuit precedent. FID, 77-79. For example, the FID disregards Van Urk's disclosure of rHSA "produced in . . . transgenic plants" (JX-0030.0003 (1:1-9), e.g., "transgenic plant[] such as tobacco, potato or corn (maize)" (a grain, *id.*, 0024 (22:26-27), that is "non-pyrogenic"—meaning "no detectable endotoxin" (*id.*, 0065, 75-75), and "up to 1% dimeric albumin" (*id.*, 0065) that "is used . . . to supplement media for growing higher eukaryotic cells . . . ." (*id.*, 0003 (1:9-15). These disclosures satisfy all limitations of claims 1, 11, and 12, contrary to the clearly erroneous findings in the FID. *Infra*, Section VI.A. The FID's analysis of nonobviousness includes the flaws in its anticipation analysis. For example, it finds limitations absent from the art, where such limitations are plainly disclosed, and conclusorily dismisses strong motivations to combine when doing so. *Infra*, Section VI.D.

[2] Van Urk refers to WO 00/44772 (JX-0030). Berezenko is U.S. Patent No. 6,034,221 (JX-0027). Deeter is WO 2007/002762 (RX-0030). Huang the publication of JX-0028.

The FID's findings on economic prong of the domestic industry requirement also include several serious legal and factual errors and should therefore be reversed. *Infra*, Section VII. The FID grossly overstates Ventria's domestic industry investments by giving full credit to all Ventria's alleged DI products, including those which do not practice any claim of the '951 patent. *See* FID at 101-107. Once the DI products are limited to include only Optibumin—the only Ventria DI product that actually practices the '951 patent—Ventria's DI investments total a mere [redacted]. The FID further fails to properly allocate the Optibumin-only investments and improperly relies on qualitative factors to significance and substantiality for the low Optibumin investment numbers. *Id.*

Healthgen thus seeks review and reversal of the FID.

II. SUMMARY OF ISSUES REQUIRING COMMISSION REVIEW

Healthgen seeks review of the following issues:

- Whether Healthgen's medium grade products infringe claims 1 and 11-13 of the '951 patent;
- Whether Healthgen's clinical grade products infringe claims 1 and 11-13 of the '951 patent;
- Whether Exbumin, Cellastim, and products containing Cellastim satisfy the technical prong of the domestic industry requirement;
- Whether claims 1, 11, and 12 of the '951 patent are anticipated by Van Urk;
- Whether claims 1 and 11 of the '951 patent are anticipated by Berezenko;
- Whether claims 1 and 11-13 of the '951 patent would have been obvious over Deeter in view of Van Urk or Berezenko;
- Whether claim 13 of the '951 patent would have been obvious over Van Urk in view of Deeter and/or Huang;
- Whether claims 12 and 13 of the '951 patent would have been obvious over Berezenko in view of Deeter and/or Huang;

- Whether Ventria satisfied the economic prong of the domestic industry requirement.

III. STANDARD OF REVIEW

The Commission may review a FID when (1) a finding or conclusion of material fact is "clearly erroneous;" (2) a legal conclusion is "erroneous, without governing precedent, rule or law, or constitutes an abuse of discretion;" or (3) a determination affects "Commission policy." 19 C.F.R. § 210.43(b)(1). A petition will be granted review "if it appears that an error or abuse of the type described in paragraph (b)(1) of this section is present or if the petition raises a policy matter connected with the initial determination, which the Commission thinks it necessary or appropriate to address." 19 C.F.R. § 210.43(d)(2). Healthgen seeks review on issues that fall within those standards.

"[O]nce a sufficient basis for review has been shown and review has been ordered, the Commission examines for itself the record on the issues under review." *Certain Acid-Washed Denim Garments and Accessories*, Inv. No. 337-TA-324, Comm'n Op., 1992 ITC LEXIS 697, at *10 (Nov. 1992). The Commission conducts a de novo review of the issues in an ID that it elects to review. *Certain EPROM, EEPROM, Flash Memory, and Flash Microcontroller Semiconductor Devices and Products*, Inv. No. 337-TA-395, Comm'n Notice, 2000 ITC LEXIS 318, at *8-9 (Oct. 16, 2000). With respect to those issues, "the Commission may affirm, reverse, modify, set aside, or remand for further proceedings, in whole or in part, the initial determination of the administrative law judge. . . . The Commission also may make any findings or conclusions that in its judgment are proper based on the record in the proceeding." 19 C.F.R. § 210.45(c).

IV. THE COMMISSION SHOULD REVIEW AND REVERSE THE FID'S FINDINGS ON INFRINGEMENT

A. Introduction

The central dispute on infringement is whether Healthgen's rHSA products contain "less than 2% aggregated albumin," as required by all claims of the '951 patent. The FID's conclusion that this limitation was met is based on clearly erroneous factual findings that directly contradict the evidentiary record.

B. The FID Erroneously Concluded that Healthgen's Medium Grade Products Infringe Claims 1 and 11-13 of the '951 Patent

1. The FID Failed to Address Ventria's Testing Establishing Healthgen's Medium Grade Products Do Not Infringe

In total, Ventria tested ***nine*** Healthgen medium grade products in this investigation, including six samples it purchased commercially and tested pre-litigation, and three samples produced by Healthgen during the course of this investigation. Every sample tested contained more than 2% aggregated albumin required by the asserted claims of the '951 patent. Accordingly, the Medium Grade Products do not infringe. JX-0080C; JX-0129.

The FID discusses testing performed on ***only three*** of Healthgen's nine medium grade samples. It ignores the testing conducted by Ventria itself pre-litigation, erroneously finding in conclusory fashion that the three samples it considered are "outliers." FID, 55. The data on all nine samples tested by Ventria—including the six pre-litigation samples ignored in the FID—are remarkably consistent, however, and refute the conclusory characterizations of Healthgen's

products in the FID.[3] These data—all generated by or on behalf of Ventria—are summarized below.

Table 1				
Grade of product	**Aggregated Albumin**	**Monomeric Albumin**	**Assay (Party Responsible for Testing)**	**Citation**
medium	9.3%	90.7%	Native-Page (Ventria)	JX-0080C
medium	5.8%	94.2%	Native-Page (Ventria)	JX-0080C
medium	7.0%	93.0%	Native-Page (Ventria)	JX-0080C
medium	5.5%	94.5%	Native-Page (Ventria)	JX-0080C
medium	7.1%	92.9%	Native-Page (Ventria)	JX-0080C
medium	7.7%	92.3%	Native-Page (Ventria)	JX-0080C
medium	9.67%	86.20%	Reducing SDS-PAGE (Ventria)	JX-0129.0007
medium	6.82%	90.36%	Reducing SDS-PAGE (Ventria)	JX-0129.0007
medium	7.27%	86.28%	Reducing SDS-PAGE (Ventria)	JX-0129.0007

Indeed, Ventria's Vice President of Product Development, Dr. Randall Alfano, admitted that the test method used by Ventria, called Native-PAGE, appropriately provides test results on the level of albumin aggregation in a sample product. RX-0007C (Alfano Dep. Tr.) at 39:1-20; *see also id.*, 87:14-88:8. As Dr. Alfano explained, Native-PAGE "does not involve any of the addition of bond-breaking agents" employed with a different test method, called SDS-PAGE. *Id.*, 38:16-25; *see also* JX-0132.0005 (noting Native-PAGE "analyzes native protein (aggregates)").

The overwhelming evidence adduced at trial, whether through the literature or by the parties' experts, agree with Dr. Alfano that some test methods (e.g., SDS-PAGE under reducing conditions) will break apart the albumin aggregates in a test sample, while others will not (e.g.,

[3] The results for the samples tested by Native-PAGE contain from 5.5% to 9.3% aggregated albumin, while the samples tested by Reducing SDS-PAGE contain 6.8% to 9.7% aggregated albumin. While Reducing SDS-PAGE is generally expected to decrease aggregated albumin (*infra*, Section IV.C.2), it appears that these lyophilized/freeze dried powder products may contain irreversibly aggregated albumin (aggregates not broken up during sample treatment for Reducing SDS-PAGE). *Id.* (explaining the impact of Reducing SDS-PAGE on aggregated albumin).

Native-SDS PAGE and SEC-HPLC). JX-0060.0006-08; JX-0132.0008-09; Tr. (Wilken) at 467:15-468:2, 503:14-19; Tr. (DeFilippi) at 1162:10-14 (explaining that Native-PAGE does not involve a detergent (SDS) or a reducing agent, while Reducing SDS-PAGE includes both), 1181:2-16 (testifying that next to SEC-HPLC, Native-PAGE would be the next best technique, because "you're not pretreating the sample in such a way that the sample will be altered."); Tr. (Wilken) at 467:15-468:2 (Dr. Wilken explaining that comparing the results of SDS-PAGE and Reducing SDS-PAGE would show how the chemical treatment with a reducing agent affected the sample). The difference in which test method is used to measure the percent of aggregated albumin can be—and in fact is—dispositive on issues on infringement.

The FID's failure to acknowledge that Ventria's pre-litigation testing of six commercially purchased Healthgen samples by Native-PAGE established noninfringement is clear, reversible error. FID (failing to cite JX-0080C; RX-0010C (Deeter Dep. Tr.); RX-0351C; or RX-0352C). In the same vein, the FID's reliance on test results using methods like SDS-PAGE with reducing agents is fatally flawed and erroneous (a person skilled in the art would not look to these tests to determine the percent of aggregated albumin in a sample). JX-0060.0008; JX-0132.000; *Infra*, Section IV.C.2, 3.

a. Detailed Analysis of Ventria's Native-PAGE Data

Ventria's pre-litigation test report provides "purity" values for Healthgen's samples by Native-PAGE. JX-0080C. Importantly, "purity" has different meanings in different contexts, such that [redacted]. Tr. (Wilken) 478:1-3 ("Q. Doctor, you would agree with me that there's a lot of different ways to

calculate purity, right? A. Yes."); *id.*, 478:4-19 (admitting that purity could be defined differently based on different methods).

[redacted]

[redacted]

This was explained in simple terms at trial, with reference to the demonstratives such as the one below. RDX-0002C.13-19.



The data for the other three Healthgen samples that Ventria tested pre-litigation are similar, with the gel in RX-0352C.



RX-0352C; JX-0080C (annotated).

Again, Ventria's % Purity calculation reflects 100% minus the albumin aggregates, i.e., 5.5%, 7.0%, and 7.1% aggregated albumin in three commercially acquired samples of Healthgen's products. [redacted] Tr. (DeFilippi) at 1162:15-1169:15. All of them calculated to be noninfringing.

It is telling that Ventria's expert, Dr. Wilken did not address any of Ventria's own testing during trial. Tr. (Wilken) at 303:17-432:22. Ventria's tests are uncontroverted proof that Healthgen's medium grade powder products do not infringe any Ventria patent claim. Not only did Dr. Wilken ignore Ventria's own testing, so did the FID. Shockingly, the FID contains no discussion of any of Ventria data, proving that the six Healthgen medium grade samples tested by Ventria pre-litigation all contained more than the 2% aggregated albumin.

2. The FID Erroneously Relied on Healthgen's Customer Communications to Show Infringement

In place of clear test data, the FID relies on mischaracterizations of Healthgen's customer communications to incorrectly conclude that Healthgen's medium grade products contain less than 2% aggregated albumin.[4] FID, 52-54. This analysis conflicts with the record and constitutes reversible error.

First, the FID states that [redacted] FID, 53. That is factually wrong. CX-0052C was attached to an email sent dated August 2, 2013—nearly eight years before the '951 patent issued.

[4] The FID cites Dr. DeFilippi's testimony that "sales catalogs and marketing materials are 'tear sheets' that 'describe[] what the product is to the customer,' 'you tear out and hand [] to the customer.'" FID, 52. Notably, the documents referred to as "tear sheets" in the FID do not appear to be "tear sheets" based on Dr. DeFilippi's use of that term. *Id.*

CX-0026C (email dated August 2, 2013 attaching CX-0052C). Reliance on statements in these documents is clear error.

Moreover, the FID wholly misinterprets the document, conflating total albumin, with aggregated albumin:

> [Customer question] 2. Is SEC-HPLC the method for determining purity for [redacted]

CX-0052C.0003.

The FID erroneously finds this purity of [redacted] relates to aggregated albumin. FID, 53. But as recited above, [redacted] *Id.* [redacted] Tr. (DeFilippi) at 1217:11-1218:2. [redacted] *Id.* This is the only reading of the document that makes sense in view of all the data generated on Healthgen's rHSA samples (none of which indicate that any product contains less than [redacted] aggregated albumin).

[redacted]

Infra, Section IV.B.1.

[redacted]

CX-0052C.0006. [redacted]

[redacted]

The FID also wholly misunderstands data in Healthgen's customer communications.[5] FID, 52-55. For example, the FID refers to [redacted] FID, 53; CX-0052C.0003.

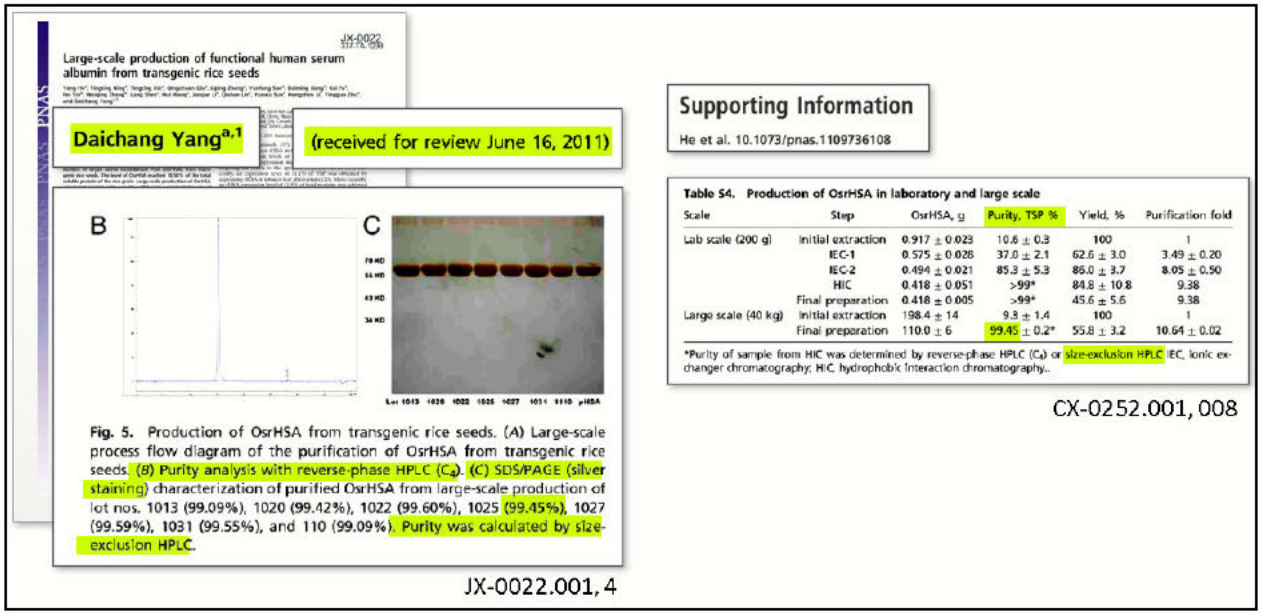
The FID relies on Dr. Wilken's interpretation of these data, but Dr. Wilken's recollection of Healthgen's method of calculating purity with respect to this same chromatogram was erroneous. FID, 52-55. For context, Dr. Wilken testified as follows:

> A. ***If you look at purity in the methods for SEC, it was the ratio of monomeric albumin over total albumin***. I think over all -- so the area of the peak, of the main peak, over the total areas of the peaks, if I –
>
> Q. The paragraph discussed --
>
> A. -- ***if I remember this particular method correctly***.
>
> Q. The paragraph that you're referring to, I believe, discusses all forms of albumin, not just monomeric albumin; is that fair?
>
> A. We would ***refer to the methods***, which are in the appendix or the ***supplemental material for this PNAS table, and I think it specifies in there the ratio of monomeric albumin or the area of that main peak over all peak areas***. So that would be the percentage of monomeric albumin.

Tr. (Wilken) at 560:3-18.

[5] The FID fails to note that the certain data in the 2013 customer communication were originally published in 2011—nearly a decade before the '951 patent issued on April 14, 2020. *Compare* CX-0052C.0003, *with* JX-0022.0004 (Fig. 5); *see* Tr. (DeFilippi) at 1214:7-12 (explaining that data from 2011 is "out-of-date").

The "supplemental material" for Healthgen's 2011 PNAS publication (referred to in the testimony above) directly contradicts Dr. Wilken's recollection. CX-0252.0008. The data images and supplemental information are provided below:



Large-scale production of functional human serum albumin from transgenic rice seeds

Daichang Yang[a,1] (received for review June 16, 2011)

B C

Fig. 5. Production of OsrHSA from transgenic rice seeds. (A) Large-scale process flow diagram of the purification of OsrHSA from transgenic rice seeds. (B) Purity analysis with reverse-phase HPLC (C_4). (C) SDS/PAGE (silver staining) characterization of purified OsrHSA from large-scale production of lot nos. 1013 (99.09%), 1020 (99.42%), 1022 (99.60%), 1025 (99.45%), 1027 (99.59%), 1031 (99.55%), and 110 (99.09%). Purity was calculated by size-exclusion HPLC.

JX-0022.001, 4

Supporting Information

He et al. 10.1073/pnas.1109736108

Table S4. Production of OsrHSA in laboratory and large scale

Scale	Step	OsrHSA, g	Purity, TSP %	Yield, %	Purification fold
Lab scale (200 g)	Initial extraction	0.917 ± 0.023	10.6 ± 0.3	100	1
	IEC-1	0.575 ± 0.028	37.0 ± 2.1	62.6 ± 3.0	3.49 ± 0.20
	IEC-2	0.494 ± 0.021	85.3 ± 5.3	86.0 ± 3.7	8.05 ± 0.50
	HIC	0.418 ± 0.051	>99*	84.8 ± 10.8	9.38
	Final preparation	0.418 ± 0.005	>99*	45.6 ± 5.6	9.38
Large scale (40 kg)	Initial extraction	198.4 ± 14	9.3 ± 1.4	100	1
	Final preparation	110.0 ± 6	99.45 ± 0.2*	55.8 ± 3.2	10.64 ± 0.02

*Purity of sample from HIC was determined by reverse-phase HPLC (C_4) or size-exclusion HPLC IEC, ionic exchanger chromatography; HIC, hydrophobic interaction chromatography..

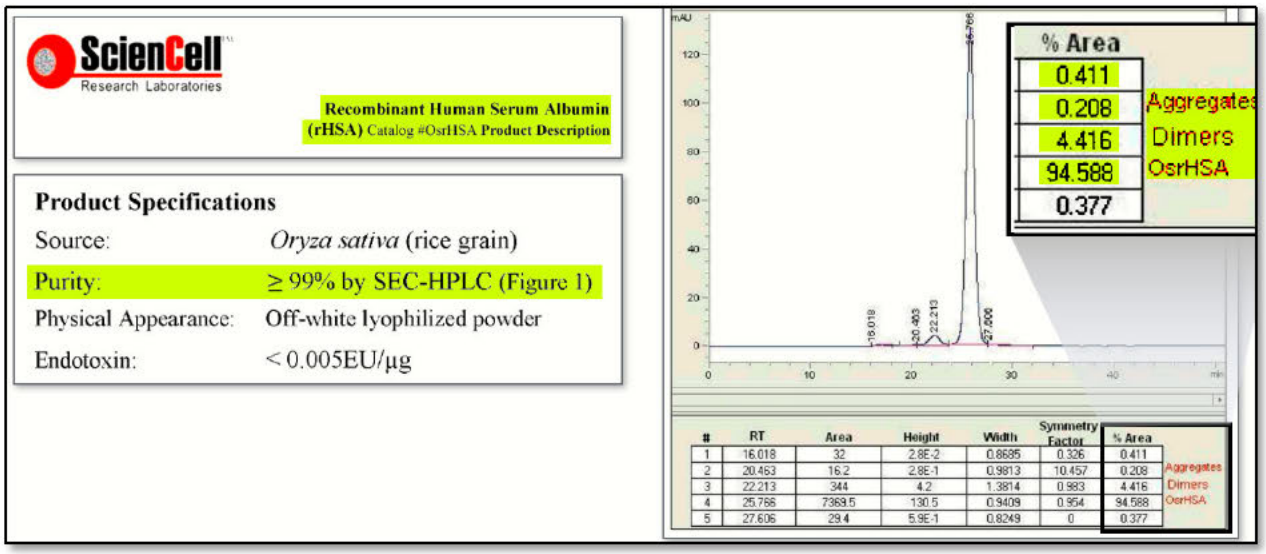
CX-0252.001, 008

JX-0022.0001, 0004 (2011 publication, left); CX-0252.0001, 0008 (supporting information, right).

The images in the 2011 PNAS article, [redacted], are shown above on the left. JX-0022.0004. The supporting information explains that the purity values of, e.g., 99.45%, were calculated as "TSP %," which means "total soluble protein." This distinction is important, because it is undisputed that the ***total soluble proteins (TSP) include soluble albumin aggregates, including albumin dimers***. Tr. (DeFilippi) at 1215:5-25. As such, the supplemental material directly contradicts Dr. Wilken's recollection regarding how purity was calculated with respect to these data. CX-0252.0007. The FID's reliance on Dr. Wilken's flawed recollection, instead of the clear documentary evidence, constitutes clear error. FID, 52-55.

The FID erroneously relies on other statements regarding the "purity" of Healthgen's samples, again without considering what "purity" means in the context of the documents. FID, 53-54 (citing CX-0053C). But it is undisputed that there are different meanings of purity, and thus there are different ways of calculating it. Tr. (Wilken) 478:1-3 ("Q. Doctor, you would agree with me that there's a lot of different ways to calculate purity, right? A. Yes."); *id.*, 478:4-19 (admitting that purity could be defined differently based on different methods). As such, one must look at the data to understand how purity is calculated, which the FID repeatedly failed to do. FID, 52-55.

As the documents show, Healthgen calculates purity by SDS-PAGE and SEC-HPLC as total albumin—monomer plus aggregates. *E.g.*, JX-0018C.0001, 0002. As an example, a brochure for Healthgen's rHSA (below) promotes purity of ***greater than 99% by SEC-HPLC***, and the accompanying data show that ***monomeric albumin was only 94.588%***. *Id.* Looking at the data (which the FID failed to cite), it is clear that to reach the purity of greater than 99% by SEC-HPLC, albumin monomers, dimers, and larger aggregates must be added together. *Id.* If "purity" by SEC-HPLC were simply the percent of monomeric albumin, then purity would be reported as 94.588% purity—but of course, it is not:



JX-0018C.0001, 0002 (highlighting added, red text in original). The FID, notably, fails to cite or discuss this document.

Similarly, [redacted]



The FID [redacted] SDS-PAGE data may be "quantified." FID, 26. It is true that, if densitometry is performed, the relative amounts of each species can be quantified, as above. The quantification [redacted] however, contrasts with the images in the 2011 publication (and all customer communications that contain such data), which contain no quantitative information or indication that densitometry measurements were performed. JX-0022.0004; CX-0052C.0003.

The FID cites several additional documents with little or no discussion. FID, 54. None of these documents show that Healthgen's medium grade products contain less than 2% aggregated albumin, as addressed below.

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]

In short, none of these documents establish that Healthgen's medium grade products contain "less than 2% aggregated albumin," as required by all claims of the '951 patent.

3. The FID Erroneously Concludes Healthgen's Medium Grade Products Are the Same as the Clinical Grade Products

a. Healthgen's Medium Grade Products Are Different from the Clinical Grade Products

The FID wrongly finds that Healthgen's medium grade products manufactured and purified using the same process as the clinical grade products. FID, 37-39. If that were true, then the two different grades of products would be expected to have the same properties, but they do not, as the data tabulated below confirm.

Table 2.

Grade of product	Aggregated Albumin	Monomeric Albumin	Assay (Party Responsible for Testing)	Citation
clinical	[redacted]	[redacted]	SEC-HPLC (Healthgen in China)	JX-0032C.0002
clinical	0.64%	96.27%	Reducing SDS-PAGE (Ventria)	JX-0129.0007
clinical	1.81%	98.20%	Reducing SDS-PAGE (Ventria)	CX-0904.0007
medium	9.3%	90.7%	Native-Page (Ventria)	JX-0080C
medium	5.8%	94.2%	Native-Page (Ventria)	JX-0080C

[6] [redacted]

Table 2.				
Grade of product	**Aggregated Albumin**	**Monomeric Albumin**	**Assay (Party Responsible for Testing)**	**Citation**
medium	7.0%	93.0%	Native-Page (Ventria)	JX-0080C
medium	5.5%	94.5%	Native-Page (Ventria)	JX-0080C
medium	7.1%	92.9%	Native-Page (Ventria)	JX-0080C
medium	7.7%	92.3%	Native-Page (Ventria)	JX-0080C
medium	9.67%	86.20%	Reducing SDS-PAGE (Ventria)	JX-0129.0007
medium	6.82%	90.36%	Reducing SDS-PAGE (Ventria)	JX-0129.0007
medium	7.27%	86.28%	Reducing SDS-PAGE (Ventria)	JX-0129.0007

If Healthgen's medium and clinical products were all the same, then the data would reflect consistent levels of aggregated albumin between the two grades of products, but they do not, as shown in Table 2. Moreover, why would Healthgen market two different grades of products, if they were all the same?

b. The FID's findings based on Mr. Shi's testimony and the flow chart are clearly erroneous.

The FID relies on Mr. Bo Shi's testimony and a process flow chart to conclude that Healthgen [redacted], implying the products themselves should be no different. FID, 37-39. This finding is belied by the data above (Table 2) and common sense. Additionally, this finding is based on mischaracterizations of the record.

First, Mr. Shi testified that [redacted]

A. The specification of -- sorry. The specific parameters are normally [redacted]

CX-1081C (Shi Dep. Tr.), 77:19-79:14. [redacted] Healthgen subsequently designated Dr. Yang as its representative on [redacted]. Dr. Yang explained Healthgen's processes in detail over three days of deposition, and Dr. DeFilippi reasonably relied on that sworn testimony in forming his

opinions, while Ventria chose to focus on [redacted] in to obfuscate the facts. *Certain Automated Teller Machines, ATM Products, Components Thereof, and Products Containing the Same*, Inv. No. 337-TA-972, Order No. 34, 2016 WL 5076114, at *1 (Aug. 26, 2016) ("[E]xpert witnesses are not precluded from relying upon deposition transcripts or other inadmissible evidence in forming their opinions. *See* Fed. R. Evid. 703 [parenthetical omitted]. Accordingly, none of the expert testimony highlighted in Diebold's motion is inadmissible merely because it references or relies upon a deposition or interrogatory response.").

The FID further misinterprets [redacted] FID, 37-39. [redacted]

[redacted]

As shown above, [redacted]

By contrast, the [redacted]

[7] The FID [redacted]

[redacted]

For example, the FID incorrectly states that [redacted] The cited testimony states as follows:

[redacted]

[8] This typo appears to have been copied from Complainant's initial post-hearing brief [redacted]

[redacted]

CX-1081C, 186:2-22. As reflected in the transcript, [redacted]

As noted in the FID, [redacted]. FID, 40 [redacted]

The FID's discussion of Healthgen's purification flow chart is similarly erroneous. FID, 37-38. [redacted]



Finally, the FID cites to a book chapter co-authored by Healthgen's Dr. Yang and Mr. Shi to conclude that "Healthgen purifies its OsrHSA in part to remove what Healthgen characterizes as aggregated albumin." FID, 38-39. This book chapter fails to establish that Healthgen's clinical and medium grade products are the same (and indeed, does not appear to be cited for that point).

[9] Dr. DeFilippi's understanding is based on Dr. Yang's deposition transcript, which Ventria chose not to designate. However, experts are entitled to rely on evidence that is reliable, even if it is inadmissible, and sworn testimony is the type of evidence on which experts may reasonably rely. *Certain Automated Teller Machines*, 2016 WL 5076114, at *1.

See JX-0023. Notably, the chapter focuses exclusively on rHSA as a pharmaceutical, explaining how OsrHSA was purified sufficiently for "clinical trials" and thus does not appear to relate to Healthgen's medium grade products (a fact not mentioned in the FID). *Id.*, 0017.

C. The FID Erroneously Concluded that Healthgen's Clinical Grade Liquid Product Infringes Claims 1 and 11-13 of the '951 Patent

The FID's analysis of Healthgen's clinical grade liquid product is fundamentally flawed, as it relies on (1) test data from a fresh sample one day after manufacture in China where the percentage of aggregation is at its lowest—data collected at the wrong time; and (2) test data generated in the U.S. after treating the sample with a reducing agent that breaks the bonds of aggregated albumin thereby artificially decreasing the percent of aggregated albumin—data collected using the wrong test. FID, 41-50. The FID relies on these data but none of these results reliably or accurately reports the percent level of aggregated albumin in the product in the United States. JX-0032C.002 (Healthgen testing its clinical grade product in China using SEC-HPLC); CX-0904.007 (SGS testing Healthgen's same clinical grade product in the United States using SDS-PAGE under reducing conditions); Tr. (Wilken) at 467:18-25, 503:14-19 (testifying that the reducing agents used by Ventria's laboratory, DTT and TCEP, break disulfide bonds).

1. The FID Erroneously Relied on Data Collected in China

Data collected in China, one day after manufacture, is not representative of the level of aggregated albumin upon importation into the United States, because aggregation increases over time and in response to stress—it is not a fixed property. Tr. (DeFilippi) at 1203:5-19. Two peer-reviewed articles became the centerpiece of the experts' testimony on these issues, and both confirm that percent aggregation increases based on a variety of factors:

- "Agitation stress such as stirring, pumping, and shaking during manufacturing and transport has been described to cause aggregation." JX-0060.0004 (Mahler).

- "Aggregates . . . can be formed during production, storage, shipment or delivery to the patient. Numerous stresses (e.g., temperature fluctuations, light, shaking, surfaces, pH adjustments, etc.) can induce protein aggregation during each of these stages (3, 4)." JX-0132.0002 (den Engelsman).

Indeed, Ventria's expert Dr. Wilken did not dispute that aggregation can increase over time. Tr. (Wilken) at 451:9-12 (agreeing that aggregate formation "can be induced by process and storage conditions"); *see also id.*, 455:11-456:8.

The specification for Healthgen's clinical grade products accommodates for the expected increase in aggregation over time and during shipping by permitting up to [redacted] JX-0032C.0002; JX-0015C.0002. The relevant portion of the specification is highlighted below.

[redacted]

JX-0032C.0002.

The FID erroneously found that Healthgen represents that its clinical grade product contains less than 2% aggregated albumin as imported into the United States. FID, 47-50. The documents cited in the FID do not support that finding but instead, at most, show that Healthgen represents that its products should remain within the acceptance criteria, which permit up to [redacted] aggregated albumin prior to the expiration date. *E.g.*, JX-0007C; JX-0009C; CX-0193C; JX-

0015C; CX-0391C; CX-0456; CX-0470C; CX-0474C; CX-0478C. Healthgen has never represented that aggregation is a fixed property that does not change over time. As noted above, Healthgen's product specifications accommodate the expected change in aggregation over time by permitting up to [redacted] aggregated albumin—[redacted] The FID's findings to the contrary are clearly erroneous. RRPostHB, 38-40. The facts here are thus readily distinguishable from *Conoco, Inc. v. Energy & Env't Int'l, L.C.*, 460 F.3d 1349, 1362-63 (Fed. Cir. 2006).

That aggregation increases over time is confirmed by the data on Healthgen's clinical grade product. JX-0032C.0002; CX-0904.0007. Specifically, when batch no. C001202009001 was tested in China one day after manufacture on September 15, 2020, by SEC-HPLC, it contained [redacted] aggreged albumin (shown above), which increased to **1.81%** by June 2021 when tested in the United States by Reducing SDS-PAGE (a technique that breaks up aggregated albumin linked by disulfide bonds, *infra*, Section IV.B.2). *Compare* JX-0032C.0002, *with* CX-0904.0007. It is thus clear error to conclude that data generated in China one day after manufacture is representative of Healthgen's clinical grade product, as it exists in the United States.[10] Ventria's attorney argument and conclusory expert testimony cannot overcome the clear peer-reviewed teachings on these critical issues. Ventria did not offer evidence sufficient to prove infringement in any accused product.

[10] The FID notes that Dr. DeFilippi did not review Healthgen's shipping protocols or certain customer communications. FID, 47. But the materials cited in the FID do not change the data, which show an increase in aggregated albumin over time and after shipment (from [redacted] to at least—and likely more than—1.81%). Curiously, the FID does not cite Mr. Shi's admission that Healthgen's products [redacted]

Healthgen's clinical grade products contain aggregates that are broken up by reducing/bond-breaking agents in Reducing SDS-PAGE, meaning that this is not a hypothetical exercise, contrary to the FID. *See* JX-0129.0007 (results for HB012 by Reducing SDS-PAGE showing aggregates were reduced to 0.64% while creating over 3.5% fragments). The finding is thus erroneous: undeniably, the observed 1.81% aggregated albumin is artificially low and not representative of the product as sold in the United States. *Infra*, IV.B.2. Ventria did not meet its burden.

Tellingly, Ventria does not practice what it preached before the ALJ. [redacted] The same holds true for the independent lab that Ventria used to test Healthgen's products. RX-0184. Dr. Wilken either did not know or could not refute that SGS Life Sciences Services ("SGS") used SEC-HPLC when measuring aggregates, not SDS-PAGE. Tr. (Wilken) at 488:19-490:17. Dr. Wilken also did not have an adequate response as to why Ventria would have asked SGS to break from their standard protocols when instructing them to use SDS-PAGE. Tr. (Wilken) at 488:2-491:4.

The evidence at trial showed that Ventria manipulated the test results by manipulating the test methodology that were used. It is uncontroverted that Ventria purposefully chose a test method known to break up aggregated albumin by instructing their lab to use Reducing SDS-PAGE when SGS's standardized and reproducible protocols used a method known not to artificially lower the

percent aggregated albumin in SEC-HPLC. For Ventria to use one test method in its ordinary course of business outside the course of this investigation—one that is accurate and true—only to use a different test methodology in order to get lower aggregate percentages to try to prove infringement speaks volumes to the insufficiency of their case.

2. The FID Erroneously Relied on Reducing SDS-PAGE Data

a. Reducing SDS-PAGE Breaks Up Certain Albumin Aggregates

It is undisputed that Reducing SDS-PAGE involves pre-treating a sample with a reducing agent—a bond-breaking agent—that breaks up certain aggregates, specifically, those linked by covalent disulfide bonds. Tr. (Wilken) at 467:15-468:2 (admitting that Reducing SDS-PAGE can dissociate covalent disulfide bonds), 503:14-19 (Dr. Wilken admitting that reducing agents such as TCEP and DTT "break[] disulfide bonds."), 462:2-23 (Dr. Wilken further admitting that reducing agents in Reducing SDS-PAGE "should reduce" covalent disulfide bonds); RX-0007C (Alfano Dep. Tr.) at 29:24-30:24, 38:21-25; JX-0060.0008; JX-0132.0009; Tr. (DeFilippi) at 855:18–856:6, 1181:17–1182:8. As a result, Reducing SDS-PAGE can and does often provide an artificially low level of aggregated albumin (as aggregates linked by disulfide bonds are converted to single albumin units such as monomers and fragments). As Dr. Wilken explained, comparing the results of SDS-PAGE and Reducing SDS-PAGE would show how the chemical treatment with a reducing agent affected the sample. Tr. (Wilken) at 467:21:468:2.

The FID's reliance on Reducing SDS-PAGE is perhaps the most egregious error in the FID, as the following overview of the different assays for characterizing aggregated albumin explains:

- **Native-PAGE** is an assay designed to characterize proteins in their natural state. JX-0032.0005. As explained by Ventria's VP of Product Development, Dr. Alfano, this technique does not involve the use of a bond-breaking agent to alter the level of aggregated albumin in the sample and thus is an appropriate technique for

evaluating aggregated albumin. RX-0007C (Alfano Dep. Tr.) 39:1-20, 87:14-88:8. This is also the test establishing noninfringement of Healthgen's medium grade products (the data ignored in the FID). *Supra*, Section IV.B.1.

- **SEC-HPLC** is an assay for quantifying the relative amounts of protein species, which are separated on a column based on their size. JX-0060.0006; JX-0032.0005. SEC-HPLC does not involve pre-treating a sample to alter the level of aggregated albumin. [redacted] *Infra*, 29, 47.

- **SDS-PAGE** is an assay for characterizing the sizes of protein species, and it can provide quantitative information *on the levels of species observed*. The method involves treating a sample with a surfactant (sodium dodecyl sulfate, SDS), which partially denatures the proteins. The peer-reviewed literature states that SDS-PAGE may not observe non-covalently linked aggregates, e.g., loosely associated aggregates may be broken up during sample preparation. JX-0132.0005 (reporting that SDS-PAGE "does not detect noncovalent aggregates"); JX-0060.0006.

- **Reducing SDS-PAGE** is a term used in the parties' briefing and the FID to refer to SDS-PAGE performed on samples that have been pre-treated with a reducing agent. The reducing agent reduces—breaks—covalent disulfide bonds linking proteins such as albumin together. Tr. (Wilken) at 467:15-468:2, 503:14-19; RX-0007C (Alfano Dep. Tr.) at 29:24-30:24, 38:21-25; JX-0060.0008; JX-0132.0009; Tr. (DeFilippi) at 855:18–856:6, 1181:17–1182:8. As a result, the sample treatment for Reducing SDS-PAGE converts aggregates held together by covalent disulfide bonds to simpler albumin units, which will artificially decrease the observed level of aggregated albumin in any sample where such aggregates are present. JX-0060.0006; JX-0032.00005; Tr. (Wilken) at 467:15-468:2, 503:14-19.

In view of the available techniques for characterizing aggregated albumin, it is basic common sense that a person skilled in the art would not choose reducing SDS-PAGE to determine the percent of aggregated albumin in any sample product because it artificially lowers aggregates. It is also common sense that the results yielded between reducing SDS-PAGE under reducing conditions, which artificially lowers the percent of aggregates, and (SEC-HPLC) which does not, is going to yield different results of percent aggregated albumin on even the same sample. Some results may infringe. Some may not. Accordingly, a person skilled in the art would uniformly

choose one test method to employ and the only common-sense approach would be to use, SEC-HPLC.

In this regard, the dramatic reduction in aggregated albumin observed in Ventria's rHSA when analyzed by Reducing SDS-PAGE versus SDS-PAGE and SEC-HPLC is telling:

Table 3. Percent Aggregated Albumin by Various Techniques			
Sample	**SEC-HPLC**	**SDS-PAGE**	**Reducing SDS-PAGE**
Exbumin sample 1	4.41%	6.4%	**2.0%**
Exbumin sample 2	3.65%	3.4%	**1.4%**
Cellastim sample 1	4.60%	4.4%	**1.5%**
Cellastim sample 2	3.88%	3.3%	**1.0%**

RX-0311.002, 5-8.

As shown above, while SEC-HPLC and SDS-PAGE provided comparable results (albeit with one outlier at 6.4%), Reducing SDS-PAGE reduced the aggregates present by two- to four-fold.[11] *Id.* These data show that as expected, chemically treating the samples with a reducing agent prior to measuring the protein species present can dramatically change the result.

Indeed, Ventria's Vice President of Product Development, Dr. Randall Alfano, explained that SDS-PAGE does not indicate anything about the level of aggregated albumin because the sample preparation may involve the use of a "bond-breaking agent" (the reducing agents employed in Reducing SDS-PAGE). RX-0007C (Alfano Dep. Tr.) at 29:24-30:10, 30:11-24, 38:21-25. Excerpts of this testimony are below:

> Q. And 99.3 percent is albumin. ***Does purity indicate anything about the level of dimerization or aggregation of the albumin***?

[11] The FID seeks to disregard these data because they did not include molecular weight standards. FID, 25-26. Such markers are only relevant if the construction of "aggregated albumin" requires specific molecular weights, which is does not. RRPostHB, 60-61. While the precise weights of the aggregates are not known, they are all "non-monomeric albumin," as required by the adopted construction. *Infra*, Section V.B.

A. ***With SDS-PAGE, no***.

* * *

Q. ***Under what circumstances would dimers and aggregates of albumin be broken up using SDS-PAGE***?

A. With essentially the right sample prep.

Q. And what kind of sample prep would break up the dimers and aggregates?

A. ***Addition of agents that may break covalent bonds*** between those -- between the molecules.

* * *

Q. And how is the sample preparation different for native PAGE than SDS-PAGE?

A. It does not involve any of the addition of ***bond-breaking agents*** that I mentioned previously

RX-0007C (Alfano Dep. Tr.) at 29:24-30:10, 30:11-24, 38:21-25. While the FID takes issue with Dr. Alfano's testimony (largely adopting Ventria's attack on its own scientist), none of the issues raised in the FID undermine the scientific premise of Dr. Alfano's testimony—that SDS-PAGE with a bond-breaking agent does not provide information on the total aggregated albumin in an unaltered sample.[12] FID, 25 n.20.

[12] The FID states that Dr. Alfano "testified that he did not remember what DTT was," but that is irrelevant, as he knew that DTT was a bond-breaking agent. FID, 25 n.20; RX-0007C, 30:11-24, 38:21-25. Next, the FID notes that Dr. Alfano "did not know 'whether [Ventria] uses an agent, such as heat [or a reducing agent] when performing SDS-PAGE,' and was 'not familiar with the [SDS-PAGE] methodology at that level.' (RX-0007C (Alfano Dep. Tr.) at 31:2-9.)" and that "he was not the right person at Ventria to address the specifics of such testing." FID, 25 n.20. This is also irrelevant, as Ventria had a third-party laboratory perform Reducing SDS-PAGE, and the third-party laboratory disclosed its methodology (including the use of the reducing agent/bond-breaking agent DTT). JX-0129.0001, 3-8; CX-0904.0001, 3-8.

In short, while Reducing SDS-PAGE can confirm that a product contains ***more than*** 2% aggregated albumin, it is entirely inappropriate for evaluating whether a product has ***less than*** 2% aggregated albumin, as the claims require.

To be clear, Healthgen does not dispute that Reducing SDS-PAGE is a common and an appropriate technique for characterizing protein samples, it is, but the question is for characterizing what? It is ***not*** an appropriate technique for determining whether a product (as sold), *contains less than 2% aggregated albumin* (which is the ***only*** question at issue here). It is an excellent test for measuring *total albumin* found in a product (without discerning whether that albumin is monomer or aggregated, but total albumin is not at issue here). That can be further broken down based on whether reducing conditions are used. For example, testing a product using SDS-PAGE under first reducing and then non-reducing conditions is a common way to discriminate between the types of bonds holding the aggregates together, whether disulfide bonds (broken apart by reducing agents)

Finally, the FID selectively quotes Dr. Alfano's testimony, noting that "Healthgen failed to mention that Dr. Alfano testified that 'SDS-PAGE . . . is still a very viable method for determining . . . aggregation.'" FID, 25 n.20. But the FID fails to note that—in the same answer—Dr. Alfano testifies that Reducing SDS-PAGE "can absolutely identify aggregation, but it can only identify ***the irreversible aggregated protein***." RX-0007C (Alfano Dep. Tr.), 88:6-8; *see also id*., 88:14-20 ("Q. So when you add the reducing agents to the SDS-PAGE assay, the irreversible aggregates are still covalently linked? A. Again, I'm not a chemist and I'm not a biochemist, but the aggregation that would be essentially resistant to that type of reduction would still be visible."). But the adopted construction of "aggregated albumin" is not limited to "irreversible" aggregated albumin—it includes all "non-monomeric albumin," regardless of the forces or bonds that hold the aggregates together. Order No. 14, Chart A, 1.

The FID also cites a passage of Dr. Alfano's testimony as indicating Reducing SDS-PAGE is "an accurate method of determining the level of aggregation in albumin even if a reducing agent is used in the assay" (FID, 25 n.20), but the answer—when read in its entirety—provides the caveat that SDS-PAGE "is an accurate method for the quantification of aggregates" that "***are not dissolved or broken using the reducing agents***." RX-0007C (Alfano Dep. Tr.) at 93:21-94:3. In other words, Reducing SDS-PAGE can accurately identify the aggregates that it does not destroy with bond-breaking agents.

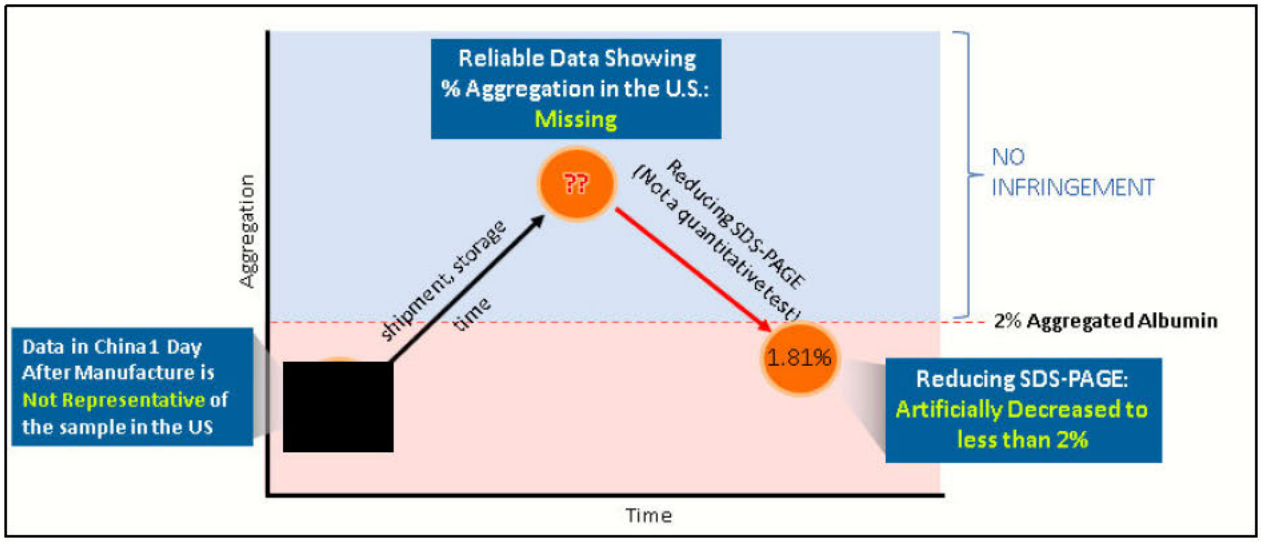
or "covalent bonds" (broken down by SGS-PAGE under non-reducing conditions). JX-0132.0009. It can also provide information about the sizes of protein species present in a sample. *See* JX-0060.0006 (listing applications for SDS-PAGE page as "[s]ize estimation and to distinguish reducible covalent from noncovalent aggregates.").

b. Reducing SDS-PAGE Artificially Decreased the Percent of Aggregated Albumin in Healthgen's Clinical Grade Products

Ventria unfairly and improperly mixed and matched its infringement proofs. Ventria's choice in its testing methodology artificially decreased aggregated albumin in Healthgen's clinical grade liquid product by nearly half in one assay, from [redacted] **aggregates** (on a fresh sample in China by SEC-HPLC) to **0.64% aggregates** by Reducing SDS-PAGE in the United States, generating over **3.5% fragments** while doing so. JX-0032C.0002 (SEC-HPLC results on fresh sample); JX-0129.0007 (first set of results by Reducing SDS-PAGE using TCEP as the reducing agent). The only sense to make out of these tests were that once imported into the United States months after the [redacted] percent as reported by Healthgen, Ventria used a different test—one it knew would lower the percentages even more. It is not in dispute that Ventria did not conduct testing on that sample using SEC-HPLC, the same test method Healthgen used in China months earlier. Tr. (Wilken) 536-11-537:1 ("Q. Did SGS specifically quantify the percent of aggregated albumin using SEC-HPLC. A. No."), 537:11-13 ("Q. But SGS was instructed by Ventria to use reducing SDS-PAGE to calculate aggregated, albumin, right? A. Yes."); Tr. (DeFilippi) at 1198:7-1199:2 (Dr. DeFilippi confirming Ventria tested Healthgen's clinical sample "by SDS-PAGE under reducing conditions").

Ventria's second set of Reducing SDS-PAGE data reported 1.81% aggregated albumin in Healthgen's clinical grade liquid product.[13] CX-0904.0007; FID, 45 (showing Dr. Wilken's redlined version of Ventria's data). As noted above, the observed 1.81% aggregated albumin confirms that aggregation increases over time, as the result on a fresh sample in China by a reliable method was only 1.1%. JX-0032C.0002.

Combining these results, we know (1) aggregation increases over time and (2) Reducing SDS-PAGE destroys aggregates in Healthgen's clinical grade product. JX-0032C.0002; JX-0129.007; JX-0060.003, 004; JX-0132.0002; CX-0904.007; RDX-0002C.50; Tr. (DeFilippi) at 1199:18-1204:25. This is shown conceptually in the graphic below.



JX-0032C.0002 (result of [redacted] one day after manufacture); CX-0904.0007 (result of 1.81% by Reducing SDS-PAGE in the United States).

As the data confirm, and as shown graphically above, the observed 1.1% aggregated albumin, as tested in China, is not representative of the true level of aggregation in the United

[13] The FID relies on Ventria's attorney argument that the tests in CX-0904 intentionally omitted low molecular weight impurities. FID, 51-52.

States. Nor is the value of 1.81% representative of the true level of aggregation in the United States, as aggregates were destroyed during the analysis. As a result, if tested using an appropriate technique in the United States, the result would very likely have been substantially greater than 2%. Tr. (DeFilippi) at 1197:24-1205:14; RDX-0002C.47-54.

3. The FID Erroneously Concluded that Reducing SDS-PAGE Is an Appropriate Test for Quantifying *Total* Aggreged Albumin

The FID identifies six factors to justify its reliance on Reducing SDS-PAGE in the FID:

> (i) the '951 patent quantifies aggregates in multiple samples of rice-produced rHSA (i.e., Cellastim) using reducing SDS-PAGE and compares their percent aggregate values; (ii) the non-patent literature confirms reducing SDS-PAGE is a standard, recommended method to quantify and characterize aggregates; (iii) Healthgen relied on reducing SDS-PAGE in an effort to show invalidity and noninfringement; (iv) Dr. Wilken personally analyzed aggregates in rice-produced rHSA samples she ran under reducing SDS-PAGE conditions, which she testified can be readily quantified; (v) Healthgen acknowledged in customer communications and internal testing that reducing agents do not "drive up" the amount of monomeric albumin in a sample when compared with HPLC; and (vi) Healthgen quantified what it considered aggregated albumin using SDS-PAGE.

FID, 17. These factors have no merit and are addressed in turn below.

a. The '951 Patent Does Not Quantify *Total* Aggregated Albumin Using Reducing SDS-PAGE

The '951 patent does not describe using Reducing SDS-PAGE to quantify the total aggregated albumin—it merely compares the amounts of large aggregates at around ***250 KDa*** in different samples (2% observed for old samples, and less than 1% for newer samples). JX-0001, 72:51-55. These are far from the same thing, and the FID is erroneous. These values reflect the amounts of aggregates at 250 kDa that remain after chemical treatment with a bond-breaking agent. Relying solely on the method used to identify such aggregates is improper for the simple reason that "aggregated albumin" is not limited to "aggregates with molecular weights around 250 kDa observed by Reducing SDS-PAGE." Order No. 14, Chart A, 1.

Notably, the '951 patent reports detecting species that are "mostly likely" albumin dimers at 130 kDa by SEC-HPLC, noting that "the Cellastim dimer peak is significantly smaller than the plasma derived albumin." JX-0001, 72:18-21. These dimers are not reported (much less quantified) in the results for Reducing SDS-PAGE. JX-0001, 70:17-24 (reporting sample treatment for SDS-PAGE included a reducing agent), 72:29-57 (results in analysis). These albumin dimers constitute "aggregated albumin," as construed, and it is improper to rely on a purported quantification method that fails to include them. Order No. 14, Chart A, 1; RRPostHB, 10-11.

b. The Peer-Reviewed Literature Confirms *Reducing* SDS-PAGE Is Not a Suitable Method for Quantifying *Total* Aggregates in an *Unaltered* Sample

The FID mischaracterizes the peer-reviewed literature in the second prong of its flawed analysis, finding that "the non-patent literature confirms Reducing SDS-PAGE is a standard, recommended method to ***quantify*** and characterize aggregates." FID, 17.

While the non-patent literature may be a standard recommended method to ***characterize*** *aggregates* (as compared to total albumin) it is not standard to ***quantify*** *aggregates*—that is simply wrong. For example, the FID relies on den Engelsman's discussion of SDS-PAGE—not Reducing SDS-PAGE, perhaps failing to recognize the difference between the two. FID, 18-19. For example, the FID quotes a portion of the passage below:

> SEC and SDS-PAGE/CE-SDS are methods that are robust enough for reproducible quantification of aggregates and that allow routine use with sufficient sample throughput. These methods use specific separation principles and ***sample preparation methods which may impact the result*** both qualitatively and/or quantitatively, so orthogonal methods should be used to confirm that the applied method, e.g. SEC, provides adequate results. Below we list recommendations regarding the assessment of protein aggregates in biotech product development:
>
> Employ robust, quantifiable methods for QC testing: SEC (quantification of covalent and non-covalent aggregates, but not low-affinity aggregates and larger aggregates); SDS PAGE and/or CE-SDS (covalent aggregates).

JX-0132.0013.

The passage above says nothing about relying on ***only Reducing*** SDS-PAGE (a technique that breaks up aggregates). *Id.* Rather, it focuses on SDS-PAGE. *Id.*

The FID notes that "no single method" covers all aspects of the analysis, but that does not mean one should select a technique known and intended to decrease the quantity of aggregated albumin when seeking to determine whether a sample as "less than 2% aggregated albumin." FID, 19 (citing JX-0132.0012). No technique is perfect, but that does not excuse chemically manipulating a sample to alter the result, particularly when more appropriate techniques are available. *See* JX-0060.0006 (Mahler) (identifying SEC-HPLC as a technique for quantifying soluble aggregates).

As noted above, Reducing SDS-PAGE is an appropriate technique, ***just not for quantifying total aggregated albumin***. As den Engelsman explains, Reducing SDS-PAGE "can discriminate between aggregates held together by **disulfide bonds** and those held together by other (non-reducible) covalent bonds." JX-0132.0009; *see also* JX-0060.0008 (Mahler) ("An important feature of SDS-PAGE under nonreducing conditions versus reducing conditions is its ability to differentiate between noncovalent and covalent aggregates by disulfide bridges."). Implicit in this discussion is the fact that Reducing SDS-PAGE breaks up aggregates held together by disulfide bonds, such that a comparison of data generated by SDS-PAGE (which does not break up aggregates held together by disulfide bonds) and Reducing SDS-PAGE (which does) reveals how many aggregates were linked by disulfide bonds. JX-0132.0009; JX-0060.0008.

The FID misreads the non-patent literature relied on by both experts, and the ALJ's reliance on Reducing SDS-PAGE is inappropriate for quantifying percentages of aggregated albumin, as required by the asserted claims. After misinterpreting the peer-reviewed literature, the FID faults

Healthgen for advocating for reliance on the most reliable technique available, SEC-HPLC. FID, 19-20. While SEC-HPLC may not observe very large aggregates (insoluble aggregates), everyone in the ordinary course of business outside this investigation (Ventria, Healthgen, Mahler and den Engelsman) all agree it is far more reliable than Reducing SDS-PAGE, as it does not involve chemical manipulation to artificially reduce the level of aggregated albumin in a sample. *See* JX-0060.0006. Indeed, Mahler identifies SEC-HPLC as a technique for quantification and SDS-PAGE only for "[s]ize estimation and to distinguish reducible covalent from noncovalent aggregates." *Id.*

Table 1. Frequently Used Methods for the Analysis of Protein Aggregation

Category	Method	Application
Quantification and/or size estimation	SE-HPLC	Size estimation and quantification (soluble aggregates)
	RP-HPLC	Size estimation and quantification (soluble aggregates)
	SDS–PAGE	Size estimation and to distinguish reducible covalent from noncovalent aggregates

Id.

As noted in the FID, the claims do not require any particular technique for quantifying aggregated albumin. FID, 20. The claims, however, must be compared to the products as sold. Chemically altering a sample prior to analysis by Reducing SDS-PAGE is thus wholly inappropriate.

c. The FID's Criticism of Dr. DeFilippi's Testimony Is Misplaced

In the third prong of its analysis, the FID mischaracterizes to only then criticize Dr. DeFilippi's invalidity and noninfringement testimony. FID, 21. For example, the FID states that Dr. DeFilippi "admitted during cross-examination that he was willing to accept Van Urk's use of reducing SDS-PAGE ***in arriving at some of his opinions***," and further quoted deposition testimony indicating that "***if*** there is no other assay to rely upon" (other than Reducing SDS-PAGE), his opinion "might be a stretch." FID, 21-22 (emphasis added). But that inappropriate

hypothetical conflicts with the real-world text of the Van Urk prior art reference (and Dr. DeFilippi's testimony at the hearing), as Van Urk discloses evaluating aggregated albumin using both Reducing SDS-PAGE and gel permeation HPLC (also called HPLC). JX-0030.071. While Van Urk's rHSA contained up to 1% dimeric albumin (aggregated albumin), the level of aggregation was reduced to nearly 0% when treated by Reducing SDS-PAGE. JX-0030.0065 (reporting up to 1% dimeric albumin), 0071 (reporting that treatment with a reducing agent provided "at least 99.9%" monomeric albumin). Van Urk further discloses that its rHSA contains up to 1% dimeric albumin—and that disclosure is not tied to Reducing SDS-PAGE. *See infra*, Section VI.A.4; Tr. (DeFilippi) at 854:14-859:17.

Next, the FID incorrectly states that Dr. DeFilippi relied on data from Reducing SDS-PAGE "to quantify what he believes is the amount of aggregated albumin in the Accused Products." FID, 22 (citing Tr. (DeFilippi) 1169:16-1170:15). Not true. Dr. DeFilippi testified regarding the results of ***Ventria's*** testing by Reducing SDS-PAGE and explained that even using that technique, the samples contained more than 2% aggregated albumin. Tr. (DeFilippi) at 1169:16-1170:15. As Dr. DeFilippi explained, Reducing SDS-PAGE may be used to show a product contains ***more than 2% aggregated albumin***, but not ***less than 2% aggregated albumin***. Tr. (DeFilippi) at 1182:14-1183:5. The reason is simple: Reducing SDS-PAGE "reduce[s] the observed level of aggregated albumin." *Id.* 1182:9-13. As such, Reducing SDS-PAGE can confirm the presence of more than 2% aggregated albumin, but not less than 2% (as some of the aggregated albumin may have been broken up during sample treatment). Contrary to the FID findings, this is not "cherry-picking" opinions, but common-sense fact.

d. Dr. Wilken's Testimony Regarding SDS-PAGE Does Not Support the FID's Conclusion Regarding *Reducing* SDS-PAGE

In the fourth prong of its analysis, the FID conflates SDS-PAGE with Reducing SDS-PAGE, seeking to apply Dr. Wilken's testimony regarding SDS-PAGE with Reducing SDS-PAGE. FID, 22-23. For example, the FID notes that Dr. Wilken performed "**reducing** SDS-PAGE on rice-produced rHSA samples." FID, 22. The quoted testimony, however, concerns ***SDS-PAGE***, not Reducing SDS-PAGE. *Id.* (quoting Tr. (Wilken) at 312:2-13) ("We use SDS-PAGE."). Similarly, the FID states that Dr. Wilken "repeatedly testified that reducing SDS-PAGE is a common technique that can be used to quantify aggregated albumin samples of rice-produced rHSA." *Id.*, 22-23. But once again, the cited testimony concerns SDS-PAGE, not Reducing SDS-PAGE. *See* Tr. (Wilken) at 344:6-24 (agreeing "SDS-PAGE" is a technique that can measure protein aggregation), 346:11-17 (referring to den Engelsman's discussion of SDS-PAGE). The FID again and again conflates reducing SDS-PAGE and non-reducing SDS-PAGE, along with other tests, which are more appropriate—understanding their difference is critical to an appropriate noninfringement finding in this investigation.

e. Statements that Agents Like "SDS" Do Not Increase Monomer Content Say Nothing about the Impact of *Reducing* Agents

The FID again fails to appreciate the difference between SDS-PAGE (performed under non-reducing conditions) and Reducing SDS-PAGE in its discussion of Healthgen's customer communications. FID, 23-24. In particular, Healthgen explained that HPLC and SDS-PAGE (not Reducing SDS-PAGE) provided comparable results for its rHSA samples. FID, 24; JX-0063C.0001. Again, there is no evidence that Healthgen was referring to "Reducing SDS-PAGE"—the document says "SDS-PAGE." JX-0063C.0001.

The comparable results achieved by SEC-HPLC and SDS-PAGE (the green highlighted columns below) are not surprising, as data obtained using these same techniques on samples of Ventria's Cellastim and Exbumin reflect comparable levels of aggregated albumin, as tabulated below. *See* RX-0311; RX-0310 (methodology). By contrast, ***Reducing*** SDS-PAGE (column highlighted in red)—the technique relied on in the FID—dramatically reduces aggregated albumin.

Table 3. Percent Aggregated Albumin by Various Techniques

Sample	SEC-HPLC	SDS-PAGE	Reducing SDS-PAGE
Exbumin sample 1	4.41%	6.4%	2.0%
Exbumin sample 2	3.65%	3.4%	1.4%
Cellastim sample 1	4.60%	4.4%	1.5%
Cellastim sample 2	3.88%	3.3%	1.0%

The FID insinuates that the technique used may have been Reducing SDS-PAGE, as different documents indicate that "purity" is evaluated by SDS-PAGE under both reducing and non-reducing conditions. FID, 25, n.19 (citing CX-0178C.0004 and JX-0008C.0002). Neither of the cited documents, however, say anything about quantifying aggregated albumin using Reducing SDS-PAGE (or even SDS-PAGE). CX-0178C.0004; JX-0008C.0002. Rather, Healthgen uses ***SEC-HPLC*** to quantify the "percent polymer" in its rHSA (e.g., the level of larger albumin aggregates). JX-0008C.0001 (In the entry for "Percent Polymer," Healthgen explains that "[t]he polymer content of rHA is detected by Size exclusion chromatography – high performance liquid chromatography SEC-HPLC method from ChP 2015 Vol. Ill <3121>."); *see also* CX-0178C.0006 (describing assay for "Determination of Polymer").

f. Healthgen's Internal Documents [redacted]

In the sixth prong and final of its analysis, the FID mischaracterizes Healthgen's internal document, RX-0366C. FID, 26-27. First, the FID inappropriately relies on a misstatement by

Healthgen's counsel during closing arguments to find that RX-0366C [redacted]. *Id.*, 26. The FID thus erroneously concludes that the document shows Healthgen quantifies aggregated albumin using [redacted]. *Id.*

The document—on its face—describes [redacted] not [redacted]. RX-0366C.010-12. Notably, the document lists [redacted]. *Id.*, 10 ([redacted] It is improper for the FID to rely on a comment during closing arguments to change the documentary record, as closing arguments are not evidence—they are arguments. *Gemtron Corp. v. Saint-Gobain Corp.*, 572 F.3d 1371, 1380 (Fed. Cir. 2009) (noting that "unsworn attorney argument" is not evidence).

Moreover, the document does not purport to quantify aggregated albumin in the product by any method, [redacted]. RX-0366C.002, 12. Instead, it reports the "purity" of the product as [redacted]. RX-0366C.011 [redacted] .012 ([redacted] W[redacted] RX-0366C.003, 12.

D. The FID Does Not Address Arguments Presented by Healthgen

While the FID contains a section purporting to address Healthgen's arguments, that section is largely copied from Ventria's post-hearing brief, contains the same mischaracterizations, and does not actually address the arguments presented by Healthgen. *Compare* FID, 56, *with* RRPostHB, 43-57. For example, as noted above, the FID does not discuss Ventria's prelitigation

testing or the documents evidencing Healthgen's "purity" calculations, as detailed above. RRPostHB, 43-45.

The FID discusses "salted" samples, without fairly presenting Healthgen's arguments on that issue. FID, 56; RRPostHB, 35-36. First, the FID mischaracterizes Dr. DeFilippi's testimony as saying, [redacted] FID, 56. This is Ventria's incorrect spin on Healthgen's argument—not the argument presented by Healthgen or its expert. As Dr. DeFilippi explained, [redacted]. Tr. (DeFilippi) at 1175:4-14. [redacted] RRPostHB, 51 n.17. [redacted] Tr. (DeFilippi) at 1173:24-1175:14. [redacted] *Certain Automated Teller Machines*, 2016 WL 5076114, at *1.

The FID further disregards the undisputed evidence that lyophilization (freeze drying) can increase aggregation. FID, 56-57. As Mahler explains, "[a]ggregation can be induced by a wide variety of conditions, including . . . pumping, freezing, and/or thawing [the] formulation," e.g., freeze drying/lyophilization. JX-0060.0003.

To refute the peer-reviewed literature, the FID cites an [redacted], which the FID characterizes as stating [redacted]

[redacted] FID, 56. This is a mischaracterization of [redacted]

[redacted]

CX-0196C.0007. [redacted] does not undermine the undisputed science that lyophilization would be expected to increase aggregation. RRPostHB, 47; Tr. (DeFilippi) at 1176:4-11.

V. THE COMMISSION SHOULD REVIEW AND REVERSE THE FID'S FINDINGS ON DOMESTIC INDUSTRY – TECHNICAL PRONG

A. The FID Improperly Relied on Reducing SDS-PAGE for Technical ID

Same as with FID's erroneous infringement analysis, the FID erred again by relying on Reducing SDS-PAGE quantifications of percent of aggregated albumin in Ventria's DI products, Exbumin, Cellastim, and products containing Cellastim. Had the FID relied on the more appropriate test method of SEC-HPLC (as a person skilled in the art would have done), none of these products would have met all the limitations of the asserted claims.

As an initial matter, Healthgen did not dispute that Optibumin satisfies all limitations of the '951 patent, [redacted]

In contrast to Optibumin, Ventria's other purported DI products contain far more than 2% aggregated albumin when tested using SEC-HPLC, as shown below.[14] RX-0311; RX-0310 (methodology); Tr. (DeFilippi) at 1186:24-1188:23, 1220:4-1225:11; RDX-0002C.38, 74-80.

Table 3. Percent Aggregated Albumin by Various Techniques			
Sample	**SEC-HPLC**	**SDS-PAGE**	**Reducing SDS-PAGE**
Exbumin sample 1	**4.41%**	6.4%	**2.0%**
Exbumin sample 2	**3.65%**	**3.4%**	**1.4%**
Cellastim sample 1	**4.60%**	**4.4%**	**1.5%**
Cellastim sample 2	**3.88%**	**3.3%**	**1.0%**

RX-0311.002, 5-8. It is clear error for the FID to rely on Reducing SDS-PAGE—a technique designed to decrease aggregated albumin—when evaluating whether a product contains "less than 2% aggregated albumin." *Supra*, Section IV.C.2. It is irrelevant that the laboratory may have performed Reducing SDS-PAGE properly, because the technique itself is not proper. FID, 62.

The FID seeks to disregard the SEC-HPLC data, because the data do not include molecular weight markers. FID, 25-26. The FID further seeks to change the SDS-PAGE results by redlining the data to remove aggregates larger than twice the size of monomeric albumin. FID, 70. Both analyses are improper, as determining the amount of "aggregated albumin" does not require an analysis of molecular weights, as addressed in Section V.B.

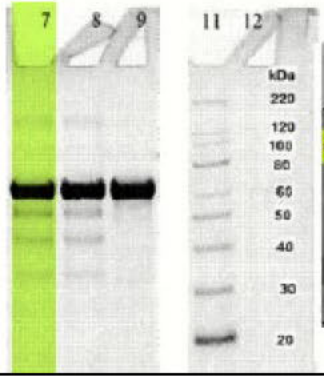
B. The FID's Interpretation of the Data Is Based on an Error of Law

The FID clearly erred in its analysis of data collected on behalf of Ventria by Reducing SDS-PAGE. FID, 63-66. Not only does the FID rely on the wrong test (Reducing SDS-PAGE), it

[14] [redacted]

adopts Ventria's arbitrary redlining of the data to bring the level of observed aggregates to below 2%. FID, 63-66. It is improper to arbitrarily cross-out data in this context.

Figure 14: May 2021 SGS Test Results for Cellastim



Sample	Band	Molecular weight kDa	Band volume	% band	% purity
Cellastim S Lane 7 VEN00326	HMW impurities	134	702864	1.29	86
		~~126~~	~~290793~~	~~0.54~~	
		~~106~~	~~213094~~	~~0.39~~	
	Main band	68	47134589	86.21	
	LMW impurities	59	2282714	4.18	
		57	1493716	2.73	
		46	1873232	3.43	
		33	678065	1.24	
	Sum		54675067	100.00	

FID, 64. As shown above, with no reasoned support whatsoever, the FID adopts Dr. Wilken's conclusory opinion in striking through high molecular weight impurities—aggregated albumin—finding that such aggregates would not comprise fragments of recombinant mammalian albumin that "retain the biological or therapeutic activity of native mammalian albumin." *Id.*, 64. This conclusion is unsupported by the claim construction in this case, which specifically includes fragments that retain activity. Order No. 14, Chart B, 1-2.

Even more egregiously, the FID redlines data generated by non-reducing SDS-PAGE to bring the total levels to below 2%, this time striking through aggregates with molecular weights ***more than twice that of monomeric albumin***:

NON-REDUCING GEL

Cellastim S (2 µg), non-reduced, sample 1		
Band No.	Molecular Weight (kDa)	Band %
1	118.2	2.5
2	109.3	1.9
3	52.5	83.9
4	44.4	6.5
5	34.6	5.2

NON-REDUCING GEL

Exbumin (2 µg), non-reduced, sample 1		
Band No.	Molecular Weight (kDa)	Band %
1	117.4	3.4
2	107.8	3.0
3	52.4	82.2
4	44.4	5.8
5	34.6	5.6

Cellastim S (2 µg), non-reduced, sample 2		
Band No.	Molecular Weight (kDa)	Band %
1	124.9	2.2
2	114.0	1.1
3	52.7	87.1
4	44.1	6.0
5	34.4	3.6

Exbumin (2 µg), non-reduced, sample 2		
Band No.	Molecular Weight (kDa)	Band %
1	121.4	2.0
2	112.4	1.4
3	52.6	86.5
4	43.9	6.6
5	34.4	3.5

FID, 70. The FID justifies its redlining of these data by noting that the larger aggregates could not comprise only monomeric albumin (e.g., they may comprise two units of full-length, fully functional albumin plus a fragment). *Id.*

In its redlining of the data, the FID ***changes the adopted construction*** of "aggregated albumin" to require that such aggregates comprise units conforming to the construction of "recombinant mammalian albumin."[15] *Id.* This is inconsistent with the adopted constructions, which require only that aggregated albumin comprise "non-monomeric albumin," with no functional or molecular weight limitations. Order No. 14, Chart A, 1. For example, "less than 2% aggregated albumin" was construed to mean "less than 2% non-monomeric albumin by weight." *Id.* This construction includes all aggregates [redacted]

[15] The FID does not apply this flawed construction when analyzing Healthgen's products. To the extent that Ventria argues that molecular weight must be considered to determine whether albumin species larger than monomeric albumin comprise aggregated albumin in any data on Healthgen's products, such an analysis is improper for all the reasons detailed herein.



The FID's altered claim construction is further inconsistent with the structure of the claims. To support its argument that the claims required aggregated albumin comprised of fully functional albumin units, Ventria argued that "'recombinant mammalian albumin' provides antecedent basis for all other appearances of albumin in the Asserted Claims." CPostHB, 19. This argument, which appears to have been implicitly adopted without discussion in the FID, is wrong as a matter of law. The term "aggregated albumin" does not refer back or rely on any prior instance of albumin for antecedent basis, e.g., it does not recite "the albumin" or "said albumin." RRPostHB, 20-22.

The FID's analysis is also inconsistent with the '951 patent's teaching that "[t]he creation of aggregated albumin is an indicator of protein degradation which is used as one marker for degradation or loss of stability industry wide." JX-0001, 72:21-23. In this regard, the FID's

approach is also nonsensical. Under the altered construction in the FID, the claims of the '951 patent would limit the amount of aggregated albumin comprised of "good" fully functional albumin units to less than 2%, while permitting high levels of aggregated albumin comprised of "bad" degraded albumin fragments. This is inconsistent with the teachings of the '951 patent, which seeks to decrease degraded albumin present in the form of aggregates. *Id.*

Additionally, even if the construction of "aggregated albumin" was changed to require that any aggregated fragments retain activity, the FID's analysis remains clearly erroneous, as it fails to consider the patent's teachings regarding the activity of albumin fragments. FID, 62-66. The '951 patent specifically teaches that fragments "may also have the desirable functional properties of the peptide from which they derived and may be used in any of the methods of the invention." JX-0001, 37:13-16. Yet despite advancing this flawed, untimely claim construction theory, Dr. Wilken made no attempt to evaluate the biological activity in the context of assessing aggregation. Tr. (Wilken) at 563:9-20. In response to questions from her own attorney on redirect, she testified as follows:

> *Q. Dr. Wilken, on cross-examination you said several times that you weren't assessing biological activity.*
>
> *A. Yes.*
>
> *Q. What were you assessing under the Court's claim construction?*
>
> *A. In regards to what aspect?*
>
> *Q. In regards to the aggregated albumin.*
>
> *A.* ***We're assessing the amount of aggregated – based on the molecular weight****.*
>
> *Q. And what biological activity were you assessing?*
>
> *A.* ***We weren't evaluating biological activity*** *in that particular method. That's not the intention of that method.*

Id.; *see also id.*, 474:14-22.

For at least these reasons, the FID's conclusion that Exbumin, Cellastim, and products containing Cellastim practice claims 1 and 11-13 is clearly erroneous and based on legal error.

VI. THE COMMISSION SHOULD REVIEW AND REVERSE THE FID'S FINDINGS ON VALIDITY

The FID misapplies black-letter law on anticipation. FID, 76-80. Under Federal Circuit precedent, "***anticipation does not require actual performance of suggestions in a disclosure***. Rather, anticipation only requires that those suggestions be enabling to one of skill in the art." *Bristol-Myers Squibb Co. v. Ben Venue Labs, Inc.*, 246 F.3d 1368, 1379 (Fed. Cir. 2001); *see also In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009); *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1380 (Fed. Cir. 2003) ("Anticipation ***does not require the actual creation or reduction to practice*** of the prior art subject matter"). The FID failed to apply the correct legal standard, instead requiring proof of ***actual creation and use***. *See e.g.*, FID, 77-79. The FID's analysis is further based on clearly erroneous factual findings, as detailed below.

A. The FID's Conclusion that Van Urk or Berezenko Do Not Anticipate Claims 1 and 11 Is Based on an Incorrect Legal Standard and Clearly Erroneous Factual Findings

Van Urk and Berezenko disclose all limitations of claims 1 and 11. RPostHB, 5-24. Each anticipatory publication independently discloses methods for purifying albumin, including rHSA produced in transgenic plants, to achieve a product that is "non-pyrogenic," i.e., contains no detectable endotoxins, and has less than 2% aggregated albumin, and each further discloses its suitability for use in cell culture media, satisfying all limitations of claims 1 and 11. JX-0030.0003 (1:1-15), 0024 (22:26-27), 0065, 75-75; *e.g.*, JX-0027, 1:12-22, 2:57-3:44, 21:6-9, claims 1, 21.

The FID applied the wrong legal test to conclude otherwise, finding that Van Urk and Berezenko do not sufficiently disclose (1) "a cell culture media supplement or complete media

composition" comprising a recombinant human albumin that is (2) "produced in a transgenic plant," comprising (3) "less than 1 EU of endotoxin/mg of albumin," and (4) "less than 2% aggregated albumin." FID, 79-89. When analyzed under the proper legal standard, Van Urk and Berezenko each independently anticipate claims 1 and 11.

1. "a cell culture media supplement or complete media composition"

The FID erroneously found that Van Urk and Berezenko do not disclose the claimed "a cell culture media supplement or complete media composition," contrary to the clear disclosures of each publication. FID, 77. For example, Van Urk teaches that rHSA may be used in cell culture media, and both Van Urk and Berezenko teach that albumin (which both define to include rHSA) "***is*** used to supplement media used for growing higher eukaryotic cells." JX-0030.0003 (1:8-16), 0025 (p.23:26-24:4); JX-0027, 1:16-17, 1:22-23; Trial Tr. 818:22-819:1; RDX-0006C.1; Trial Tr. 1119:2-7 (Dr. Wilken admitting that Berezenko discloses recombinant human albumin could be "used in cell culture"); RPostHB, 7, 18. Yet the FID found that these disclosures were "insufficient" to show anticipation absent disclosures of "***actual***" use in cell culture media. FID, 77. The FID's heightened standard for anticipation is an error of law, as "anticipation ***does not require actual performance of suggestions*** in a disclosure." *Bristol-Myers Squibb*, 246 F.3d at 1379 (emphasis added).

2. "produced in a transgenic plant"

The FID erroneously concluded that neither Van Urk nor Berezenko disclose rHSA "produced in a transgenic plant," again applying the incorrect standard for anticipation and disregarding the straightforward disclosures of both references. FID, 77-78. For example, Van Urk specifically teaches that its rHSA may be "produced in ***transgenic*** animals or ***plants***" and "***may be obtained from a transgenic plant***, such as tobacco, potato, or corn (maize)." JX-0030.0003

(1:3-9), 0024 (22:26-27) (emphases added); RPostHB, 10. Berezenko similarly discloses that its purification process "is particularly applicable to purifying recombinant human albumin [rHSA]," where the rHSA "may be expressed in a suitable host," of which many were known, including "plant cells." RX-0027.2:57-3:44; RPreHB, 55; RPostHB, 20. The FID faults both publications, finding that nothing short of actually producing rHSA in a transgenic plant would suffice. FID, 77. This finding, again, constitutes legal error. *Bristol-Myers Squibb*, 246 F.3d at 1379.

Van Urk and Berezenko do not need to detail the basic steps for producing rHSA from a transgenic plant, as such processes were already generally known to those of ordinary skill in the art. *Infra* 61-63.

3. "less than 1 EU of endotoxin/mg of albumin"

Van Urk and Berezenko both further disclose the claimed rHSA containing "less than 1 EU of endotoxin/mg of albumin." For instance, both Van Urk and Berezenko teach that their rHSA products are "essentially free of" (i.e., with "below detectable levels" of) endotoxin. JX-0030.0023 (21:5-11), 0073; Trial Tr. 852:4-15; JX-0027, 1:41-49; Trial Tr. 1123:12-18; *id.*, 852:16-21; JX-0030.0065; RX-0018.020, 061; JX-0134.003; *see also* Trial Tr. 1099:24-1100:3; JX-0027, 21:7-8, claims 1, 21; Trial Tr. 813:12-16; RPostHB, 11, 21. The FID again applied the wrong legal standard, dismissing these express disclosures because, e.g., Van Urk and Berezenko "***do not show data that demonstrate***" the recited endotoxin level. FID, 78-79. This misapplication of the law warrants a reversal of the FID on this issue. *Bristol-Myers Squibb*, 246 F.3d at 1379.

The FID found that because "endotoxin" appears as one of a few "optional characteristics" of Van Urk's rHSA products, "including the word 'or' directly prior to the word 'endotoxin'," "these characteristics are not necessarily present." FID, 78. This conclusion violates Federal Circuit precedent. *Upsher-Smith Labs., Inc. v. Pamlab, L.L.C.*, 412 F.3d 1319, 1322 (Fed. Cir.

2005) (prior art's disclosure of an optionally included component anticipates compositions that both do and do not contain that component.).

The FID also found that Van Urk and Berezenko do not even "show data that demonstrate that the [tested] yeast compositions are endotoxin-free." FID, 78-79. This finding is clearly erroneous in view of these references' express teachings. For example, both publications report that their respective purified rHSA products are "non-pyrogenic," which the parties agree to mean the actual rHSA products contain no detectable endotoxin, which is far below the claimed 1 EU endotoxin/mg albumin. JX-0030.0065; Trial Tr. 1099:24-1100:3, *id.*, 852:16-21; JX-0027, 21:6-9, claims 1, 19-21.

Acknowledging Van Urk's actual achievement of rHSA products with "no detectable endotoxin," the FID still concluded that Van Urk does not "indicate" what solution contains no detectable endotoxin. FID. 78. This finding is also clearly erroneous, as Van Urk's sole focus is on rHSA—not some mysterious drug product. RPostHB, 12; JX-0030.2:1-9 (Van Urk summarizing that its invention "relates to a process for purifying the protein ***human serum albumin (HSA)***," including rHSA); JX-0030.0023, 0074-75 (other purity testing all referring to rHSA); *see general* Examples 1-10 (purifying yeast-derived rHSA and testing purify, including endotoxin level).

4. "less than 2% aggregated albumin"

The FID also erroneously found that Van Urk failed to show "less than 2% aggregated albumin" level in any rHSA.[16] FID, 79-80. This finding not only applies a wrong legal standard

[16] The FID does not appear to find fault with Berezenko's disclosure of this limitation. FID, 77-78. Irrespective of any implication from its silence, as Healthgen explained, Berezenko expressly teaches the "less the 2% aggregated albumin limitation." JX-0027, 1:58-59, claim 1; Trial Tr. 1124:16-24; *see also* JX-0027, 21:6-8; RPostHB, 23.

but also contradicts Van Urk's express disclosures. *Bristol-Myers Squibb*, 246 F.3d at 1379. Van Urk expressly discloses that in its purified rHSA products, "[t]here may be up to 1% dimeric albumin but no larger polymers or aggregates are detectable," meaning its rHSA contains less than 2% aggregated albumin. JX-0030.0065; Trial Tr. 1121:16-1122:4 (Dr. Wilken admitting the same); RPostHB, 14.

Importantly, Van Urk further characterizes the level of albumin aggregation using a variety of techniques, not solely Reducing SDS-PAGE. Tr. 857:15-859:9; *see id.*, 1122:18-1123:1; JX-0030.0071; RDX-0001C.36; JX-0030.0069; Tr. 859:4-9; *see also id.*, 465:3-20; JX-0027, 16:64-18:17, 19:45-49, 23:42-57; RPostHB, 15-16, 23. The FID characterized these disclosures as "a single sentence" and then concluded that Healthgen "failed to present ***any evidence*** regarding the monomer content disclosed in Van Urk." FID, 79-80 (emphasis added). That finding, however, entirely misses the point because the asserted claims require less than 2% aggregated albumin—there is no requirement, express or otherwise—regarding the percent of *monomeric* albumin. The FID again seeks to disregard the straightforward disclosures of Van Urk while also misreading the claim requirements. Van Urk reports "up to 1% dimeric albumin" with "no larger polymers or aggregates detectable," e.g., less than 2% aggregated albumin, which is all the claims require. JX-0030.0065.

5. The FID's Misapplied the "At Once Envisage" Precedent

The FID found that Healthgen failed to show disclosures of the asserted limitations in a combination such that "one of ordinary skill would at once envisage such a combination." FID, 80 (citing *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015)).

But *Kennametal* only becomes relevant when a reference "d[oes] not expressly spell out all the limitations arranged or combined as in the claim." *Kennametal*, 780 F.3d at 1381. Here,

Van Urk and Berezenko expressly spell out the limitations as they are combined in the claim—they both disclose purifying rHSA, including those produced in transgenic plants, to achieve reduced level of impurities. JX-0030.0003 (1:3-9); JX-0030.0024 (22:26-27); JX-0027, 1:41-49, 3:12-44. This is not a case where these disclosures would be "arranged" or "combined" in a different manner than the claimed invention. The FID erroneously divorces Van Urk and Berezenko's yeast-derived rHSA purification working examples from the express teachings in their respective disclosures that the same purification methods are also suitable for plant-derived rHSA purification. The FID's reliance on *Kennametal* is legal error and contrary to established Federal Circuit authority based on the express disclosures in both Van Urk and Berezenko. FID, 80-81.

6. The FID's Finding that the PTO Considered the "Substance" of Van Urk is Clearly Erroneous

The FID also made a specific finding that the "substance" of Van Urk was considered by the PTO because the PTO had considered Berezenko. FID, 85-87. While that is factually wrong, as an initial matter, whether the PTO considered Van Urk or other asserted references does not change Healthgen's burden to prove anticipation. *Sciele Pharma Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1260 (Fed. Cir. 2012) ("As the Supreme Court explained in *i4i*, there is no heightened burden of proof when a reference was previously considered by the PTO.").

Van Urk was never before the PTO during the prosecution. RPostHB, 61. And the Examiner only discussed teachings of yeast-derived rHSA in Berezenko during prosecution and never indicated he recognized Berezenko's teaching of rHSA expressed in "***plant cells***." *See generally* JX-0002; RPostHB, 62. Much less did the Examiner distinguish the asserted claims from Berezenko's teachings relating to transgenic plants. *See generally* JX-0002. The FID's findings contradicting these facts, thus, is thus clear error.

B. The Commission Should Reverse FID's Finding that Van Urk Does Not Anticipate Claim 12

Claim 12 depends from claim 1 and further recites "a transgenic grain." The FID again applied the wrong legal test to conclude that Van Urk fails to disclose this limitation. In particular, Van Urk expressly teaches that rHSA may be produced "from a transgenic plant, such as tobacco, potato or ***corn (maize)***"—which is a grain. JX-0030.0024 (22:25-27); JX-0138.003. The FID faulted this disclosure because Van Urk does not also expressly describe making rHSA in a transgenic corn. FID, 89. But this, again, is the wrong legal test, as anticipation does not require actual performance. *Bristol-Myers Squibb*, 246 F.3d at 1379.

The FID made another legal error by finding that Van Urk's disclosure of a grain species (maize, corn) does not anticipate the claimed "transgenic grain." FID, 89 (stating "the term 'grain' is not mentioned even once in Van Urk."). The FID's requirement that Van Urk needs to expressly disclose the "grain" genus contradicts the long-standing precedent that a species anticipates a claim to a genus covering the species. *E.g., In re Gosteli*, 872 F.2d 1008 (Fed. Cir. 1989).

C. The FID's Analysis of Prior Art Enablement Is Based on Legal Error and Clearly Erroneous Findings

1. The FID's Finding that Van Urk and Berezenko "are specific to yeast-derived rHSA" and would not "read on" the recited plant-derived rHSA is Clearly Erroneous

At the hearing, Ventria through its expert Dr. Wilken, spent much of its time trying to show that the prior art was not enabled. CDX-0004.6-19. Indeed, Ventria bears the burden to overcome the presumption that Van Urk and Berezenko's disclosures are enabling. *Apple Inc. v. Corephotonics, Ltd.*, 861 F. App'x 443, 449 (Fed. Cir. 2021); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1355-56 (Fed. Cir. 2003) ("It was error to shift the burden of 'proving the prior art reference's enablement of the claimed invention on the alleged infringer.'").

The FID, however, does not address the presumption of enablement in view of the express disclosures (which are all present) and whether Ventria met its burden. Instead, the FID concluded that Van Urk and Berezenko's disclosures "are specific to yeast-derived rHSA" and would not "read on" the recited plant-derived rHSA. FID, 81-85.

The FID's characterization of Van Urk and Berezenko's disclosures as being "specific to yeast-derived rHSA" entirely misses that those references' *also* expressly teach that the disclosed purification methods are suitable for rHSA produced in plants. *Supra*, 54 (Section VI.A.2).

The FID found that there may be differences in unspecified "profile of impurifies" and potentially co-purified fatty acids in yeast- and plant-derived rHSA. FID, 81-83. But those alleged differences, even if true, are irrelevant because they are not tied to any claim limitation. RPostHB, 57. Unlike unspecified "profile of impurities," i.e., host cell proteins, the claimed impurities—endotoxins and aggregated albumin—are not unique to transgenic yeast or transgenic rice. *Id.* As a result, the same processes that reduced the levels of endotoxin and aggregated albumin in albumin produced in yeast, such as those in Van Urk and Berezenko, may be used for albumin produced in transgenic rice. *See* Trial Tr. 886:15-894:12; RDX-0001C.62-64.

The FID's finding that that rice hosts may contain a higher level of endotoxin contaminants than yeast (FID, 82-83), contradicts a the '951 patent's clear teachings that the claimed plant-derived rHSA can be purified by "using ***any of*** … art recognized processes listed" in the patent, including those disclosing actual purification of yeast-derived recombinant albumin (e.g., U.S. Patent No. 6,638,740). JX-0001, 50:1-12; RDX-0006C.4; RPostHB, 12-13. *Id.*; Trial Tr. 872:18-873:3. This point was acknowledged by Dr. Wilken during her cross examination, and is dispositive on this issue. RDX-0006C.4.

The FID's finding that yeast-derived rHSA and rice-derived rHSA have different isoelectric points is irrelevant in view of the claim requirements, and also does not support a conclusion that it takes "intense experimentation" to make Van Urk and Berezenko's techniques work for rice-derived rHSA. FID, 84-85. Although the disclosed isoelectric point (PI) of certain prior art commercial recombinant albumin may not be measured to be exactly the same value of that of the recombinant albumin in the '951 patent, Ventria's own cited document shows that PI values of recombinant albumin within a narrow range are considered to be consistent. JX-0009C.0028 (noting that the PI values of recombinant albumin can be measured to be within a range of approximately 4.7 to 5.2). RPostHB, 40, n.9.

Moreover, the FID's finding that Dr. Yang reported "challenges associated with developing downstream processing techniques (e.g., purification) for the recovery of rHSA" (FID, 85) contradicts the publication's express teachings, which is not relevant to enabling the recited claims. The publication discussed challenges with respect to cost, absolute content of host cell proteins, and reducing endotoxin level to below 0.0083 EU/mg, which is more than 100-fold lower than level the asserted claims allow for. JX-0023.004. As such, the cited statements do not specify any challenge of achieving rHSA with less than 1 EU/mg endotoxin or prove Van Urk and Berezenko are non-enabling.

2. The FID's Finding that Van Urk and Berezenko Are not Enabling is Based on a Wrong Legal Standard and Clearly Erroneous

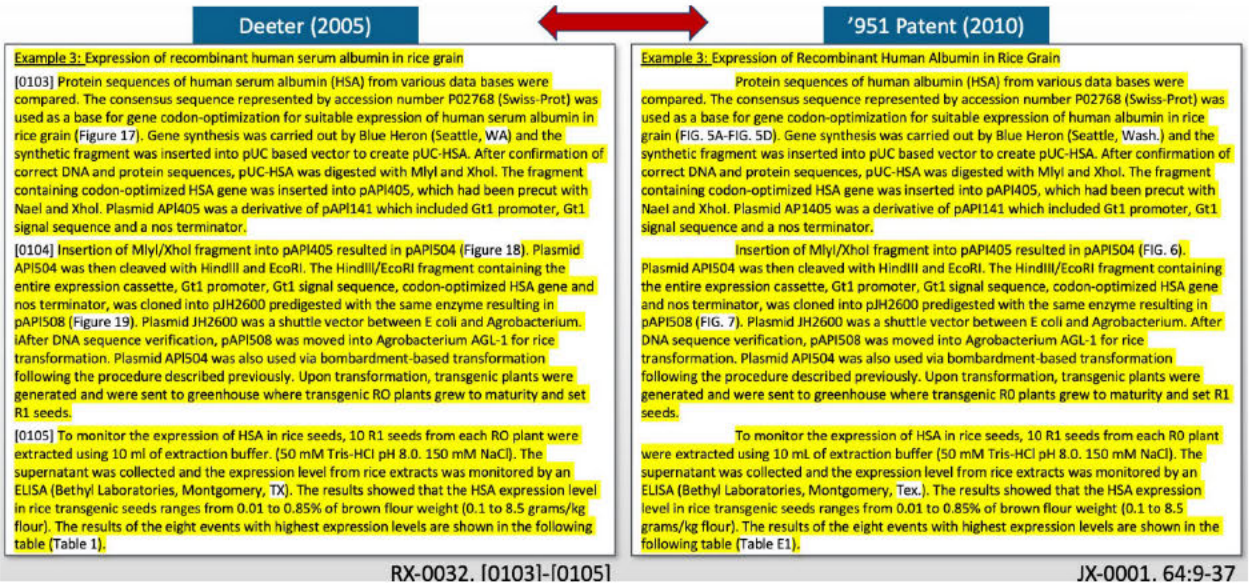
The FID found that Van Urk and Berezenko are not enabling because these references do not have "accompanying data, instructions, evidence, disclosure, or experiments demonstrating how such non-yeast organisms can be genetically modified to express rHSA, and that said rHSA could successfully be produced, extracted, and purified therefrom." FID, 87. The FID also

emphasized that "the only working examples in each reference involve rHSA derived from yeast." *Id.*

The FID's requirement of actual data or working example of producing, extracting, and purifying plant-derived rHSA to show Van Urk and Berezenko are enabling is legally wrong. *Novo Nordisk Pharms., Inc. v. Bio-Tech. Gen. Corp.*, 424 F.3d 1347, 1355 (Fed. Cir. 2005) ("Significantly, we have stated that 'anticipation does not require actual performance of suggestions in a disclosure. Rather, anticipation only requires that those suggestions be enabled to one of skill in the art.'").

The FID's finding also contradicts the evidence adduced at the hearing. For instance, Van Urk teaches that rHSA can be expressed from transgenic plants "with known techniques," and Berezenko also teaches the process of introducing an albumin-encoding DNA into "known expression systems" including "plant cells" to express rHSA. JX-0030, 1:3-9, 25:15-19; JX-0027, 3:19-44; RPreHB, 49, 58; Trial Tr. 876:2-877:2. Other evidence also consistently shows that producing rHSA in a transgenic plant such as rice were well-known long before the '951 patent. RPreHB, 49; *see e.g.*, RX-0032, [0048], [0103]-[0105]; JX-0028.002-03, 005, 011; RX-0034.001; RX-0027.001, 003, 004; JX-0143.001, 002 (acknowledging that transgenic plants and cell cultures were first used to produce human albumin as early as 1990). Equipped with these known techniques and prior knowledge of successful plant-derived rHSA production, a POSA would have been enabled to express rHSA in a transgenic plant as described in Van Urk and Berezenko. RPreHB, 49, 58.

In addition, as shown below, Deeter describes in detail the genetic materials and process used to introduce HSA-encoding DNA into plants and successful expression of rHSA from the transgenic plants. RX-0032, [0103]-[0105].



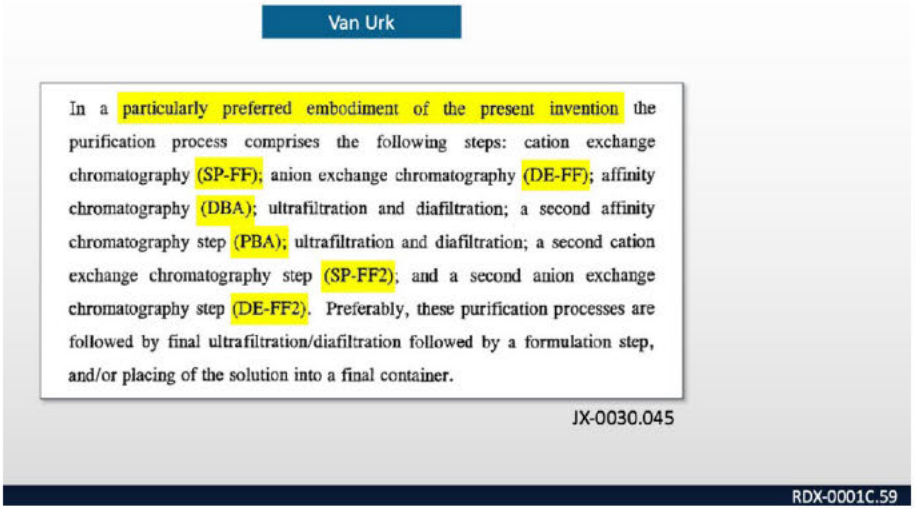
RDX.0001C.56 (yellow highlights showing the identical wording in Deeter's and the '951 patent's descriptions of expressing rHSA from transgenic plants).

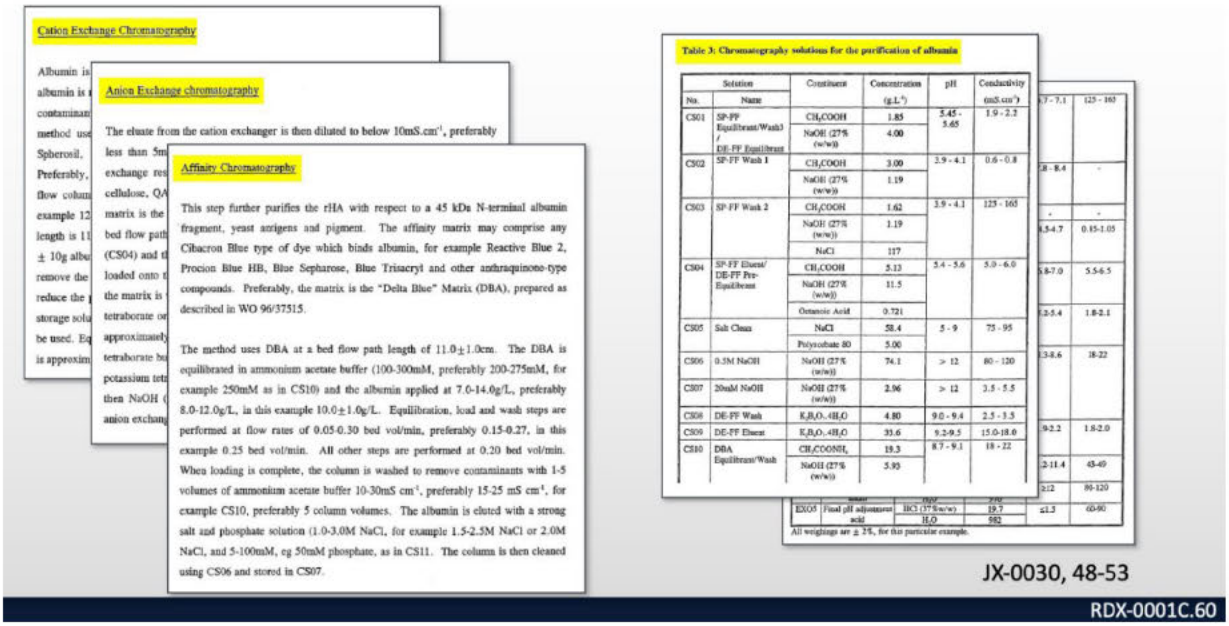
Indeed, it is undisputed that Deeter disclosed expressing rHSA in transgenic plants (using the identical genetic materials and methods) years before it appeared in the '951 patent, and thus, its disclosures may be relied on to demonstrate enablement of Van Urk and Berezenko. RX-0032, [0103]-[0105]; RDX-0001C.56; Trial Tr. 1103:2-5; Trial Tr. 1120:25-1121:3; *see also e.g.*, Trial Tr. 1120:25-1121:3 ("Q. You understand that a person of skill in the art reading Berezenko would have the Deeter reference to guide them in making a transgenic plant, right? A: Yes."); RPostHB, 55; Trial Tr. 1082:14-20 (Dr. Wilken admitting that based on the Deeter patent, a person of skill in the art would know how to make a recombinant human serum albumin from a transgenic plant); RPostHB, 40.

The FID's finding that Van Urk and Berezenko do not enable a POSA to extract rHSA from plants also contradicts the facts. For example, Deeter disclosed a very simple method for extracting recombinant albumin from rice involving de-husking, grinding and extracting along with the conditions used in the simple extraction process, including the buffer and pH. RDX-

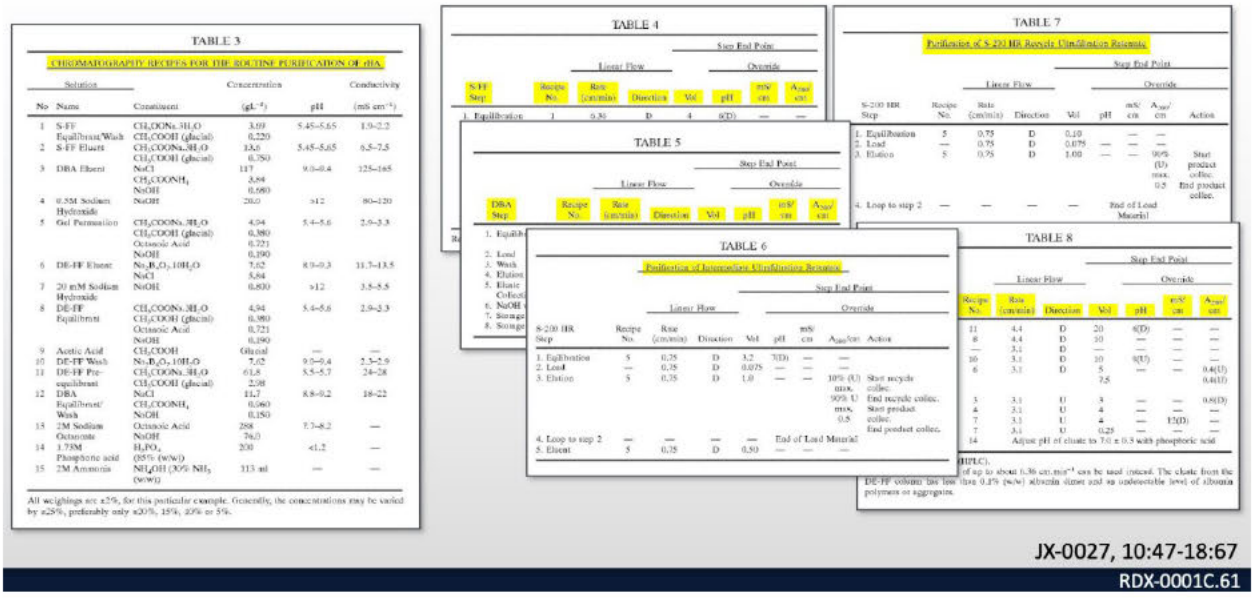
0001C.57; RX-0032, [0116]; RPostHB, 55-56. Mr. Deeter also admitted that the "ease of extracting the recombinant protein out of rice grain" was one of the benefits of using that production system. RPostHB, 55-56; Trial Tr. 231:21:232:9; RX-0077C.033 ("Production costs can be kept low when expressing proteins in rice grain because of the ***ease of extraction*** and purification with simple saline buffers.") (emphasis added).

Regarding rHSA purification, the FID further noted that Van Urk and Berezenko disclose "numerous permutations without any guidance" and do not provide "accompanying … instruction." FID, 88. This finding is also clearly erroneous. As shown below, Van Urk provides detailed guidance in its preferred embodiment explaining how to obtain highly purified albumin from any "impure albumin solution," including the sequence purification of steps, equipment used for purification, and specific instructions on implementing each step (e.g., buffers, solutions, pH, and conditions used during each steps). JX-0030, 22:4-5, 25:8-11; JX-0030.043-55, Table 3; *see also* JX-0137.010-11 ("ion exchange resins are the most common depyrogenation method for proteins."); RDX-0001C.59-61; JX-0030.0045, 048-53; JX-0027, 10:47-18:67; RPreHB, 50; RPostHB, 55-56.

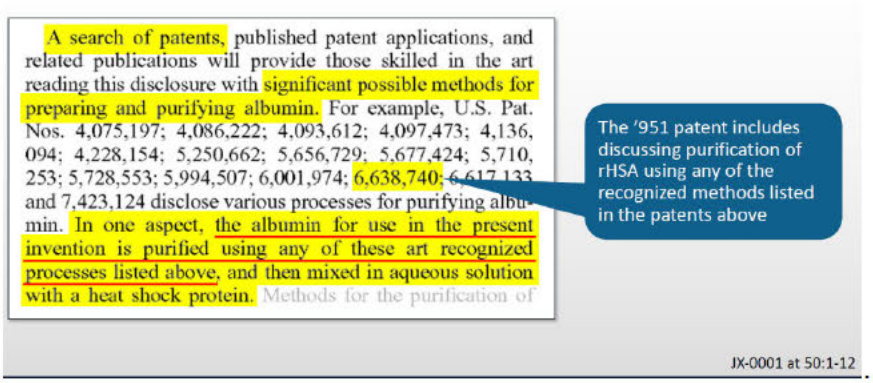




As further illustrated below, Healthgen also pinpointed Berezenko's very detailed description of its process for purifying rHSA, including the preferred steps, preferred equipment (e.g., chromatography columns), and preferred methods for implementing each step (e.g., buffers, solutions, pH, and conditions used during each step). JX-0027, 2:60-61; *see also id.*, 1:40-49, 3:39:44; 10:36-19:50; RPreHB, 59; RPostHB, 59.



The FID's generalized conclusion that "a significant amount of experimental design is required to properly express and purify ***recombinant proteins***" (FID, 88) is inapplicable to the specific case of endotoxin removal from rHSA proteins. The FID's emphasis on theoretical difficulties also stands in direct contradiction to the '951 patent's own admission that the plant-derived rHSA in the claimed invention can be purified "using ***any of … art recognized processes*** listed" in the patent, including those disclosing actual purification of yeast-derived recombinant albumin (e.g., U.S. Patent No. 6,638,740). JX-0001, 50:1-12; RDX-0006C.4; RPostHB, 12-13.



In conclusion, the FID's findings that Van Urk and Berezenko are not enabling should be reviewed and reversed.

D. The FID's Conclusion that The Asserted Claims Are Nonobvious is Based on Legal Errors and Clearly Erroneous Factual Findings

The FID's findings of non-obviousness include the same clearly erroneous factual findings regarding Van Urk and Berezenko addressed in Section VI.A. FID, 89-95. The FID's analysis is additionally flawed for at least the reasons that follow.

1. The FID's Conclusion that a POSA Would Not Have Been Motivated to Combine Deeter with Van Urk or Berezenko Is Clearly Erroneous

The FID's conclusion that a POSA would not have been motivated to combine Deeter with Van Urk or Berezenko is based on legal errors and clearly erroneous factual findings. FID, 89-91. For context, Deeter is a prior patent application assigned to Ventria that discloses nearly all aspects

of the claims, including a cell culture media supplement comprising rHSA produced in the same transgenic rice described in the '951 patent. RX-0032, [0103]-[0105], [0116]-[0120], Table 3 (p. .0031), Figs. 23-24 (pp. .0066-67). While Deeter's rHSA was expressed in very high yield, it contained high levels of endotoxin (a ubiquitous and undesirable contaminant). *Id.*, [0105]. Van Urk and Berezenko each independently disclose methods for purifying rHSA, including rHSA produced in transgenic plants, to achieve a non-pyrogenic product, e.g., a product that is free of detectable endotoxin. *Supra*, VI.A.1-4.

The FID concluded that a POSA seeking to reduce the endotoxin level in Deeter's rHSA "would not even look" to Van Urk and Berezenko because they only "concern the purification of yeast-derived HSA." FID, 90. This finding only considered preferred embodiments and discarded other express teachings in those publications, and thus, is clearly erroneous and also legally wrong.

In a recent Federal Circuit opinion, the Court chided both the PTAB and the ITC for incorrectly referring to what "is" obvious in their decisions. *Broadcom Corp. v. ITC*, No. 20-2008, slip op. at 5 n.2 (Fed. Cir. Mar. 8, 2022). "Because § 103 addresses what 'would have been' obvious, we recommend usage of the statutory language that looks to the past in order to avoid the appearance of hindsight bias." *Id.* Judge Rich made the same point years ago in *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383 n.6 (Fed. Cir. 1986):

> It bears repeating that it is crucial that counsel set forth the law accurately. More particularly, it is the duty of counsel to impart to the judge that the obviousness question properly is whether the *claimed* invention *as a whole would have been* obvious to one of *ordinary* skill in the art *at the time the invention was made* . . . . [A]rguing that 'it would be obvious' rather than it would *have been* obvious shifts the court's focus to the wrong period of time, namely to a time long after the invention was made, in which, more likely than not, the prior art and the level of ordinary skill in the art are more advanced.

This very mistake permeates the FID, and it requires review and reversal.

Both Van Urk and Berezenko expressly teach the suitability of their processes for plant-derived rHSA. JX-0030.0003 (1:3-9), 0027 (25:8-11), 0024 (22:26-27); JX-0027, 2:57-3:44. For example, Van Urk teaches:

- "***The present invention relates to a process for purifying*** the protein human serum albumin (HSA) . . . or ***recombinant human albumin (rHA)*** produced by transforming or transfecting an organism with a nucleotide coding sequence encoding the amino acid sequence of human serum albumin, including rHA ***produced using transgenic*** animals or ***plants***. In this specification, the term 'albumin refers generically to HSA and/or rHA." JX-0030.0003 (1:3-9).

- "Whereas the processes of the present invention can be utilised to obtain highly purified albumin from an impure albumin solution from a number of sources, such as serum, it is particularly applicable to purifying recombinant human albumin (rHA)." JX-0030.0027 (25:8-11).

- "[T]he albumin may be obtained from a transgenic plant, such as tobacco, potato or corn (maize)." JX-0030.0024 (22:26-27).

Berezenko similarly teaches that is rHSA may be obtained from a suitable expression system, including plant cells. JX-0027, 2:57-3:44. The PTO issued Berezenko with claims to "[h]ighly purified albumin which is at least 99.5% monomeric" (i.e., less than 2% albumin) and "non-pyrogenic," (i.e., less than 1EU endotoxin) without restricting the invention to any particular production or expression system. *Id.*, claims 1, 21. These express teachings would have motivated a POSA to use Van Urk and Berezenko's purification methods to reduce the endotoxin level in Deeter's rHSA.

The FID disregarded these express disclosures (and claims) in view of the preferred embodiments of Van Urk and Berezenko, which exemplify the purification of albumin using rHSA produced in transgenic yeast. FID, 90-91. The FID's consideration of only the preferred embodiments in Van Urk and Berezenko instead of looking to the teachings as whole, and their suitability of purification processes to rHSA produced in transgenic plants violates the long-standing precedent that "all of the disclosures in a reference," not just certain embodiments, "must

be evaluated for what they fairly teach one of ordinary skill in the art." *In re Inland Steel Co.*, 265 F.3d 1354, 1364 (Fed. Cir. 2001) (quoting *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989)); *Arthrocare Corp.*, 406 F.3d at 1372-1374 (reversing denial of JMOL on anticipation because "[t]he court's analysis… focused on only one embodiment in the Roos patent. There are other embodiments in the patent" that are anticipatory); *Ultradent Products*, 127 F.3d at 1068 ("The district court thus erred by construing the scope of the Rosenthal disclosure as limited to the preferred embodiment."); *see also Novartis Pharms. Corp. v. W.-Ward Pharms. Int'l Ltd.*, 923 F.3d 1051, 1059 (Fed. Cir. 2019) ("[O]ur case law does not require that a particular combination must be the preferred, or the most desirable, combination described in the prior art in order to provide motivation for the current invention.").

Disregarding critical disclosures of the prior art, the FID erroneously concludes that it would not be "suitable" to apply a processed used to rHSA produced in transgenic yeast to rHSA produced in transgenic rice because of the "need to discriminate between the properties of the impurities and the recombinant protein." FID, 90.

The FID fails to appreciate the impurity at issue—the one that a POSA would have been motivated to remove—is not host-specific. It is basic science that endotoxins are not unique to transgenic rice or to yeast, or to animals—they are generated by gram negative bacteria (e.g., *E. coli*) and expectedly contaminate proteins expressed in all types of expression systems. *See e.g.*, CX-0894.0008; JX-0135.0003; RX-0018.020; RDX-0001C.13. While the FID discusses different impurities and contaminants that may be unique to the host, endotoxins are ubiquitous. *See e.g.*, RX-0018.020; RDX-0001C.13; JX-0135.0003.

Similarly, the recombinant protein—rHSA—is the same in Deeter, as it is in Van Urk, and Berezenko—they are all albumin, a concept that seems to have escaped the FID. The FID refers

to "the stark differences between recombinant proteins produced in a transgenic plant from yeast-derived proteins" and further refers to testimony in the abstract that there are differences in production, extraction, and purification of rHSA from different hosts. FID, 90-91. But there is no evidence anywhere that these purported differences would require a different process to remove ***endotoxin***, as opposed to, e.g., host-specific non-albumin proteins. Thus, the FID's cited testimony does not support the finding that a person skilled in the art would not have looked to Van Urk and Berezenko's purification methods.

Indeed, the FID fails to address the simple fact that the '951 patent expressly teaches that processes for purifying rHSA from yeast (e.g., U.S. Patent No. 6,638,740) can be used to purity the rHSA of the invention. JX-0001, 50:1-12. Notably, U.S. Patent No. 6,638,740—disclosed as providing a suitable purification method for the albumin of the purported invention—exemplifies purification of rHSA produced in transgenic yeast. RX-0206.027; RDX-0006C.6; JX-0030.0001; JX-0027, claims 1, 21; RDX-0001C.19-20. The FID's finding that purification processes would necessarily be different depending on the transgenic host cannot be squared with the '951 patent's admission to the contrary. X-0001, 50:1-12.

2. The FID Applied the Wrong Analysis for Reasonable Expectation of Success

The FID's reasonable expectation of success analysis is also replete with legal errors and clearly erroneous factual findings.

First, the FID erroneously attacked prior art references individually. *In re Merck & Co., Inc.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986) ("Non-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references.") (citing *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981)). For instance, the FID found that Deeter's rHSA, as purified by Van Urk or Berezenko's methods,

would not be expected to contain less than 1 EU endotoxin/mg albumin because "Deeter does not disclose a recombinant mammalian albumin produced in a transgenic plant which has less than 1 EU endotoxin/mg albumin, nor do Van Urk or Berezenko." FID, 91. Regarding the claim limitation "less than 2% aggregated albumin," the FID similarly erroneously concluded that "Deeter also does not disclose a recombinant mammalian albumin produced in a transgenic plant having less than 2% aggregated albumin…, nor do either Van Urk or Berezenko." *Id.*, 93. In making these conclusions, the FID failed to consider the ***combined*** teachings of these references, and instead, chose to attack them individually.

Second, the FID wrongly required evidence of "absolute certainty" to show obviousness. *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 965 (Fed. Cir. 2014) (Obviousness does not require absolute predictability); *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988) ("Obviousness does not require absolute predictability of success. Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice.").

For instance, instead of analyzing a reasonable expectation of success, the FID *required*—(as if it should the same exact words)—Berezenko to "disclose a plant composition possessing the less than 2% aggregated albumin." FID, 93. As another example, the FID also criticized Healthgen for not showing that "the result of this combination ***would 'remain' a cell culture media supplement***," demanding Healthgen to provide specific evidence on exactly "what steps or conditions one of ordinary skill would alter, employ, remove, and/or add from Deeter" for the resulting rHSA to remain a cell culture media supplement. *Id.* at 93-94.

But it is undisputed that Deeter teaches rHSA, and a person skilled in the art would have routinely used Deeter teachings as a cell culture media component, years before the alleged invention. RPostHB, 4; RX-0032, [0103]-[0105]; JX-0028; Trial Tr. 1119:2-7 (Dr. Wilken

admitting that Berezenko discloses recombinant human albumin "could be" "used in cell culture"); *id.*, 1082:6-13 (Dr. Wilken admitting that "purified recombinant human serum albumin product" "has been used as [a] cell culture media component."). Deeter's rHSA, after being further purified and optimized by Van Urk and Berezenko's methods, would have been reasonably expected to continue working as a cell culture media component. Moreover, there is no temporal requirement to the asserted claims, so the FID's conclusion and request for further evidence of "absolute certainty" is legal error.

The FID also made numerous clearly erroneous factual findings in determining that there was not a reasonable expectation of success in achieving the claimed invention.

First, the FID repeated its clearly erroneous findings in the anticipation analysis:

> endotoxin is only mentioned in a single passage of Van Urk, which merely indicates a 'solution of drug product' was assayed for endotoxin Berezenko merely indicates the medium for rHA production '***can*** be' filtered to remove endotoxins. Neither reference describes any yeast-derived rHSA (much less plant-derived) being free of or having any particular level of endotoxins… Neither reference provides data associated with a claim that either composition may allegedly be free of or have low levels of endotoxin.

FID, 91-92 (emphasis as original). As explained in Section VI.A.3, these findings directly contradict Van Urk's express teachings that (1) highlighted "essentially free of" endotoxin as one of the features of the rHSA of the invention, (2) demonstrated no detectable endotoxin in a rHSA working example, and (3) further reported that its purified rHSA is nonpyrogenic, i.e., with no detectable endotoxin. Berezenko disclosed purified rHSA product that was non-pyrogenic, i.e., containing no detectable endotoxin, and the FID's finding to the contrary is erroneous. *Supra* VI.A.3.

Second, the FID found that Van Urk and Berezenko do not describe "which of the limitless sets of yeast-specific purification permutations would allegedly result in rHSA with the level of

endotoxins claimed in the '951 patent." FID, 91-92. As explained in Section VI.C, this finding is also clearly erroneous in view of Van Urk and Berezenko's stepwise detailed descriptions of specific purification methods, including conditions, reagents, techniques, and instruments.

Third, the FID's assumption that different isoelectric points of plant-derived rHSA and yeast-derived rHSA "will fundamentally alter the purification process" (FID, 92) also contradicts the evidence that there is a narrow PI range of approximately 4.7 to 5.2 for different rHSA proteins. JX-0009C.0028; RPostHB, 40, n.9. Contrary to the FID's findings (FID, 92), Healthgen referred to "***Ventria's cited documents***," which includes JX-0009. *See e.g.*, CPreHB, 32. Here the FID found that JX-0009 "does not relate to a comparison of yeast-derived and plant-derived HSA," but rather the isoelectric point of certain plant-based OsrHSA and plasma-derived HSA. FID, 92. The FID, however, ignores that the yeast-derived rHSA product shown at trial has a PI of 4.7, which is consistent with JX-0009's teachings of the narrow PI range of approximately 4.7 to 5.2. RX-0030.006; RDX-0001C.15. Indeed, Ventria didn't identify any yeast-derived rHSA that has a PI beyond this narrow range of approximately 4.7-5.2. Moreover, the DEAE-Sepharose FF chromatography had been shown to successfully remove endotoxin from both plasma HSA and yeast-derived rHSA. *Infra*, Section VI.D.3. Thus, the FID's finding that different isoelectric points support that Van Urk and Berezenko are non-enabling contradict the documentary evidence adduced at trial and thus, is clearly erroneous.

3. The FID's Finding that Healthgen Waived its Argument Regarding "DEAE-Sepharose" Chromatography is Clearly Erroneous

The FID erroneously found that Healthgen waived arguments regarding prior art DEAE-Sepharose chromatography, which support the reasonable expectation of success when removing endotoxin from Deeter's rHSA using the processes of Van Urk or Berezenko. FID, 93, n. 29. In particular, both Van Urk and Berezenko disclose purifying rHSA to achieve no detectable

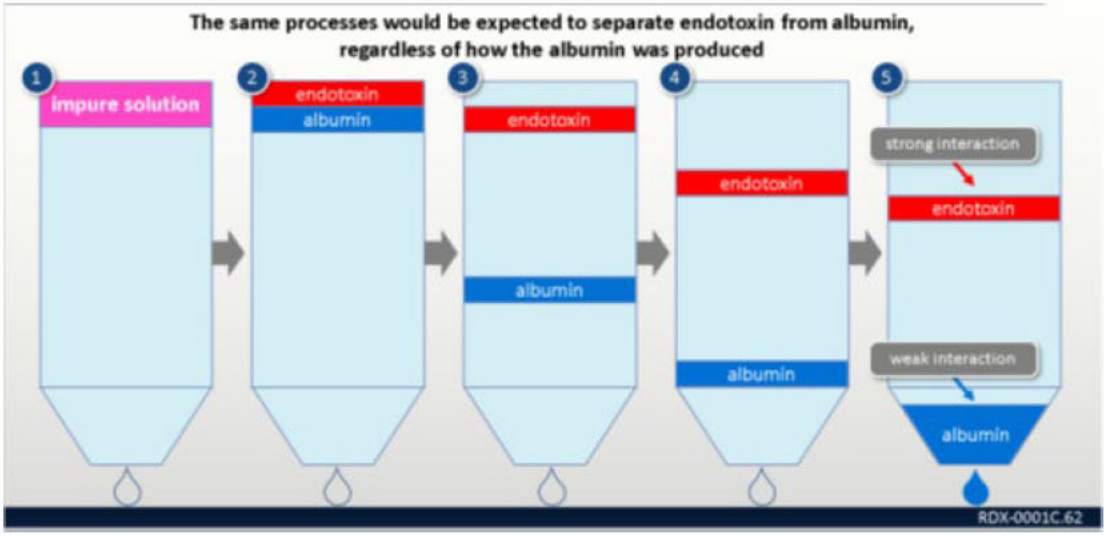
endotoxin ("non-pyrogenic" products) in processes employing DEAE Sepharose chromatography. JX-0030.0048-52, 57, 74-75; JX-0027, 1:40-49, 12:1065 (Table 3), 21:6-9, 18:55-67, claims 1, 21. This same process step was previously reported to "consistently" lower endotoxin levels in pHSA, as the endotoxins remain bound to the column, while the albumin flows through. RX-0024.006.

After refusing to consider this evidence, the FID concluded that Healthgen failed to provide documentary support for its position that the same chromatography steps would work to remove endotoxin from albumin, regardless of how the albumin was produced (e.g., in a human, yeast, or rice)—because albumin is albumin. *Id.* at 93. These findings are prejudicial and clearly erroneous, as they directly contradict the facts.

In the Pre-Hearing Brief, Healthgen cited the same page in the same prior art reference relied on during trial, Matejtschuk 2000 (RX-0024), and expressly explained that: "***Berezenko discloses*** reducing the amount of endotoxin in the medium for production of rHSA by ultrafiltration and further ***eliminating endotoxin in its rHSA by multiple chromatography steps using columns reported to substantially reduce the endotoxin level in HSA products***. JX-0027, 7:17-19, 10:46-19:50; ***RX-0024.006*** and Figs. 1 and 2; JX-0137.010-11 ('ion exchange resins are the most common depyrogenation method for proteins.')." RPreHB, 56 (emphasis added). Healthgen further explained in the Pre-Hearing Brief that "[t]he reasonable expectation of success would have been bolstered by ***prior knowledge that endotoxins had been removed from HSA products using the types of steps employed by Van Urk and Berezenko (e.g., ion exchange chromatography)***. ***RX-0024.006*** and Figs. 1 and 2; JX-0137.010-11." *Id.* at 70 (emphasis added).

Thus, Healthgen had already explained in the Pre-Hearing Brief how a reasonable expectation of success is bolstered by the fact that the ion exchange chromatography technique in Van Urk and Berezenko had also removed endotoxin from albumin produced from other sources

(plasma-derived). The only ion exchange chromatography disclosed on the cited page of Matejtschuk 2000 is the DEAE-Sepharose FF chromatography, which Healthgen further specified during hearing and in the Post-Hearing Brief.[17] RDX-00001C.63 (citing RX-0024.006); RPostHB, 42-43; RX-0024.006 (teaching that "***DEAE-Sepharose Fast Flow chromatography***" can be used for "albumin solution" such that "impurities are … removed" and that "concentrations of endotoxin and aluminium were consistently lowered" using the DEAE- Sepharose Fast Flow chromatography; RDX-0001C.63-64; JX-0030.0052 (Van Urk teaching the anion exchange chromatography used during its purification process is "[p]referrably" "***DEAE-Sepharose-FF*** (Pharmacia)"); JX-0027.18:55-67 (Berezenko teaching that "[p]referably, the matrix is the commercial anion exchange matrix ***DE Sepharose-FF*** (Pharmacia) at any convenient bed height"). The schematic of a DEAE-Sepharose-FF is further shown below. RDX-0001C.62; Trial Tr. 889:5-10.



[17] Ventria did not raise any objection to Healthgen's demonstrative slides on the DEAE-Sepharose FF chromatography during hearing.

Healthgen's more specific reference to the type of ion exchange chromatography that was successfully used by Matejtschuk 2000, Van Urk, and Berezenko is far from making a new argument. *Harris Corp. v. Ericsson Inc.*, 417 F.3d 1241, 1264 (Fed. Cir. 2005) ("'Clarifying' arguments are not new, and not within the rule of waiver"). The FID's finding of waiver is clearly erroneous. In conclusion, the FID's decision that the asserted claims would not have been obvious over Deeter in view of Van Urk and/or Berezenko should be reviewed, vacated, and reversed.

4. The FID's Failure to Address Two of Healthgen's Obviousness Grounds Against Claims 12 and 13 Warrants Review and Remand/Reversal

The FID fails to meaningfully address two additional asserted grounds of obviousness: (1) claim 13 over Van Urk in view of Deeter and/or Huang; and (2) claims 12 and 13 over Berezenko in view of Deeter and/or Huang. FID, 94-95. The FID mischaracterizes these grounds of invalidity as Deeter and/or Huang in view of Van Urk or Berezenko, and, relatedly, fails to address at all the motivation of a POSA to replace the preferred rHSA of Van Urk or Berezenko (expressed in yeast) with the beneficial rHSA of Deeter and/or Huang (expressed in rice). FID, 94-95. The errors in the FID concerning the disclosures of Van Urk, Berezenko, and Deeter also infected its analysis of these combinations, as did its erroneous conclusions regarding reasonable expectation of success. *Supra*, VI.D.

Indeed, the FID fails to even mention the many advantages of the transgenic rice expression systems of Deeter and (separately) Huang. *Id.* For example, Deeter discloses a high yield of rHSA that [redacted] RX-0032, [0105] (reporting

expression level of up to 0.85% brown flour weight); [redacted]

Similarly, Huang discloses that as of 2005, transgenic rice cell culture had proven to be a "***powerful system*** for the production of recombinant proteins," including rHSA. JX-0028.002, 004 (emphasis added). Huang further disclosed "a very good yield" for producing recombinant human albumin in transgenic rice cell culture. Trial Tr. 862:21-23; JX-0028.0001 (reporting a yield of 76.4 mg/L). Huang also describes transgenic rice cells as a "valuable alternative" for the production of recombinant proteins susceptible to proteolytic degradation. JX-0028.0011. Huang discloses additional advantages of rice cell culture as a transgenic production system, including "relatively high growth rate, with minimal aggregate clumping," ease of cultivation, and the absence of "toxic secondary metabolites found in some plant cell cultures, such as those derived from tobacco."[18] *Id.*

Thus, in view of the undisputed advantages and popularity of transgenic rice taught in Huang and/or Deeter, a POSA would have been motivated to purify rHSA produced in transgenic rice using Van Urk's or Berezenko's process to achieve high production yields of Huang and/or Deeter and the low levels of endotoxin and aggregated albumin reported in Van Urk or Berezenko. JX-0028.002-04, 011, 012; JX-0030.0003 (1:3-9), 0023(21:5-11), 0072-73, 0069-70; *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (finding it obvious to use amlodipine besylate when prior art taught its superiority and expectation that besylate salt would show improved physicochemical

[18] Ventria's expert, Dr. Wilken, published an article touting certain advantages as of 2003 of transgenic plants for the expression of recombinant proteins. RX-0374.001; RDX-0006C.20; Tr. 1129:15-1130:13 (Dr. Wilken admitting that she published on "some potential advantages [of] using rice.").

characteristics); *see also Ecolab, Inc. v. FMC Corp.*, 569 F.3d 1335, 1350 (Fed. Cir. 2009), *amended on reh'g in part*, 366 F. App'x 154 (Fed. Cir. 2009) (citing *KSR*, 550 U.S. at 418).

Rather than addressing the motivation or reasonable success in these grounds for obviousness, the FID found that Huang does not discuss "purifying or achieving any composition of said rHSA capable of encompassing the claims of the '951 patent." FID, 95. The FID thus fails to appreciate the entire premise of this combination (Healthgen did not argue that Huang disclosed purification processes), and its attack on Huang in isolation is improper. *In re Merck & Co., Inc.*, 800 F.2d at 1097.

The FID's failure to meaningfully address these combinations constitutes legal error. *Tris Pharma, Inc. v. Actavis Lab'ys FL, Inc.*, 755 F. App'x 983, 990 (Fed. Cir. 2019) (finding the district court's obviousness decision cannot be affirmed because the district court failed to "resolve [] specific fact issues with an explanation to support those findings" and "does not address a fundamental aspect of the obviousness inquiry—i.e. why a skilled artisan would have been motivated to use a single mean peak PK profile to achieve a formulation with a 45-minute onset of action and/or a 12-hour duration of effect with a reasonable expectation of success."); *see also Golden Blount, Inc. v. Robert H. Peterson Co.*, 365 F.3d 1054, 1061 (Fed. Cir. 2004) ("Because the district court's sparse opinion provides this court with only bald conclusions for review, we conclude that the district court's judgment ... is insufficient under Rule 52(a). We thus vacate those portions of the district court's opinion and remand those issues to the district court for specific factual findings."); *see also Atlantic Thermoplastics Co., Inc. v. Faytex Corp.*, 5 F.3d 1477, 1479 (Fed. Cir. 1993) (finding the court's opinion too conclusory and sparse to provide a factual basis for determining whether the invention was on sale within the meaning of 35 U.S.C. § 102(b)).

E. Ventria Failed to Overcome a Strong Prima Facie Case of Obviousness

The FID concluded that "[b]ecause this determination finds that the '951 patent is not obvious, secondary considerations need not be examined." FID, 95. As Healthgen explained above, the FID's determination that the asserted claims are not prima facie obvious should be reviewed and reversed. For completeness, Ventria's alleged secondary consideration evidence is insufficient to overcome a strong prima face case of obviousness. RPreHB, 81-87; RPostHB, 44-54. Thus, the Commission's reversal decision should not be disturbed by Ventria's secondary consideration arguments.

VII. THE COMMISSION SHOULD REVIEW AND REVERSE THE FID'S FINDINGS ON DOMESTIC INDUSTRY – ECONOMIC PRONG

The FID's findings on economic prong of the domestic industry requirement should be reversed, as they include several serious legal and factual errors. First, the Final ID grossly overstates Ventria's domestic industry investments by giving full credit to all of Ventria's alleged DI products—many of which, in fact (and as discussed in Sect. V, *supra*) do not practice any claim of the '951 patent. *See* FID at 101-107. The FID also improperly avows that Ventria's investments in Optibumin—the only Ventria DI product that actually practices the '951 patent—are significant and substantial on their own, despite the objectively low investment figures using Ventria's own expert's allocation methodology. *See* FID at 107-111. The FID compounds this error by failing to properly allocate the Optibumin-only investments and by improperly relying on qualitative factors to explain away the low Optibumin investment numbers. *Id.* The FID's errors result in an erroneous legal conclusion of significance and substantiality for Ventria's small investments in Optibumin and undermine Commission policy by obscuring the clear guidance from the Commission regarding satisfaction of the economic prong.

A. The FID Improperly Included Investments in Non-Domestic Industry Products in Ventria's Domestic Industry Total

The FID erroneously concludes that six Ventria products practice the '951 patent and, consequently, all claimed investments may be considered for domestic industry. FID at 58-71, and 101-107. When properly considered, however, the evidence of record shows that only one of Ventria's six alleged DI products, Optibumin, actually practices the '951 patent. *See* Sect. V, *supra*. Therefore, under a proper economic prong analysis, Ventria may only claim investments in Optibumin and not in the five other, non-practicing products. 19 U.S.C. § 1337(a)(3); *see also InterDigital Commc'ns, LLC v. Int'l Trade Comm'n*, 707 F.3d 1295, 1303-04 (Fed. Cir. 2013); *Certain Computer Forensic Devices & Products Containing Same*, Inv. No. 337-TA-799, ID at 11 (Oct. 26, 2012) ("[Complainant's] estimates are necessarily improper because they include expenses of non-domestic industry products.").

The FID recognized that Ventria employed a sales-based allocation methodology to apportion its alleged investments in the six domestic industry products it claimed—a methodology adopted by its economic expert, Mr. LaMotta. FID at 100-101; *see also* Complaint at Ex. 29, Second Declaration of Scott Deeter at ¶¶ 28, 36, 41; LaMotta Tr. 61:5-13; Reed Tr. 1315:3-8. Healthgen's economic expert, Brett Reed, agreed that Ventria's chosen approach of a sales-based allocation is frequently used by the Commission to evaluate domestic industry investments and is an acceptable methodology in this instance. Tr. (Reed) 1314:16–1315:2. Notably, this was the investment methodology Ventria chose when filing its complaint, throughout fact and expert discovery, and at the evidentiary hearing. *Id.*

Ventria's complaint pleaded the existence of a domestic industry—it did not plead a domestic industry was "in the process of being established" (*see* Complaint; 19 U.S.C. § 1337(a)(2)) and Ventria did not offer any evidence of investments after the filing of the complaint

(Tr. (LaMotta) 753:19-21). Consistent with Commission precedent, domestic industry investments are evaluated as of the filing date of the complaint—in this instance, December 2020.

The FID credits Ventria with more than [redacted] in total domestic industry investments from 2015 to 2020 for its six alleged Domestic Industry products, constituting approximately [redacted] of Ventria's total expenditures during that period. FID at 100-107; *see also* Tr. (Reed) 1316:22–1317:8; RDX-0003C.07-08. Based on Ventria's own analysis, the FID also recognizes that Ventria's sales of Optibumin comprise only approximately [redacted] of Ventria's total sales from 2018 (when sales of Optibumin began) through the December 2020 filing of the complaint. FID at 108 (citing investments calculations based on Optibumin's sales figures); *see also* Tr. (Reed) 1323:19–1324:18; RDX-0003C.06; CX-0975C; CDX-0002C:20.

Ventria's Six Alleged Domestic Industry Products and Other Revenue
Percent of Total Ventria Sales (2018-2020)

[redacted]

CX-0975C (2018-2020); CDX-0002C:20; RDX-0003C.06. As a result, when properly limited to include only investments attributable to Optibumin, the FID agrees with the evidence produced by Ventria showing that Ventria's domestic industry investments plummet to approximately [redacted]

in plant and equipment under sub-prong (A), approximately [redacted] in labor under sub-prong (B), and approximately [redacted] in research and development under sub-prong (C)—combined, a mere [redacted] or roughly [redacted] of Ventria's total expenditures[19,20]. FID at 108; *see also* Tr. (LaMotta) 736:21–737:8, 737:24–738:16, 742:10–743:10; CDX-0002C.25, .31, .36; Tr. (Reed) 1316:16–1320:5; RX-0304C; RDX-0003C.08-09.

Ventria's Claimed Domestic Investments (2015-2020)

[redacted]

CDX-0002C:25, 31, 36; RDX-0003C.08. The Final ID adopted these numbers—the ***only*** investments Ventria alleged in Optibumin throughout this investigation. FID at 108.

B. Ventria's Alleged Domestic Industry Investments Are Neither Significant Nor Substantial by Any Appropriate Quantitative Measure

Ventria's claimed investments in Optibumin are very low in absolute and relative terms. The FID, however, engaged in a series of logical gymnastics to create "significance" and

[19] The statute is written in the disjunctive, which requires looking at investments *separately* under each sub-prong. 19 U.S.C. § 1337(a)(3). The aggregate, which may double-count, simply highlights the meagerness of Ventria's investments allocated to Optibumin.

[20] Mr. Reed's calculations of Ventria's domestic industry figures, highlighted in RDX-0003C.09, are similar to, but slightly lower than, Mr. LaMotta's calculations, due to rounding differences. Tr. (Reed) 1319:8-20.

"substantiality" from those investments where none, in fact, exists. FID at 108-110. The FID acknowledges Healthgen's argument that Ventria's "Optibumin sales were actually meager" (FID at 109), but it attempts to explain away this meagerness with flawed "quantitative" analyses and qualitative considerations despite the fact Ventria's investments in Optibumin account for roughly [redacted] of Ventria's total investments (FID at 108-111). Each attempt to treat Ventria's investments as "significant" or "substantial," however, ignores the plain context of Ventria's meager investments and flouts the Commission's prohibition against relying exclusively on qualitative considerations to find significance or substantiality where quantitative factors fail, as they do here.

First, the FID repeatedly, and mistakenly, claims that because Ventria's investments are entirely within the United States, that is itself dispositive of significance or substantiality. FID at 108-109 ("it is notable that 100% of Ventria's investments in Optibumin® occur in the United States. . . . this weighs heavily in favor of finding that Ventria's investments are significant and substantial."), 105, and 106. That a complainant may operate entirely within the United States, however, does not automatically transform *any* investments (no matter how low) into "significant" or "substantial" investments. *See Certain Stringed Musical Instruments and Components Thereof*, Inv. No. 337-TA-586, Comm'n Op. at 25-27 (May 16, 2008) (complainant's operations were located entirely in the United States but nonetheless found insignificant and insubstantial). Yet this is what the FID suggests by focusing merely on the locus of operations while ignoring the actual investments. FID at 108-111. Lack of outside-the-U.S. investments may be *a factor* in considering the existence of a domestic industry, but it is not dispositive and it cannot override the statutory requirement. *See Certain Printing and Imaging Devices and Components Thereof*, Inv. No. 337-TA-690, Comm'n Op., at 31 (Nov. 1, 2011). Ventria's extremely low sales of Optibumin—and

the resulting meager allocation based on Ventria's own sales-based allocation method—underscores the limited benefit of this "comparison" in this context, particularly when other quantitative contextual tests are available. The figures showing Ventria's investments in Optibumin are based on Ventria's own analysis—Ventria chose a sales-based allocation, and does not dispute the calculations showing its investments in Optibumin. *See*, *e.g.*, Tr. (LaMotta) 720:15-19, 736:21-737:1, 738:7-10, 742:10-16. Finding investments significant or substantial merely because they may occur entirely within the United States risks importing into the statute a construction that such investments could never be "insignificant" or "unsubstantial," rendering the plain language of the statute meaningless.

Next, the FID improperly gives credence to Ventria's contrived investments-to-revenues analysis. FID at 109. Ventria's analysis allows a complainant to manufacture a "large" number by comparing one small number against a smaller number. Specifically, a complainant with small investments and few sales may show a facially impressive percentage simply because one small number is larger than another small number. But comparing two small numbers cannot magically transform a meager investment into something quantitatively "significant." In this instance, Ventria has alleged that its plant-and-equipment expenditures in Optibumin from 2018 to 2020 comprised [redacted] of its revenue for Optibumin; its labor expenditures comprised [redacted] of revenue; and its research-and-development expenditures [redacted] of revenue. FID at 109; CPostHB at 97. But that contrived quasi-analysis does not distinguish between whether Ventria simply failed to sell much of its product or whether Ventria's alleged investments are somehow significant or substantial. Moreover, applying this analysis across Ventria's six alleged DI products for the asserted 2015 to 2020 timeframe results in expenditures in plant-and-equipment at [redacted] of revenue; labor at [redacted] of revenue, and research-and-development at [redacted] of revenue. Ventria's

investment-to-revenue ratio in Optibumin is thus unexceptional compared to the other alleged DI products. It also conveniently conceals the economic reality that Ventria's investments in Optibumin account for roughly [redacted] of its total investments. *See* FID at 108-111.

Further exacerbating the problem, the FID improperly credits unidentified and uncontended "investments" in Optibumin pre-dating Ventria's own claimed investments, ignoring Ventria's failure to submit any evidence of actual investments in Optibumin before 2018 (*see* Sect. VII.A, *supra*; Tr. (LaMotta) 736:7-20). Although the FID acknowledges Ventria did not provide any evidence of domestic industry investments in Optibumin before 2018 (FID at 110), the FID nonetheless attributes some undisclosed portion of an alleged [redacted] increase in "product development" in Ventria's Optibumin investments, alleging the spending was "due at least in part to investments in Optibumin" (FID at 111). If Ventria had actually made any of these expenditures for Optibumin, it could have and should have demonstrated the alleged investments during fact and expert discovery. Ventria instead presents (and the FID cites) no evidence that any of those alleged investments related to the Domestic Industry products generally or specifically—Ventria and the FID merely alleged some portion might relate to Optibumin. A generic claim without any analysis, however, is not—and cannot be—enough. *See Certain Electronic Stud Finders, Metal Detectors and Electrical Scanners*, Inv. No. 337-TA-1221, Comm'n Op. at 48-49 (March 14, 2022) (finding no domestic industry where the complainant failed to allocate alleged investments among different domestic industry products.).

Instead, Ventria's own expert attributed less than [redacted] to R&D spending for Optibumin, and these were the *only* contentions of R&D investments in Optibumin that Ventria advanced during the entire investigation. CDX-0002C:25, 31, 36; RDX-0003C.08; Tr. (LaMotta) 736:21–737:8, 737:24–738:16, 742:10–743:10; Tr. (Reed) 1316:16–1320:5; RX-0304C.

Moreover, neither Ventria nor the FID ever allege what portion of that alleged [redacted] increase supposedly relates to Optibumin. The FID's attempts to backfill Ventria's own claimed investments with some undisclosed and unclaimed amount is inappropriate and constitutes clear error.

Finally, the FID further committed clear error by permitting and relying on a grossly inapposite contextual analysis comparing Ventria's alleged research-and-development investments in the domestic industry products to the gross investments of other companies, merely on the basis the other companies are publicly traded. FID at 107, 109 fn. 38. The FID compares Ventria's research-and-development expenditures-to-revenue to those of publicly traded "peers" suggested by Ventria's CEO, Mr. Deeter. *Id.* But the contraposition of Ventria, a relatively young, privately held company, to Repligen and Biolife Solutions, two decades-old, publicly traded biotech companies with very different corporate structures, numbers of products, and numbers of employees, yields a self-serving "analysis" lacking any meaningful comparison to aid context. *See* LaMotta Tr. 747:1–749:6. The FID acknowledges that these two companies "are not competitors" of Ventria, but employs the analysis regardless because "they are publicly-traded companies and thus, [Ventria's expert] had access to their publicly-available data." FID at 107, fn 36. Simply because their data is publicly-available, however, does not make it relevant. The FID therefore adopts the position that inapposite and irrelevant data, in the absence of any other data, is sufficient and acceptable. This is inappropriate and should be rejected by the Commission as clear error.

Ventria's own claimed investments in Optibumin are meager, at best. If "significant" and "substantial" are to have meaning in the context of section 337, there must be a bottom below which the investments are "insignificant" or "unsubstantial." Ventria's claimed investments of roughly [redacted] of Ventria's total expenditures—or approximately [redacted] in plant and equipment,

approximately [redacted] in labor, and approximately [redacted] in research and development—fall below that bottom. FID at 108.

C. Ventria Fails to Demonstrate a Nexus between Its Alleged R&D Investments and the Alleged Domestic Industry Products

Ventria's claimed investments in R&D under sub-section (C) of the domestic industry requirement is additionally deficient. Section 337 requires a nexus between the alleged investments in research and development and the exploitation of the claimed intellectual property right. *Certain Integrated Circuit Chips and Products Containing the Same*, Inv. No. 337-TA-859, Comm'n Op., 38, 42-43 (Aug. 22, 2014). Ventria has not shown that required nexus. Indeed, far from showing the required nexus of alleged research-and-development investments to the claims of the '951 patent for Optibumin—Ventria's sole remaining domestic industry product—Ventria stated that its research-and-development efforts in Optibumin "are not readily segregated from its investments in the other [five non-practicing] products. Ventria uses the same equipment, the same facilities, and the same rice to produce both Optibumin and the other [five non-practicing] products." Deeter Tr. 186:6–187:12; LaMotta Tr. 696:2-12. Thus, by Ventria's own admission, there is no way to discern investments in a product practicing the '951 patent from products not practicing the '951 patent, much less properly attribute those investments to any claimed invention in the '951 patent. Consequently, Ventria's claimed investments in Optibumin under sub-section (C) should be disregarded for this additional reason.

VIII. THE COMMISSION SHOULD REVIEW AND REVERSE THE FID'S FINDING OF A VIOLATION BASED ON THE LANHAM ACT BY THE DEFAULTING RESPONDENTS

Ventria offered no evidence at the evidentiary hearing against the Defaulting Respondents or substantiating its allegations of a violation based on a Lanham Act violation, and Healthgen consequently had no evidence supporting those allegations to rebut. Tr. (Reed) at 1311:3-7,

1333:11-1338:18. Notably, allegations of a violation based on a Lanham Act violation are based on 19 U.S.C. § 1337(a)(1)(A), which requires a showing of harm to the domestic industry.

The FID incorrectly finds "the Commission shall presume the facts alleged in the complaint to be true" against the Defaulting Respondents (*see* FID at 121), citing 19 U.S.C. § 1337(g)(1). That statutory provision, however, only applies if "the complainant seeks relief *solely limited to that person*." 19 U.S.C. § 1337(g)(1) (emphasis added). But Ventria (the complainant) does not seek relief *solely limited to* the Defaulting Respondents. Ventria clearly also seeks relief against Healthgen, which means 19 U.S.C. § 1337(d)(1) governs. Consequently, Ventria was obliged to (and admittedly did not) introduce evidence of a Lanham Act violation, including evidence of a harm to its domestic industry. Tr. at 1333:11-1338:18.

Ventria's failure to offer any evidence supporting its allegations of a Lanham Act violation precludes a finding of violation by the Defaulting Respondents. 19 U.S.C. §§ 1337(a)(1)(A), (d)(1); *see also* 19 U.S.C. § 1337 (g)(1)(E).[21]

IX. REMEDY & BOND

The ALJ issued a Recommended Determination on Remedy and Bond ("RD") concurrently with the Final ID. This petition seeks review of the FID. 19 C.F.R. § 210.43. Healthgen will more fulsomely address any issues related to remedy, bond, and the public interest at the appropriate time if requested by the Commission.

Healthgen submits that the RD properly found no GEO should issue, as Ventria did not meet the statutory prerequisites for such extraordinary relief. FID/RD at 113-21. Healthgen

[21] As a practical matter, an exclusion order against any Healthgen's Accused Product would preclude the Defaulting Respondents from importing the banned product. Ventria's effort to end run the statutory requirements for obtaining a remedial order based on a Lanham Act violation in the absence of any evidence should nevertheless be rejected.

submits any LEO Should be limited to those products found to infringe (*see* § IV, *supra*) and agrees a certification provision is appropriate. Healthgen also agrees cease-and-desists orders are not warranted. FID/RD at 122-23. Although for the reasons noted above, no remedial orders should be directed to the Defaulting Respondents. *See* § VIII.

X. PUBLIC INTEREST

Public interest was not delegated to the ALJ (86 Fed. Reg. 6916-17); consequently the parties were not permitted to submit evidence on public interest (19 C.F.R. § 210.10(b)(2)). Although the FID/RD states Healthgen waived a Fifth Affirmative Defense in its Response to the Complaint based on public interest factors (FID/RD at 127), Healthgen could not have waived any arguments based on public interest when it was precluded from offering (and the ALJ was precluded from receiving) any evidence on public interest. Healthgen will submit any evidence and comments on public interest at the appropriate time permitted under Commission rules. *See* 19 C.F.R. § 210.50.

XI. CONCLUSION

For all the reasons above, the Commission should review and reverse the Final ID's finding of a violation as the Healthgen's accused products do not infringe the '951 patent, the asserted claims of the '951 patent are not valid, the alleged DI products do not practice the claims of the '951 patent, and the attributable investments in Optibumin (the only product that ostensibly practices the '951 patent) are not significant or substantial.

Dated: April 19, 2022

Respectfully submitted,

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CERTIFICATE OF SERVICE

I, Isabella P. Downey, hereby certify that on May 3, 2022, copies of the foregoing were filed with and served upon the following as indicated:

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