

23-1389

IN THE
UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

WUHAN HEALTHGEN BIOTECHNOLOGY CORP.,

Appellant,

v.

INTERNATIONAL TRADE COMMISSION,

Appellee,

VENTRIA BIOSCIENCE INC.,

Intervenor.

Appeal from the United States International Trade Commission in
Investigation No. 337-TA-1238.

NON-CONFIDENTIAL BRIEF OF APPELLANT WUHAN HEALTHGEN
BIOTECHNOLOGY CORP.

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REPRESENTATIVE PATENT CLAIM AT ISSUE

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

a recombinant mammalian albumin wherein said albumin is:

- i) produced in a transgenic plant;
- ii) has less than 1 EU of endotoxin/mg of albumin; and
- iii) less than 2% aggregated albumin.

**UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT
CERTIFICATE OF INTEREST**

Case Number: 23-1389

Short Case Caption: Wuhan Healthgen Biotechnology Corp. v. ITC

Filing Party/Entity: Wuhan Healthgen Biotechnology Corporation

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Date: May 26, 2023 Signature: /s/ Erik R. Puknys

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Provide the full names of all entities represented by undersigned counsel in this case.	Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities. ☒ None/Not Applicable	Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities. ☒ None/Not Applicable
Wuhan Healthgen Biotechnology Corporation		

☐ Additional pages attached

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☒ None/Not Applicable ☐ Additional pages attached

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CONFIDENTIAL MATERIALS OMITTED

The materials omitted from the Non-Confidential Brief contain confidential business information designated under the administrative Protective Order, dated January 21, 2021, entered in Investigation No. 337-TA-1238 in the ITC and were confirmed to be confidential before the filing of this brief. The materials omitted from pages 9-13, 20-22, and 52 describe methods used to determine the purity of and quantify the amounts of aggregates in certain products; and the materials omitted on pages 4, 23-25, 34, 65-66, and 69-71 describe Ventria's alleged domestic-industry investments in the form of percentages and dollar amounts invested.

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Other Authorities

- David H. Friedman, *Why Scientific Studies Are So Often Wrong: The Streetlight Effect*, <https://www.discovermagazine.com/the-sciences/why-scientific-studies-are-so-often-wrong-the-streetlight-effect> (last visited May 12, 2023) 73
- Hanns-Christian Mahler et al., *Protein aggregation: Pathway, induction factors and analysis*, 98 J. Pharm. Scis. 2909 (Sept. 2009), available at [https://jpharmsci.org/article/S0022-3549\(16\)33077-5/fulltext](https://jpharmsci.org/article/S0022-3549(16)33077-5/fulltext) (last visited May 13, 2023) 9

STATEMENT OF RELATED CASES

This appeal may affect the pending district court litigation in which Ventria Bioscience Inc. (“Ventria”) has asserted against Wuhan Healthgen Biotechnology Corporation (“Healthgen”) the same patent at issue in this appeal. *See Ventria Bioscience Inc. v. Wuhan Healthgen Biotechnology Corp.*, C.A. No. 5:21-cv-04008 (D. Kan.). That district court action is stayed pursuant to 28 U.S.C. § 1659. *See id.*, Order, Dkt. 12 (D. Kan. Mar. 4, 2021).

In addition, Ventria separately appealed the Final Determination in the same ITC Investigation. *See Ventria Bioscience Inc. v. Int’l Trade Comm’n*, No. 23-1172 (Fed. Cir.). That appeal was dismissed on March 14, 2023, before briefing was completed. *See id.*, Order, Dkt. 21 (Fed. Cir. Mar. 14, 2023).

JURISDICTIONAL STATEMENT

The International Trade Commission’s determination that Healthgen violated 19 U.S.C. § 1337 by importing certain plant-derived recombinant human serum albumin (“rHSA”) and rHSA products that infringed claims 1 and 11-13 of U.S. Patent No. 10,618,951 (“the ’951 patent”) became final on November 12, 2022, the day after the close of the sixty-day Presidential review period under 19 U.S.C. § 1337(j). Healthgen’s petition for review was timely filed on January 9, 2023, within sixty days after the Commission’s determination became final. *See* 19 U.S.C. § 1337(c).

STATEMENT OF THE ISSUES

1. Whether the Commission erred in finding that Healthgen’s “clinical grade” products infringed because they allegedly contain less than 2% aggregated albumin where:

a. the Commission principally relied on pre-import testing done in China the day after manufacture that failed to account for increases in aggregation that occur before the products arrive in the United States; and

b. the Commission found the data collected in China were corroborated by results from tests performed on samples that had been altered with a reducing agent that artificially lowers the number of albumin aggregates.

2. Whether the Commission erred in finding that Ventria’s claimed investments in the Optibumin product were “significant” or “substantial” enough to satisfy the domestic-industry requirement where:

a. Ventria’s domestic investments in its patented products were tiny, not just in absolute terms, but especially when compared to its investments in similar unpatented products; and

b. the Commission excused Ventria’s failure to introduce evidence of “significant” or “substantial” investments with speculation about evidence Ventria might be able to provide in the future.

I. PRELIMINARY STATEMENT

Section 337 authorizes the Commission to stop the importation of goods that infringe a United States patent, but only if the patent owner can show infringement *in the United States* and “*significant*” or “*substantial*” domestic investments in plant and equipment, labor, or other exploitation of the patent. This appeal arises out of the Commission’s erroneous reliance on (1) evidence that failed to establish infringement in the United States, and (2) evidence of investments that cannot, under any reasonable standard, qualify as “significant” or “substantial.”

The infringement issue in this appeal centers on claim language requiring recombinant albumin to have “less than 2% aggregated albumin.” Attempting to prove Healthgen’s products satisfied this limitation, Ventria put forward two sets of data that do not accurately represent Healthgen’s products as they are sold in the United States. The first set of data was measured in China, immediately after Healthgen’s products were manufactured. It is undeniable, however, that shipping and storage *increases* the quantity of aggregated albumin in these products so that when they arrive in the United States, the quantity of aggregated albumin will be greater than it was in China. Thus, Ventria’s pre-import tests underestimated the amount of aggregated albumin in Healthgen’s imported products. Ventria supplemented those pre-import tests with testing done in the United States, but it used a technique that indisputably alters the product by artificially *decreasing* the

quantity of aggregated albumin. So, these data, like the pre-import data, underestimate the amount of aggregated albumin in Healthgen's imported products. The Commission erroneously relied on these two flawed sets of data to find that Healthgen's products infringed.

The Commission also erred by finding that Ventria's investments in its Optibumin product (the only one that practices the patent) satisfied the economic prong of the domestic-industry requirement. A domestic industry under Section 337 can exist only if "significant" or "substantial" investments related to the patent were made in the United States. But Ventria's Optibumin investments were small, both in absolute and relative terms, accounting for just % inv. of its total claimed domestic-industry investments. If Section 337's economic prong has any teeth at all, this case presents the perfect opportunity to demonstrate it.

For the reasons explained below, this Court should reverse the Commission's findings that Healthgen's accused products infringed the asserted claims and that Ventria's Optibumin product alone satisfied the economic prong of the domestic-industry requirement. A reversal on either finding is sufficient to reverse the Commission's finding of a Section 337 violation.

II. STATEMENT OF THE CASE

The ITC found that some of Healthgen’s products infringed the ’951 patent and that one of Ventria’s products satisfied both the technical and economic prongs of the domestic-industry requirement. Practicing the ’951 patent requires, *inter alia*, recombinant mammalian albumin (e.g., recombinant human serum albumin, “rHSA”) having “less than 2% aggregated albumin.” There are several tests for analyzing different properties of rHSA whose appropriateness depends on what one seeks to measure and why. Of particular interest in this appeal are techniques for analyzing the sizes of albumin species in solution, which provide different information about the type and quantity of aggregated albumin.

A. Some techniques for measuring the sizes of proteins alter the sample before analysis and some do not.

Various methods are used to analyze proteins in solution, often by distinguishing between the target protein and other proteins by molecular weight. These techniques can identify impurities, protein fragments (which are smaller than the target protein), and protein aggregates (which are larger than the target protein). Different techniques may provide different information on the types of protein in solution, and the results may vary depending on how the samples are prepared for analysis. Three techniques are pertinent to this appeal: (1) SDS-PAGE, where samples may be pre-treated with the surfactant SDS (“non-Reducing SDS-PAGE”)

or pre-treated with SDS and a reducing agent (“Reducing SDS-PAGE”);¹ (2) Native-PAGE; and (3) SEC-HPLC.²

1. SDS-PAGE and “Reducing” SDS-PAGE involve pre-treating samples with agents that break up certain aggregates before analysis.

SDS-PAGE separates protein species by size using gel electrophoresis. *See, e.g.,* Appx3383. Before analysis, protein samples are treated with a surfactant (“SDS”) that denatures (unfolds) proteins and disrupts non-covalent interactions. *See* Appx1859-1860[856:19-857:5]; Appx1467[466:17-25] (Ventria’s expert admitting that SDS-PAGE may “dissociate some noncovalent or noncovalently linked aggregates”). Gel electrophoresis is then used to separate the denatured proteins by size. Appx3383.

The treated sample is analyzed to determine the amounts of different species in solution, with the caveat that any proteins that were aggregated via non-covalent

¹ In the ITC, the parties used the phrase “Reducing SDS-PAGE” to refer to SDS-PAGE performed on a sample that had been pre-treated with a reducing agent. The parties thus also used the phrase “non-Reducing” SDS-PAGE interchangeably with SDS-PAGE to refer to SDS-PAGE performed on a sample that had not been pre-treated with a reducing agent. These terms were used by the parties for convenience and are not commonly used in the scientific literature.

² “SDS-PAGE” refers to sodium dodecyl sulfate polyacrylamide gel electrophoresis. “Native-PAGE” refers to polyacrylamide gel electrophoresis (PAGE) analysis on a protein sample in its native state (i.e., untreated with an agent that changes the nature of the protein species in solution). “SEC-HPLC” refers to size-exclusion chromatography high pressure liquid chromatography.

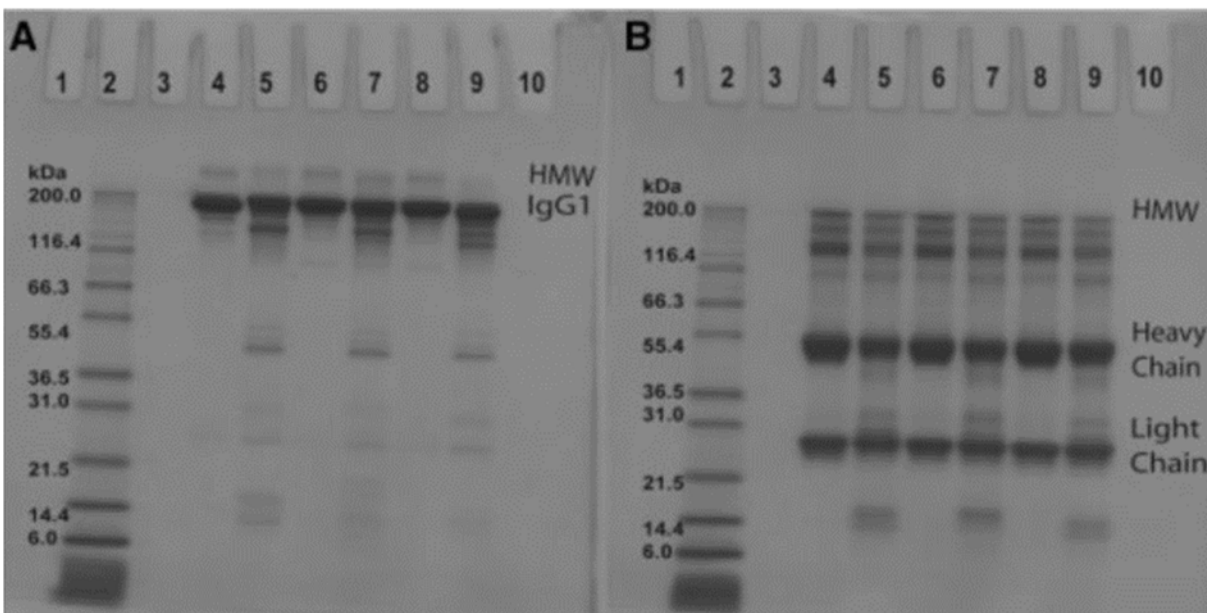
bonds will not be detected, as such aggregates are disrupted (i.e., broken into smaller species) by the surfactant (SDS). Appx3461 (“The presence of SDS means that non-covalent aggregates are disrupted, so the method only detects covalent aggregates.”); Appx3383 (“SDS-PAGE has the ability to detect covalently linked aggregates, or SDS nondissociable aggregates, however noncovalent associated proteins species are separated into their constituent polypeptide chains.”).

The samples may also be pre-treated with a reducing (bond-breaking) agent before analysis, which the parties referred to as “Reducing SDS-PAGE.” Other than the use of the reducing agent to pre-treat the sample, Reducing SDS-PAGE uses the same general methodology as SDS-PAGE. *See, e.g.*, Appx3383. The reducing/bond-breaking agent disrupts aggregation by breaking disulfide bonds that link proteins (including albumin) together. This point is undisputed. *See, e.g.*, Appx2206-2207[1181:17-1182:8]; Appx1468[467:15-20] (Ventria’s expert: Reducing SDS-PAGE breaks apart disulfide bonds); Appx1504[503:14-19] (Ventria’s expert: reducing agents TCEP and DTT “break[] disulfide bonds”); Appx1463[462:2-23] (Ventria’s expert: reducing agents “should reduce [disulfide] bonds” between aggregated albumin). After altering the sample with a reducing agent, it is analyzed by gel electrophoresis. Appx1348[347:1-10]; Appx1373[372:5-13].

Because Reducing SDS-PAGE breaks up certain albumin aggregates into albumin monomers or fragments, it cannot be used to reliably identify the absolute

number or percentage of total albumin aggregates. Appx2206-2207[1181:17-1182:13] (Healthgen’s expert: using Reducing SDS-PAGE sample treatment “would necessarily reduce the observed level of aggregated albumin”); *see also* Appx1859-1860[856:19-857:5]; Appx1468-1469[467:15-468:2] (Ventria’s expert: “potentially there would be a reduction” in aggregated albumin when using a reducing agent). Instead, it will detect only the aggregates that were not destroyed by the reducing agent. As such, Reducing SDS-PAGE generally measures an artificially lower number or percent of aggregated albumin than what actually existed in the sample before pre-treatment. *Id.*

The scientific literature describes how SDS-PAGE allows for the observation of different protein species, depending on how the sample is prepared. Appx3383-3384. For example, Mahler provides images of SDS-PAGE gels for a sample that was (A) non-reduced (pre-treated only with a surfactant, SDS) and (B) reduced (pre-treated with a surfactant and a reducing agent). Appx3384.



Appx3384 (cleaner image obtained from the on-line version of Mahler, *available at* [https://jpharmsci.org/article/S0022-3549\(16\)33077-5/fulltext#figures](https://jpharmsci.org/article/S0022-3549(16)33077-5/fulltext#figures) (last visited May 23, 2023)). The SDS-PAGE gel for the non-reduced sample A shows primarily high molecular weight (HMW) aggregates around 200 kDa, as observed by the dark band near the top of the gel. Appx3384. By contrast, the SDS-PAGE gel for the reduced sample B includes prominent bands corresponding to much smaller protein species around 55 kDa and 25 kDa. Appx3384.

While Reducing SDS-PAGE cannot measure aggregates with non-covalent bonds or covalent disulfide bonds, it has other uses. For example, it can provide information on the purity of the sample, i.e., the amount of the target protein present versus impurities, because when measuring impurities, it does not matter whether the target is a monomer or an aggregate. *See infra* § II.D.1 (discussing [REDACTED] use of Reducing SDS-PAGE to certify the purity of its [REDACTED] and [REDACTED]

products). In fact, pre-treating a sample with a reducing agent may simplify purity measurements by decreasing the number of bands/protein species that need to be analyzed, as certain aggregates will be converted to monomeric proteins. *See* Appx1859[856:7-18]. Additionally, when a sample is subjected to both non-Reducing SDS-PAGE and Reducing SDS-PAGE, comparing the results indicates the amounts of aggregates linked by disulfide bonds, which may be observed by non-Reducing SDS-PAGE but not by Reducing SDS-PAGE (because it destroys them). Appx3384; Appx3461. The literature thus describes SDS-PAGE as a technique that may be used to “discriminate between aggregates held together by disulfide bonds and those held together by other (non-reducible) covalent bonds.” Appx3461; Appx3384.

2. Native-PAGE does not alter the sample with pre-treatments before measuring the protein.

Native-PAGE is a useful technique for measuring the absolute amount or percentage of aggregated albumin in a sample because it does not “pretreat[] the sample in such a way that the sample will be altered.” *See* Appx2206[1181:11-16]; Appx2187[1162:4-14]; Appx1348-1349[347:22-348:10]; Appx3507[22:19-23:2] (Ventria’s CEO: Native-PAGE observes the protein “without any type of detergent” and without a reducing agent); Appx3507-3508[25:20-26:2] (company name Native-PAGE to see “the protein in its native state,” i.e., the “state that [it] is in natively without treatment”).

As Ventria scientist Dr. Alfano explained, Native-PAGE may be used to determine the level of aggregation in a product because it does not use a bond-breaking agent. Appx3477[38:16-39:4]. For example, Ventria performed Native-PAGE on Healthgen's products before the ITC Investigation, although the results contradicted its infringement allegations. Appx2187-2194[1162:17-1169:15] (discussing Ventria's pre-litigation Native-PAGE data); Appx3416-3418; Appx3645-3646; Appx3547-3548[185:21-186:9]; Appx3550[194:18-195:1]; Appx3431-3440; Appx3299-3301; Appx3748-3754 (demonstratives accompanying trial testimony showing how to interpret Ventria's pre-litigation Native-PAGE data).

Ventria compared [REDACTED] test methods [REDACTED] for various albumin samples. Appx3544[171:8-172:2]; Appx3419. Ventria's comparison shows that

[REDACTED] description of test results [REDACTED]

[REDACTED] description of test results [REDACTED]

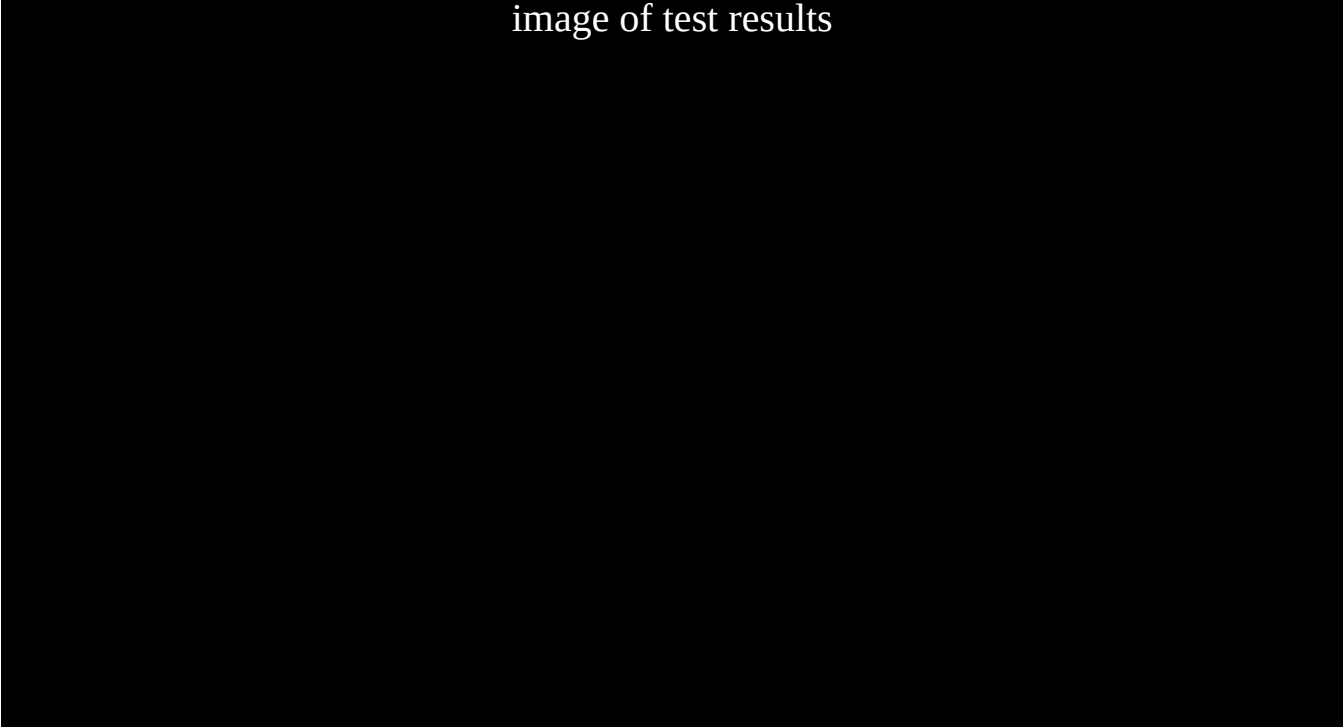
[REDACTED] description of test results [REDACTED]. While Ventria's comparison does not [REDACTED] description of test results [REDACTED]

[REDACTED] description of test results [REDACTED]

[REDACTED] description of test results [REDACTED], the

comparison demonstrates that different species were observed by the two methods.

image of test results



Appx3419 (annotated with red box).

3. SEC-HPLC is commonly performed on samples that have not been altered with pre-treatments before analysis.

SEC-HPLC—“one of the most used analytical methods for the detection and quantification of protein aggregates”—is a chromatographic technique commonly used to separate proteins by size without altering the sample before analysis. Appx3382-3383; *see also* Appx1466[465:7-16] (Ventria’s expert: SEC-HPLC is a “frequently used method”). The literature describes SEC-HPLC as a “[r]obust, sensitive, [and] precise” method for analyzing protein aggregates. Appx3457. Like Native-PAGE, SEC-HPLC generally does not use either a surfactant or a reducing/bond-breaking agent. *See* Appx2205-2206[1180:24-1181:10].

use of test method to quantify the level of aggregates reported in the certificates of analysis for its product name product. *See infra* p. 21.

Table 1 summarizes the test methods discussed above and the types of aggregates each technique may observe.

Table 1: Techniques for Analyzing Proteins and the Types of Aggregates that May Be Observed			
	Non-Reducing and Reducing SDS-PAGE	Native-PAGE	SEC-HPLC
Non-covalently bonded aggregates	Not observed; SDS breaks up non-covalent aggregates.	Observed.	Observed.
Disulfide bonded aggregates	Non-Reducing SDS-PAGE: Observed. Reducing SDS-PAGE: Not observed.	Observed.	Observed.
Non-disulfide covalently bonded aggregates	Observed.	Observed.	Observed.
Application	Measuring purity or comparatively determining the level of disulfide-bonded aggregates.	To observe sizes of protein species in their native, unaltered state.	

See, e.g., Appx3635; Appx3638-3641; Appx3774.

The impact that altering a sample with a reducing/bond-breaking agent has on measuring aggregated albumin is best shown by comparing the results in Table 2 of SDS-PAGE (before and after treatment with the reducing agent dithiothreitol, “DTT”) and SEC-HPLC testing performed on the same samples of Ventria’s

Exbumin and Cellastim products at approximately the same time. *See* Appx2212-2213[1187:2-1188:23].

Table 2: Percent Aggregated Albumin by Various Techniques			
Sample	SEC-HPLC	Non-Reducing 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%

See Appx3635-3636; Appx3638-3641.³

B. The '951 patent

The '951 patent describes cell culture media containing combinations of proteins, along with methods of making cell culture media. *See* Appx267[1:23-27]. In particular, the '951 patent relates to purified recombinant mammalian albumin for use in cell culture. Albumin is a protein and a common component of cell culture. Traditionally, blood serum and serum-derived albumin from animals have been used in cell culture; however, due to concerns about contamination and the ethics of

³ Percent aggregated albumin is calculated by adding the “Band %” for Band Nos. 1 and 2 identified by SDS-PAGE at Appx3635-3636 (i.e., by adding the % of the high molecular weight species) and by adding the “% Area” for the species larger than albumin in the SEC-HPLC data at Appx3638-3641. Appx24-25; Appx2248-2250[1223:24-1225:11]; Appx3810.

harvesting animal serum, recombinant albumin produced from other sources, such as transgenic rice, is becoming more prevalent. *See* Appx267[2:53-56].

The '951 patent describes cell culture media containing rHSA, where the recombinant albumin has less than 2% aggregated albumin. *E.g.*, Appx269[5:3-8]. The Administrative Law Judge (“ALJ”) adopted the parties’ agreed construction of the term “aggregated albumin” as “[n]on-monomeric albumin (e.g., albumin dimers).” *See* Appx2892. That is, “aggregated albumin” constitutes any form of albumin other than a single-unit albumin species (such as full-length monomeric albumin) or a fragment thereof not linked to another albumin molecule. Appx2181-2182[1156:13-1157:16]. The Commission did not alter this construction when reviewing the ALJ’s Final Initial Determination (“FID”). *See* Appx16. As a result, the term “aggregated albumin” includes all aggregates of albumin, including aggregates linked by non-covalent bonds (not observed by non-Reducing or Reducing SDS-PAGE), covalent disulfide bonds (not observed by Reducing SDS-PAGE), and other covalent bonds. *See supra* § II.A.

In one example, the '951 patent describes producing recombinant human serum albumin (“rHSA” or “recombinant HSA”) from transgenic rice, referred to as “Cellastim.” *See* Appx298[64:6-61]; Appx302[71:55-72:44]. As rHSA expressed in transgenic rice was known, the '951 patent describes a process for further purifying rHSA. Appx300-301[68:47-69:22]; Appx3585-3586, [0103]-[0105] (Ventria’s prior

patent application disclosing producing rHSA from transgenic rice); Appx298[64:6-67] (disclosing an identical method of producing rHSA from transgenic rice). The '951 patent describes comparing the rHSA to (a) rHSA purified by a “previously used” method and (b) commercially available HSA using SEC-HPLC. Appx301[69:30-70:16]. According to the '951 patent, the SEC-HPLC data showed that all albumin products tested (rHSA and HSA) “contained a peak at 130 kDa that most likely represents albumin dimers” (two albumin molecules linked together, i.e., aggregated albumin), where the “Cellastim [rHSA] dimer peak is significantly smaller than the plasma derived albumin.” Appx302[72:18-22].

The '951 patent also describes another example comparing rHSA to (a) rHSA purified by a previously used method and (b) rHSA expressed in yeast (Cellprime) using SDS-PAGE, where both samples were treated with a reducing agent before analysis. Appx301[70:1-49]; Appx302[72:29-57]. According to the '951 patent, the Reducing SDS-PAGE data of this example showed that the rHSA and Cellprime (yeast-derived rHSA) were “generally similar,” while the rHSA purified using the older process showed a relatively greater number of “aggregates” around 250 kDa, with one average “greater than 2% for the old process, and [an] average less than 1% for the new process.” Appx302[72:29-54]. The '951 patent does not specify whether the “aggregates” at 250 kDa are albumin aggregates or aggregated impurities (i.e., non-albumin proteins). *Id.* Nor does it report the relative amounts of

any aggregates having molecular weights other than 250 kDa (*id.*) or the amount of albumin aggregates that existed in any sample before it was altered with the reducing agent. Appx301[70:17-49] (describing sample preparation using a reducing agent); Appx302[72:29-57] (characterizing results of Reducing SDS-PAGE).

Claim 1 is representative of the claims on appeal:

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

a recombinant mammalian albumin wherein said albumin is:

- i) produced in a transgenic plant;
- ii) has less than 1 EU of endotoxin/mg of albumin; and
- iii) less than 2% aggregated albumin.

Appx328[123:44-51]. Dependent claims 11-13 contain further limitations on the albumin and transgenic plant that are not at issue in this appeal. Appx328[124:55-60].

C. Healthgen's products

Healthgen markets clinical and medium grade rHSA products branded as OsrHSA®.

1. Healthgen's clinical grade products

Healthgen prepares certificates of analysis for its clinical grade products describing certain properties measured shortly after manufacture. *See, e.g.*, Appx3371-3373 (certificate of analysis). These certificates report purity as determined by SDS-PAGE (non-reducing) to confirm that the amount of all albumin

species (including monomers, dimers, and larger aggregates, combined) meets the acceptance criteria. *See* Appx3656-3658; *see also* Appx3372. For example, the sample tested in this Investigation had a purity of “100.0%,” indicating that it was 100% albumin (including monomers and aggregates, i.e., different forms of albumin). Appx3372.

Healthgen does not use SDS-PAGE (reducing or non-reducing) to certify the amount of aggregated albumin present in its products, but it does use SEC-HPLC for this purpose. Appx3372. But unlike the '951 patent, which caps aggregated albumin at 2%, Healthgen, for its clinical grade product, allows up to 3.5% albumin dimers (aggregates), up to 1% albumin polymers (aggregates larger than dimers), and up to 0.5% albumin fragments (unaggregated), as long as the total amount of monomeric albumin is at least 96% of the product. Appx3372.

a. Healthgen’s clinical grade products display a marked *reduction* in aggregated albumin when treated with a reducing agent.

Healthgen’s clinical grade rHSA comprises aggregated albumin linked by disulfide bonds, which are broken when treated with a reducing/bond-breaking agent. For example, the level of aggregated albumin in one sample was cut nearly in half after altering the sample with the reducing/bond-breaking agent tris(2-carboxyethyl) phosphine (“TCEP”). *Compare* Appx3371-3372 (reporting 1.1% aggregates (the sum of 0.8% dimers and 0.3% polymers) of albumin one day after

manufacture by SEC-HPLC of Lot No. C001202009001), *with* Appx3447 (reporting 0.64% total albumin aggregates after treatment with TCEP for HGEN-RPX-001); Appx3630 (identifying Lot No. C001202009001 as HGEN-RPX-001); Appx3444-3445 (identifying TCEP as the reducing agent). Moreover, while the albumin-aggregate content decreased after the reducing pre-treatment, the number of albumin fragments increased. *Compare* Appx3372 (reporting 0.06% fragments by SEC-HPLC one day after manufacture), *with* Appx3447 (May 2021 test report showing treatment with TCEP generated 3% fragments).

b. Healthgen's clinical grade products display a marked *increase* in aggregated albumin when stored and shipped for delivery.

Healthgen's clinical grade rHSA is also susceptible to aggregation over time. For example, a sample that was shipped after approximately six months in storage contained substantially more albumin aggregates than reported one day after manufacture, even after treatment with a reducing/bond-breaking agent. *Compare* Appx3371-3372 (reporting 1.1% aggregates (the sum of 0.8% dimers and 0.3% polymers) of albumin one day after manufacture by SEC-HPLC of Lot No. C001202009001), *with* Appx3297 (reporting 1.81% total albumin aggregates by Reducing SDS-PAGE for the same sample, HB012, HGEN-RPX-001); Appx3630 (identifying Lot No. C001202009001 as HGEN-RPX-001).

2. Healthgen's medium grade products

As with its clinical grade products, Healthgen analyzes its medium grade products' purity using SDS-PAGE (non-reducing). Appx3374; Appx3658 (SDS-PAGE analysis stating purity is the sum of albumin monomers, dimers, and larger aggregates). At the time of the ITC Investigation, Healthgen's certificate of analysis for its medium grade products did not include any acceptance criteria for aggregated albumin. *See* Appx3374. A distributor of Healthgen's medium grade products, however, prepared a brochure including SEC-HPLC data showing that the medium grade product had 94.588% (unaggregated) monomers, 4.416% (aggregated) dimers, and 0.208% larger aggregates of albumin. Appx3369 (noting purity by SEC-HPLC of $\geq 99\%$); Appx3370 (showing SEC-HPLC chromatograph and amounts of the different forms of albumin).

D. Ventria's products and investments

1. Ventria's Optibumin product practices the '951 patent, while Ventria's other rHSA products do not.

Ventria's domestic-industry case relied on its assertion that all six of its rHSA products practiced the '951 patent: Cellastim, Exbumin, Optibumin, OptiPEAK, OptiVERO, and ITSE+A. Appx2997-3002.

Ventria's liquid rHSA product, Optibumin, is primarily for category of use applications. Appx3485[73:9-19]; Appx3487[79:2-8]. Optibumin is the only Ventria product that includes a limit on aggregates in its certificate of analysis, where the

acceptance criterion is less than 2%, as determined by [test method]. Compare Appx3430 (Optibumin certificate of analysis specifying less than 2% aggregates), with Appx3413 (Cellastim certificate of analysis with no acceptance criteria for aggregates) and Appx3449-3452 (Exbumin certificate of analysis with no acceptance criteria for aggregates); see also Appx1250[250:18-24]; Appx1251[251:5-10] (Ventria's CEO: Ventria uses [test method] to quantify aggregated impurities in Optibumin); Appx3279-3290 (Ventria's [test method] [test method]). Healthgen did not dispute that Ventria's Optibumin product practices the '951 patent. See, e.g., Appx2268-2269[1243:22-1244:5]; Appx3100.

Ventria also markets two powdered rHSA products, Exbumin and Cellastim, and cell culture media products comprising the rHSA in Cellastim (OptiVero, OptiPeak, and ITSE+A).

Ventria uses [test method] to assess the purity of the rHSA in its Cellastim product. Appx3474[28:17-29:23]. So, if purity by [test method] is reported as 99.3%, that means 99.3% of the protein species present (regardless of form) are albumin as opposed to other proteins. *Id.* Ventria's President and CEO, Mr. Scott Deeter, similarly explained that Ventria analyzes the purity of its Exbumin product by [test method]. Appx3545[176:11-13].

Importantly, as Ventria's own scientist Dr. Alfano admitted, SDS-PAGE, as used by Ventria after pre-treatment with a reducing agent (i.e., Reducing SDS-

PAGE), “[d]oes not indicate anything about the level of dimerization or aggregation of the albumin,” because dimers and other aggregates of albumin are “broken up” using “the right sample prep,” i.e., by pre-treating samples with a reducing agent. Appx3474-3475[29:24-30:24]. Indeed, Dr. Alfano described the reducing agents as “bond-breaking agents.” *Id.*; Appx3477[38:21-25]. Mr. Deeter also explained that Ventria [REDACTED] description of test method [REDACTED] analyses of Cellastim and Exbumin (Appx3545[176:1-13]) and does not determine the level of [REDACTED] description of test results [REDACTED] in its Exbumin product (Appx3545[177:11-13]).

Because there was no evidence in the record that the rHSA in Exbumin, Cellastim, or products containing Cellastim contained less than 2% aggregated albumin when tested using an appropriate method (e.g., without first breaking apart aggregates with a reducing agent), Healthgen disputed whether they practiced the claims of the ’951 patent. *See* Appx3095-3099. The dispute over whether the non-Optibumin products practice the ’951 patent is significant because virtually all of Ventria’s claimed domestic-industry investments relate to those products, not Optibumin.

2. Ventria’s Optibumin investments amount to only about % inv. of Ventria’s total investments in its rHSA products.

Ventria does not track investments on a product-by-product basis, so it used a sales-based allocation method to calculate its investments for its alleged domestic-industry products. Appx211-212; Appx1671-1672[669:6-670:6]; Appx2339-2340[1314:16-1315:8]. For example, Ventria’s domestic-industry product Cellastim accounted for percentage of all sales in 2015. *See* Appx3240-3241; Appx3322. Ventria allocated its investments in Cellastim in 2015 for plant and equipment, labor, and research and development by multiplying its total investments each year by percentage; Ventria then applied that analysis for each year between 2015 and 2020 for Cellastim and each other domestic-industry product; and it determined its claimed investments by tallying those investments under each category. *Id.* To highlight the disparity in sales among the different products, the average sales percent between 2015 and 2020 of Cellastim is percentage of all sales, of Exbumin is percentage, of Optibumin is percentage, of OptiVERO is percentage, of OptiPEAK is percentage, and of ITSE+A is percentage. Appx3322.

Ventria’s total claimed domestic-industry investments from 2015 to 2020 totaled more than \$dollar amount in plant and equipment (19 U.S.C. § 1337(a)(3)(A)), more than \$dollar amount in labor (19 U.S.C. § 1337(a)(3)(B)), and more than \$dollar amount in research and development (19 U.S.C. § 1337(a)(3)(C)), which was approximately percentage of Ventria’s total expenditures during that period. Appx211-

218; Appx1670-1672[668:21–670:17]; Appx3152-3239; Appx3240-3241; Appx3242-3260; Appx3261-3267; Appx3269; Appx3270-3278; Appx3427-3429; Appx3140-3151; *see also* Appx2341-2342[1316:23-1317:17]; Appx3320; Appx3327; Appx3333; Appx3338; Appx3822-3823; Appx3632.

Ventria began selling its only qualifying domestic-industry product, Optibumin, in 2018. And from 2018 through December 2020, when Ventria filed its complaint, Ventria’s sales of Optibumin comprised only about % sales of Ventria’s total sales. Appx3240-3241; Appx219-220; *see also* Appx2348-2349[1323:19-1324:18]; Appx3821; Appx3302; Appx3322.

Ventria’s sales-based methodology yielded domestic-industry investments in Optibumin of \$dollar amount in plant and equipment rather than the \$dollar amount originally claimed; \$dollar amount in labor rather than the \$dollar amount originally claimed; and \$dollar amount in research and development labor rather than the \$dollar amount originally claimed. Appx219; Appx1738-1739[736:21-737:8]; Appx1739-1740[737:24-738:16]; Appx1744-1745[742:10-743:10]; Appx3152-3239; Appx3240-3241; Appx3242-3260; Appx3261-3267; Appx3269; Appx3270-3278; Appx3427-3429; Appx3140-3142; Appx3143-3145; Appx3146-3148; Appx3149-3151; *see also* Appx3327; Appx3333; Appx3338; Appx2341-2345[1316:16-1320:5]; Appx3632; Appx3823-3824. Ventria’s qualifying investments amounted to roughly % inv of its

total claimed investments of \$**dollar amount**, and roughly **% inv.** of its total claimed domestic-industry investments of \$**dollar amount**. *Id.*

E. The ITC Investigation

1. The ALJ's Final Initial Determination

a. The ALJ determined all of Healthgen's recombinant albumin products infringed.

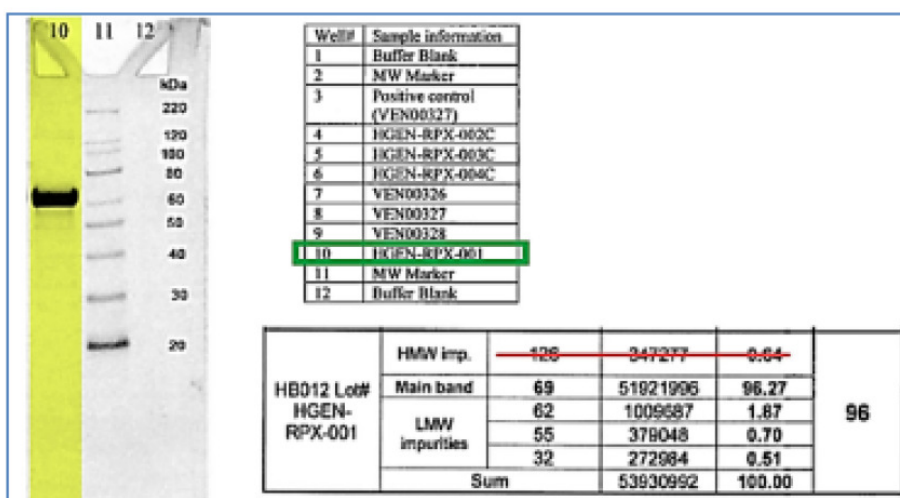
(1) The ALJ determined Healthgen's clinical grade products infringed.

The ALJ determined that Healthgen's clinical grade product contained "less than 2% aggregated albumin," as required by all claims, by relying on (1) data generated on a newly manufactured sample in China, and (2) two sets of Reducing SDS-PAGE data, i.e., data generated on a sample that had been altered with two different reducing/bond-breaking agents. Appx152-157. The three sets of data were all collected on the same batch of Healthgen's clinical grade liquid product. *See supra* § II.C.1.

First, the ALJ noted that when tested in China one day after manufacture, Healthgen's clinical grade liquid product contained less than 2% aggregated albumin by SEC-HPLC. Appx152-154 (presenting data showing 0.8% albumin dimers and 0.3% albumin polymers for a total of 1.1% aggregated albumin). The ALJ rejected Healthgen's argument that storage and shipping increase aggregation, such that data collected on a fresh sample in China did not represent the level of aggregated albumin in the United States. Appx157-161. But the ALJ did not deny that the level

of aggregated albumin in the United States, even after being subjected to a reducing pre-treatment, was measured at 1.81%, far greater than the 1.1% measured in China by SEC-HPLC one day after manufacture. Appx154; Appx156.

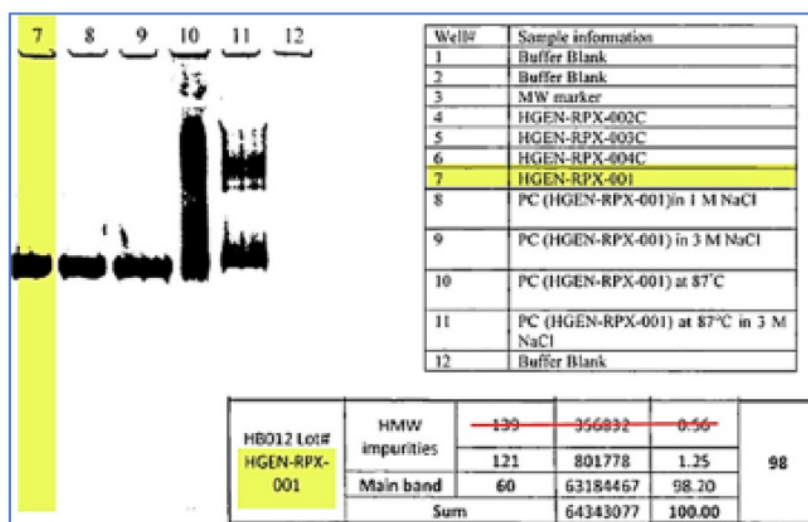
Next, the ALJ reproduced redlined versions of two sets of Reducing SDS-PAGE data on the same sample of Healthgen's clinical grade product, which had been altered with different reducing agents (TCEP and DTT). Appx155-157; Appx3444-3447 (first set of Reducing SDS-PAGE data with TCEP as the reducing agent); Appx3294-3297 (second set of Reducing SDS-PAGE data with DTT as the reducing agent). After discounting the redlined aggregates, the results indicated that 0% aggregated albumin remained after treatment with TCEP, while 1.25% aggregated albumin remained after treatment with DTT. Appx155-157. The first set of redlined data is below:



Appx156 (citing Appx3446-3447). As the underlying data show, treatment with the bond-breaking agent TCEP cut the level of aggregation in Healthgen's clinical grade

product to 0.64% and generated about 3% fragments ($1.87\% + 0.7\% + 0.51\% = 3.08\%$).⁴ Compare Appx3447, with Appx3372 (reporting 1.1% total aggregates and 0.06% fragments in China one day after manufacture).

In the second set of Reducing SDS-PAGE data, aggregates at 139 kDa—more than twice the molecular weight of monomeric albumin—were disregarded, as shown below:



Appx156-157. As the underlying data show, if all aggregates are counted, the second test of Healthgen’s clinical grade product showed that it contained 1.81% aggregated albumin, even after treatment with a reducing/bond-breaking agent. Appx3297 ($0.56\% + 1.25\% = 1.81\%$).

⁴ In the Reducing SDS-PAGE data, “HMW” means “High Molecular Weight,” i.e., species larger than monomeric albumin, and “LMW” refers to “Low Molecular Weight,” i.e., species smaller than monomeric albumin. Appx3444.

(2) The ALJ determined Healthgen’s medium grade products infringed.

The ALJ concluded that Healthgen’s medium grade products contained “less than 2% aggregated albumin” and thus infringed the asserted claims, despite test data in the record confirming that Healthgen’s medium grade products contain far more than 2% aggregated albumin. The ALJ instead relied on Ventria’s proffered interpretations of Healthgen’s statements regarding “purity.” Appx163-165. For example, the ALJ cited documents reporting that Healthgen’s medium grade products had “more than 99%” purity (Appx164-165), even though such “purity” measurements reflect total albumin content (monomers *plus aggregates*), not the percent monomeric albumin (*see supra* p. 21). The ALJ also decided that because Healthgen’s medium grade products were purified using the same process as its clinical grade products, the aggregation content for the two sets of products should be the same. Appx148-152; Appx165 (discussing, e.g., Appx3407).

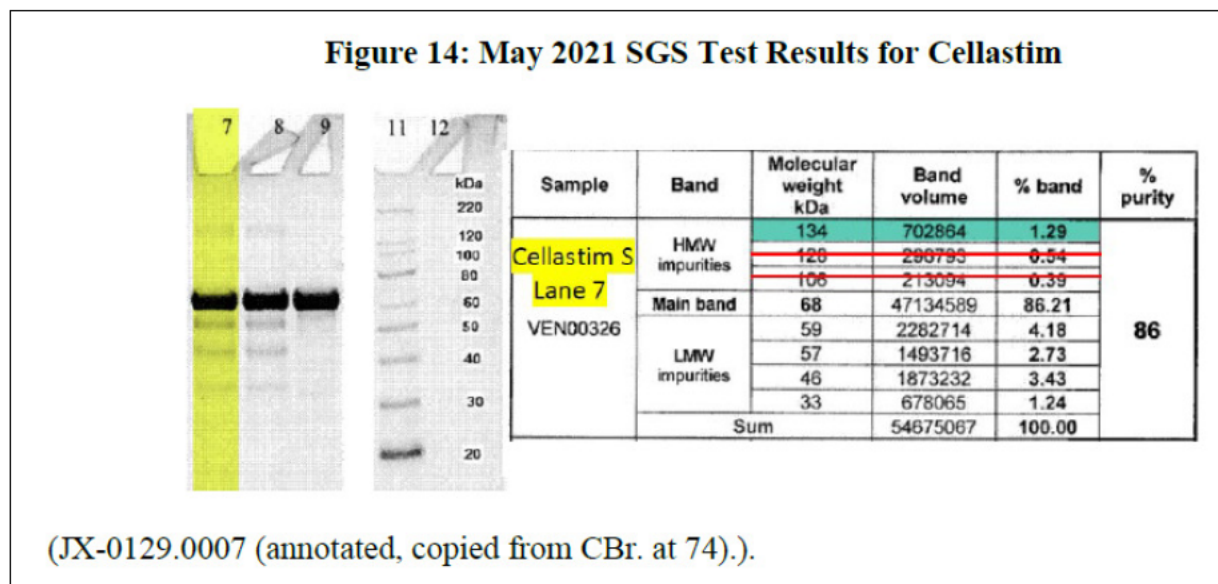
b. The ALJ determined that Ventria satisfied the domestic-industry requirement.

(1) The ALJ determined all of Ventria’s rHSA products practiced the ’951 patent.

As noted, Healthgen never disputed that Optibumin contained less than 2% aggregated albumin and thus practiced the ’951 patent. Appx169-170; Appx3100; Appx2267[1242:10-18].

The ALJ also determined that Ventria's other rHSA products contained less than 2% aggregated albumin. Appx173-182. But the ALJ reached this decision by (1) not counting (redlining) certain aggregates based on their molecular weights, and (2) relying on data collected on samples treated with a reducing/bond-breaking agent by Reducing SDS-PAGE. Appx173-181.

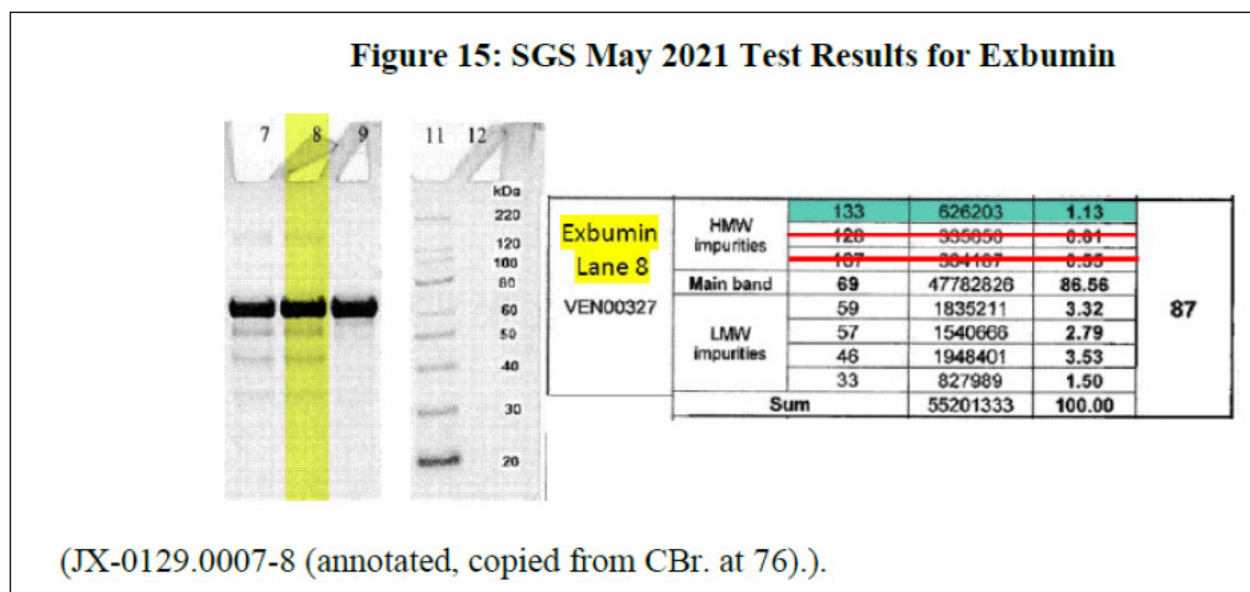
First, the ALJ adopted Ventria's redlining of the Reducing SDS-PAGE data generated by Ventria's third-party laboratory, SGS Life Sciences.⁵ Appx174-178. For Cellastim, the ALJ simply disregarded the presence of aggregates having molecular weights of 106 kDa and 126 kDa, as shown below:



⁵ Specifically, the ALJ redlined aggregates (i.e., non-monomeric albumin) that appeared to comprise albumin fragments (i.e., aggregates that did not have molecular weights corresponding to roughly twice the molecular weight of full-length monomeric albumin). Appx174-181. As the Commission did not adopt the ALJ's redlining, in the interest of brevity, the ALJ's rationale for discounting aggregates comprising fragments is not discussed herein.

Appx175 (annotations in original) (citing Appx3447). As shown in the underlying data, if the redlined aggregates are counted, the total aggregated albumin is 2.22%—above the upper limit in the asserted claims—even after treatment with a reducing agent. Appx3447 (showing data underneath the redlining, where the aggregates are identified as HMW [high molecular weight] impurities comprising $1.29 + 0.54 + 0.39 = 2.22\%$ of the sample); *see also* Appx3807 (Healthgen's expert's demonstrative calculating total aggregated albumin); *supra* p. 14 (Table 2 showing that when Cellastim is not pre-treated with a bond-breaking agent, the percent aggregated albumin is well above the claimed 2% threshold).

Similarly, for Exbumin, the ALJ disregarded aggregates having molecular weights of 107 kDa and 126 kDa:



Appx177 (annotations in original) (citing Appx3447-3448). As shown in the underlying data, if the redlined aggregates are counted, the total aggregated albumin

is 2.29%—above the upper limit in the asserted claims—even after treatment with a reducing agent. Appx3447 (showing data underneath the redlining, where the aggregates are identified as HMW [high molecular weight] impurities comprising $1.13 + 0.61 + 0.55 = 2.29\%$ of the sample); *see also* Appx3807.

The ALJ also relied on testing by Healthgen’s independent laboratory, Haemtech, which compared the level of aggregation observed by non-Reducing versus Reducing SDS-PAGE (i.e., SDS-PAGE before and after treatment with a reducing agent (DTT)). Appx178-181. When discussing these data, however, the ALJ again redlined aggregates having molecular weights two times greater than monomeric albumin, even though these aggregates fell squarely within the agreed-upon construction of “aggregated albumin”—“non-monomeric albumin”:

NON-REDUCING GEL			NON-REDUCING GEL		
Cellastim S (2 µg), non-reduced, sample 1			Exbumin (2 µg), non-reduced, sample 1		
Band No.	Molecular Weight (kDa)	Band %	Band No.	Molecular Weight (kDa)	Band %
~~1~~	~~118.2~~	~~2.3~~	1	117.4	3.4
2	109.3	1.9	2	107.8	3.0
3	52.5	83.9	3	52.4	82.2
4	44.4	6.5	4	44.4	5.8
5	34.6	5.2	5	34.6	5.6

Cellastim S (2 µg), non-reduced, sample 2			Exbumin (2 µg), non-reduced, sample 2		
Band No.	Molecular Weight (kDa)	Band %	Band No.	Molecular Weight (kDa)	Band %
~~1~~	~~124.0~~	~~2.2~~	~~1~~	~~121.4~~	~~2.0~~
2	114.0	1.1	2	112.4	1.4
3	52.7	87.1	3	52.6	86.5
4	44.1	6.0	4	43.9	6.6
5	34.4	3.6	5	34.4	3.5

Appx181 (annotations in original) (citing Appx3635-3636). If the total amount of non-monomeric albumin had been included in the calculation, the result would have

shown more than 2% aggregated albumin in Cellastim and Exbumin, i.e., outside the upper limit of the claims. Appx3635 (showing that Exbumin “non-reduced, sample 1” contained 6.4% aggregated albumin (3.4% + 3.0% of aggregates at 117.4 and 107.8 kDa, respectively) and Cellastim “non-reduced, sample 1” contained 4.4% aggregated albumin (2.5% + 1.9% of aggregates at 118.2 and 109.3 kDa, respectively)); Appx3636 (showing that Exbumin “non-reduced, sample 2” contained 3.4% aggregated albumin (2.0% + 1.4% of aggregates at 121.4 and 112.4 kDa, respectively) and Cellastim “non-reduced, sample 2” contained 3.3% aggregated albumin (2.2% + 1.1% of aggregates at 124.0 and 114.0 kDa, respectively)).

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

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	124.0	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

Appx3635-3636 (yellow highlighting added to show aggregated albumin; pale blue highlighting of band 3 was included in original to indicate full-length monomeric albumin).

The results for Exbumin and Cellastim after treatment with a reducing agent further demonstrate that Reducing SDS-PAGE alters samples to produce an artificially low content of aggregated albumin. *See supra* § II.A. For instance, where all the non-Reducing SDS-PAGE results from the previous charts showed greater than 2% aggregated albumin, the results from Reducing SDS-PAGE on the same products showed less than 2% aggregated albumin, even without redlining. Appx178-179.

REDUCING GEL

Cellastim S (2 µg), reduced, sample 1		
Band No.	Molecular Weight (kDa)	Band %
1	147.7	1.3
2	102.3	0.2
3	60.1	87.9
4	52.0	5.7
5	42.5	4.9

Cellastim S (2 µg), reduced, sample 2		
Band No.	Molecular Weight (kDa)	Band %
1	153.4	0.8
2	103.4	0.2
3	60.6	88.6
4	52.2	6.0
5	42.6	4.3

REDUCING GEL

Exbumin (2 µg), reduced, sample 1		
Band No.	Molecular Weight (kDa)	Band %
1	149.6	1.2
2	102.4	0.8
3	60.2	87.7
4	52.1	6.5
5	42.5	3.7

Exbumin (2 µg), reduced, sample 2		
Band No.	Molecular Weight (kDa)	Band %
1	155.5	1.1
2	103.4	0.3
3	60.9	89.1
4	52.6	5.2
5	42.9	4.3

Appx179 (annotations in original) (citing Appx3635-3636).

- (2) The ALJ determined that Ventria’s domestic investments for its six recombinant albumin products, combined, and for Optibumin alone, were “significant” and “substantial.”**

The ALJ found that Ventria satisfied the economic prong of the domestic-industry requirement under each of 19 U.S.C. § 1337(a)(3)(A), (B), and (C) on alternative bases: (1) through Ventria’s expenditures in its alleged six domestic-industry products from 2015 through 2020 of \$**dollar amount** in plant and equipment, \$**dollar amount** in labor, and \$**dollar amount** in research and development (Appx212-218); and (2) through Ventria’s expenditures in Optibumin alone from 2018 through 2020 of \$**dollar amount** in plant and equipment, \$**dollar amount** in labor, and \$**dollar amount** in research and development (Appx218-222).

As part of its Optibumin-only analysis, the ALJ included a discussion of unquantified investments outside Ventria’s sales-based allocation methodology, including unallocated pre-sales evidence of the development cycle of the product. Appx220-222.

2. Commission Review and Final Determination

- a. The Commission affirmed, with modification, the ALJ’s finding that Healthgen’s clinical grade products infringed.**

The Commission affirmed, with modification, the ALJ’s finding that Healthgen’s clinical grade products contained “less than 2% aggregated albumin” and thus infringed the asserted claims. Appx27-39.

The Commission first determined that Reducing SDS-PAGE is an appropriate technique for quantifying aggregated albumin in the accused products based on (1) the '951 patent's use of Reducing SDS-PAGE; (2) statements in the published literature regarding SDS-PAGE generally; and (3) test results on Healthgen's rHSA products. Appx20-25.

Specifically, the Commission found that the '951 patent "discloses that reducing SDS-PAGE was used to quantify the percent of aggregated albumin in numerous samples of rice-produced rHSA, including Ventria's Domestic Industry Product, Cellastim." Appx21. This finding was based on the '951 patent's statement that "*the new process samples have significantly less aggregates at around 250 KDa than the old process samples have. (Average greater than 2% for the old process, and average less than 1% for the new process).*" Appx21 (quoting Appx302[72:46-53]). The Commission stated that Healthgen's expert acknowledged that the '951 patent "reports aggregate quantification by reducing SDS-PAGE." Appx21 (citing Appx2275-2276[1250:23-1251:4] ("Q. . . . So this reports some quantification, does it not? A. It gives a range, yes, a greater than type number, yes.")). The Commission did not address, however, the fact that the Reducing SDS-PAGE discussion in the '951 patent discussed only "*aggregates at around 250 kDa*" (aggregates roughly four times larger than rHSA) that remained

after treatment with a reducing agent, rather than total aggregated albumin in an unaltered sample. Appx21 (quoting Appx302[72:46-53]).

The Commission next found that the published literature identifies Reducing SDS-PAGE as “a suitable, and recommended, analytical technique for quantifying aggregated albumin.” Appx22. As support, the Commission cited a publication by den Engelsman explaining, inter alia, that SDS-PAGE is a technique for quantifying “covalent aggregates” (Appx3465); that SDS-PAGE is used for “differentiation [between] disulfide mediated and non-disulfide mediated covalent aggregates” (Appx3457); that quantification by SDS-PAGE is “[p]ossible” (Appx3459 (Table IV)); and that the “presence of SDS means that non-covalent aggregates are disrupted, so the method only detects covalent aggregates. *If reducing conditions are used, SDS-PAGE can discriminate between aggregates held together by disulfide bonds and those held together by other (non-reducible) covalent bonds*” (Appx3461) (emphasis added). Appx22.

The Commission noted that den Engelsman and Mahler indicate that no technique for measuring aggregates is perfect, as “*each method covers different aggregate characteristics.*” Appx22-23. The Commission did not mention, however, that these papers recommend using more than one analytical method (“orthogonal methods”) to confirm that the applied method “provides adequate results.” Appx3465; Appx3381.

The Commission also discussed the testimony of Healthgen's expert, although none of the cited testimony indicates that Reducing SDS-PAGE is an appropriate technique for quantifying *total* aggregated albumin. Appx23.

Next, the Commission noted that for Healthgen's medium grade products, the results by Reducing SDS-PAGE were not much different from Native-PAGE. Appx23-24. The Commission acknowledged, however, that the clinical grade products are different from the medium grade products. Appx27.

Last, the Commission discussed the various results on Healthgen's clinical grade sample and stated that SEC-HPLC "showed that a sample of the clinical grade Accused Product had 0.8%⁶ or 1.1% aggregated albumin," while Reducing SDS-PAGE "showed at most 0.64% and 1.81% aggregated albumin." Appx24.

The Commission stated that it was "not persuaded by Healthgen's argument that reducing SDS-PAGE is an unreliable technique for measuring total aggregated albumin in the Accused Products." Appx24.

On the issue of infringement, the Commission did not adopt the analysis in the FID at pages 47-49 regarding some of Healthgen's communications with its customers, but affirmed the remainder of the ALJ's analysis. Appx29-30 (citing Appx158-160). The Commission stated that the SEC-HPLC data reporting 1.1%

⁶ It is unclear why the Commission referred to 0.8% aggregated albumin. It is possible that the Commission counted only the entry for dimers in Appx3135.

total aggregated albumin on a sample in China one day after manufacture were sufficient to establish that the product infringed. Appx31-32. The Commission found that Ventria's Reducing SDS-PAGE data "corroborated" that finding. Appx32. The Commission found that the SEC-HPLC data did not show the highest amount of aggregated albumin, as the level of aggregated albumin by SEC-HPLC was 1.1% in China, and the level of aggregated albumin in a sample from the same lot had increased to 1.81% in the United States (even after treatment with a reducing agent). Appx35. Despite the dramatic increase in aggregated albumin reflected in the data, the Commission found that "the evidence of record undermines" Healthgen's assertion that aggregation increases over time. Appx36.

b. The Commission determined that Healthgen's medium grade products do not infringe.

The Commission reversed the ALJ's finding that Healthgen's medium grade products infringed. Appx39-40. The Commission agreed with the ALJ that Healthgen prepares its clinical and medium grade products using a common intermediate product (Appx27), but also noted that the test data showed that the two products contained "dramatically different amounts of aggregated albumin." Appx44.

The Commission found that the ALJ "misconstrued" Healthgen's customer communications and "mistakenly" found that Healthgen's medium grade products contained "at most 0.001% aggregated albumin." Appx43. The Commission further

found that “testing data of actual medium grade Accused Products produced after the issuance of the Asserted Patent is far more probative than customer communications including data from nearly ten years prior to the issuance of the Asserted Patent.” Appx45; *see also* Appx53 (noting that the customer communications relied on in the FID “are from 2013 and 2011, respectively, and therefore prior to the issuance of the Asserted Patent”).

The Commission further found that “Healthgen calculates ‘purity’ by SDS-PAGE and SEC-HPLC as total albumin—monomer plus aggregates,” relying on actual data in making this determination. Appx47-48. The Commission noted that Ventria’s expert’s testimony that a Healthgen publication reported purity using an alternative calculation (i.e., as the percent monomeric albumin) was based on a “flawed recollection.” Appx47 n.38.

The Commission addressed other arguments advanced by Ventria and concluded that “[i]n contrast to the weighty pre-litigation testing evidence, Ventria’s evidence is weak and circumstantial.” Appx50; *see also* Appx52 (noting that the results of Ventria’s pre-litigation testing “show the presence of a significant amount of albumin species above the main band”).

- c. The Commission affirmed the ALJ's determination that Ventria's Optibumin product satisfied the domestic-industry requirement, but took no position on Ventria's five other rHSA products.**

The Commission adopted the ALJ's alternate finding that Ventria satisfied the domestic-industry requirement based on Optibumin alone. Appx54. The Commission did not provide an independent rationale. Appx54.

As to the other alleged domestic-industry products, the Commission found that "Healthgen has presented evidence that tends to show reducing SDS-PAGE may reduce the amount of measured aggregated albumin in Ventria's domestic industry products" Appx35 n.33. Accordingly, the Commission took no position on whether Ventria's other rHSA products, specifically, Exbumin, Cellastim, and products containing Cellastim (OptiPEAK, OptiVERO, and ITSE+A), practiced the '951 patent. Appx54-55; *Beloit Corp. v. Valmet Oy*, 742 F.2d 1421, 1423 (Fed. Cir. 1984). The Commission thus did not address whether it deemed Ventria's redlining of its Reducing SDS-PAGE data appropriate. Appx54-55.

III. SUMMARY OF THE ARGUMENT

To prove that Healthgen's clinical grade products infringed, Ventria needed to put forward evidence that an unaltered sample of Healthgen's clinical grade product contains less than 2% aggregated albumin in the United States. It did not. Ventria instead attempted to prove infringement using two sets of data, neither of which accurately measures the total amount of aggregated albumin in Healthgen's clinical grade product when it is imported into the United States.

First, Ventria relied on SEC-HPLC testing that occurred in China the day after manufacture. This extraterritorial testing fails to account for aggregation occurring during storage and shipping and thus substantially underestimates the amount of aggregated albumin in Healthgen's clinical grade product as it exists in the United States.

Second, Ventria's only testing of products in the United States was with Reducing SDS-PAGE, which requires pre-treating samples with a bond-breaking agent that artificially decreases the amount of aggregated albumin in a sample. Because Ventria did not provide any evidence demonstrating that an unaltered sample of Healthgen's clinical grade product contained less than 2% aggregated albumin in the United States, Ventria failed to prove its case.

The Commission also erred by finding that Ventria's investments in its Optibumin product alone are significant or substantial enough to satisfy the

domestic-industry requirement. Ventria's Optibumin-only investments were tiny, especially in comparison to Ventria's domestic-industry investments for its other five alleged domestic-industry products.

IV. ARGUMENT

A. Standard of review

The Commission’s final determinations are reviewed in accordance with the Administrative Procedure Act (“APA”), 5 U.S.C. § 706. *See* 19 U.S.C. § 1337(c). “The Supreme Court ‘has stressed the importance of not simply rubber-stamping agency factfinding The [APA] requires meaningful review; and its enactment meant stricter judicial review of agency factfinding than Congress believed some courts had previously conducted.’” *OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1382 (Fed. Cir. 2019) (citation omitted).

Under the APA, this Court must “set aside . . . conclusions found to be . . . arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law.” 5 U.S.C. § 706(2)(A); *Lelo Inc. v. Int’l Trade Comm’n*, 786 F.3d 879, 883 (Fed. Cir. 2015). The Commission’s legal determinations are reviewed de novo and its factual findings are reviewed for substantial evidence. *Guangdong Alison Hi-Tech Co. v. Int’l Trade Comm’n*, 936 F.3d 1353, 1358 (Fed. Cir. 2019). Substantial evidence is “such relevant evidence as a reasonable mind might accept as adequate to support a conclusion.” *Oak Tech., Inc. v. Int’l Trade Comm’n*, 248 F.3d 1316, 1324-25 (Fed. Cir. 2001) (quoting *Finnigan Corp. v. Int’l Trade Comm’n*, 180 F.3d 1354, 1362 (Fed. Cir. 1999)).

Infringement is a question of fact. *Kinik Co. v. Int’l Trade Comm’n*, 362 F.3d 1359, 1361 (Fed. Cir. 2004). “The question whether a complainant has satisfied the domestic industry requirement typically presents issues of both law and fact” *John Mezzalingua Assocs., Inc. v. Int’l Trade Comm’n*, 660 F.3d 1322, 1327 (Fed. Cir. 2011).

B. The Commission’s finding that Healthgen’s clinical grade products infringe should be reversed because there is no substantial evidence of infringement in the United States.

In finding that Healthgen’s clinical grade products infringe, the Commission relied on data taken (1) in China one day after manufacture, when the percentage of aggregated albumin is at its lowest, and (2) on a sample that had been altered by treatment with a bond-breaking agent that artificially reduces the number of albumin aggregates.

1. Pre-import SEC-HPLC data underestimate the amount of aggregated albumin in Healthgen’s clinical grade product in the United States.

To prove infringement, Ventria had to show that Healthgen’s clinical grade products contain “less than 2% aggregated albumin” when they are in the United States. *See Biotec Biologische Naturverpackungen GmbH & Co. v. Biocorp, Inc.*, 249 F.3d 1341, 1350 (Fed. Cir. 2001) (“Infringement of product claims by an imported product requires that the product be viewed in the form in which it is present within the United States.”); *see also Deepsouth Packing Co. v. Laitram*

Corp., 406 U.S. 518, 527 (1972) (“The statute makes it clear that it is not an infringement to make or use a patented product outside of the United States.”), *superseded in part by statute*, as codified at 35 U.S.C. § 271(f); *FastShip, LLC v. United States*, 892 F.3d 1298, 1304-05 (Fed. Cir. 2018) (noting that under 35 U.S.C. § 271(a), the patent owner must show that the alleged infringer “‘makes,’ ‘uses,’ or ‘sells’ the patented product within the bounds of this country” (citation omitted)); *Power Integrations, Inc. v. Fairchild Semiconductor Int’l, Inc.*, 711 F.3d 1348, 1371 (Fed. Cir. 2013) (“[The patent laws] do not thereby provide compensation for a defendant’s foreign exploitation of a patented invention, which is not infringement at all.”).

a. Data taken in China cannot be used to quantify aggregated albumin in the United States.

The Commission erroneously found that Ventria “met its burden of proof as to infringement of [Healthgen’s] clinical grade [products]” by relying on data from a certificate of analysis reporting that a sample of Healthgen’s clinical grade product had 1.1% aggregated albumin, as tested by SEC-HPLC in China one day after manufacture. *See* Appx30-31. These pre-import data, however, failed to account for the increase in the amount of aggregated albumin that occurs during shipping and storage, so they cannot demonstrate infringement. *Biotec*, 249 F.3d at 1350.

(1) Albumin aggregation increases during storage and shipment.

The Court in *Biotec* ultimately affirmed the district court’s finding of infringement in the United States, but only because the plaintiff had introduced evidence that the relevant product characteristic—water content—was the same both before and after import into the United States. *Id.* at 1351-52. In this case, however, the evidence indisputably shows not only that aggregation tends to occur during storage and shipment of these kinds of products, but also that aggregation *did* occur during the storage and shipment of the products that were tested.

Aggregation is not a fixed property. Appx3377-3381. It is undisputed that storage and shipment may cause an increase in aggregated albumin formation. *See* Appx1452[451:9-12] (Ventria’s expert agreeing that aggregate formation “can be induced by process and storage conditions”); Appx1456[455:11-21] (Ventria’s expert agreeing that aggregates “can be formed during production, storage, shipment, or delivery to the patient”); Appx2228[1203:5-19] (Healthgen’s expert testifying that “shipping overseas, the storage, the agitation of the sample, [and] temperatures during storage” could all result in increasing aggregated albumin when shipping samples from China to the United States).

Peer-reviewed articles confirm that aggregation can be caused by various conditions associated with storage or shipment. *See, e.g.,* Appx3380 (“Agitation stress such as stirring, pumping, and shaking during manufacturing and transport has

been described to cause aggregation.”); Appx3454 (“[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.” (citations omitted)).

Healthgen’s clinical grade products accommodate this expected increase in aggregation by allowing for up to 4% aggregated albumin throughout the life of the final product. *See, e.g.*, Appx3372 (allowing up to 1% polymer and 3.5% dimer aggregates, so long as they are less than 4% combined); Appx3367 (same); *see also* Appx1535-1536[533:12-534:4]. Therefore, Healthgen’s clinical grade products could contain an amount of aggregated albumin that exceeds the claimed “less than 2%” threshold and still meet the product specification. *See* Appx2222[1197:6-23]; Appx1535-1536[533:12-534:4] (Ventria’s expert admitting that the clinical grade product could be measured to have more than 2% aggregated albumin and still be within an acceptable range).

Because aggregation increases during shipping and storage, the SEC-HPLC data collected in China one day after manufacture do not represent the amount of aggregated albumin in the clinical grade products as they were imported into the United States. Ventria thus failed to prove infringement. *See Biotec*, 249 F.3d at 1350.

(2) Ventria's own testing confirmed that albumin aggregation actually occurred during storage and shipment of the accused products.

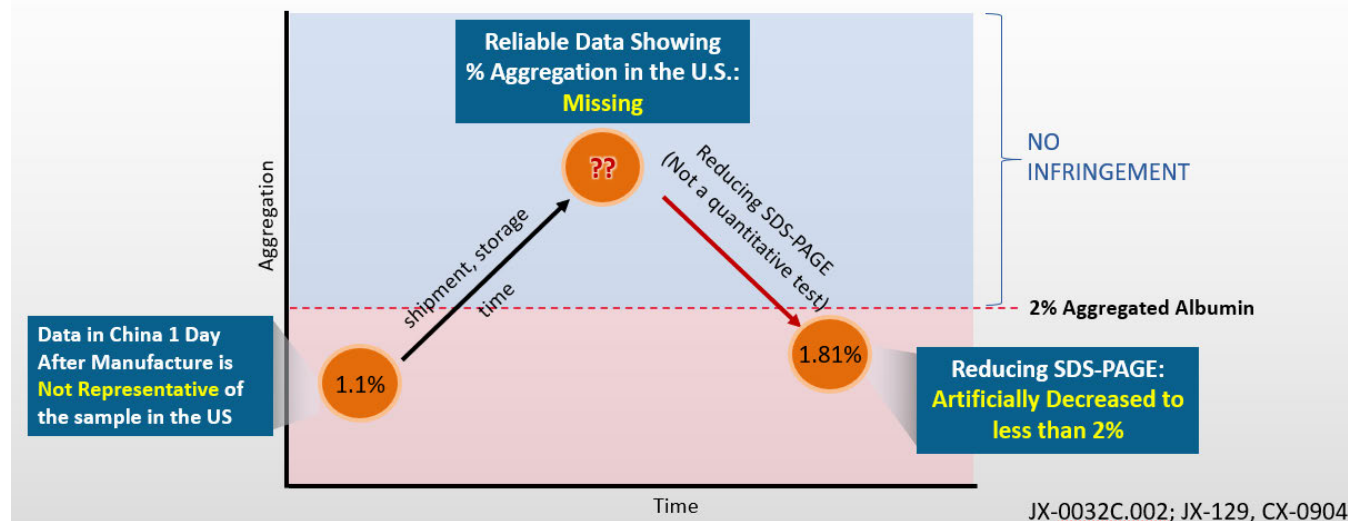
There can be no doubt that the level of aggregation in the Healthgen clinical grade product Ventria tested increased from the date of manufacture in China to when it was measured in the United States. Indeed, the amount of aggregation was so great that the increase was apparent even after the aggregate content was artificially reduced with a bond-breaking agent in the United States. *Compare* Appx3371-3372 (SEC-HPLC data taken in China one day after manufacture in September 2020 showing an aggregate content of 1.1%), *with* Appx3297 (Reducing SDS-PAGE data for HB012 Lot# HGEN-RPX-001 taken in the United States in June 2021 showing that the amount of aggregate remaining after treatment with a bond-breaking agent was 1.8%).⁷

While the data establish that the level of aggregation had increased from 1.1% (in a fresh sample) to 1.8% (in the same sample after storage, shipment, *and treatment with a bond-breaking agent*), it is unclear precisely *how much* it had increased upon the product's arrival in the United States in its native, unaltered state, because Ventria instructed its laboratory to pre-treat Healthgen's sample with a

⁷ As discussed below, *see infra* § IV.B.2, treatment with a bond-breaking agent decreases aggregation in Healthgen's clinical grade product.

bond-breaking agent (DTT⁸) before analysis. Appx3293-3295. The critical piece of missing data is depicted schematically below.

- **SGS's data: 1.81% aggregated albumin after shipment, storage, and bond-breaking agent.**



Appx3788; Appx2230[1205:8-14]; Appx2228-2229[1203:11-1204:18].

- b. The Healthgen documentation the Commission cited cannot be used to corroborate its erroneous speculation that aggregate content will be the same in the United States as in China.**

The Commission also pointed to several communications from Healthgen to its customers that “provide representations as to the stability of the rHSA protein over time periods up to 3 years” or show that “Healthgen tends to ship its products shortly after manufacture and under conditions that ensure the stability of the protein

⁸ DTT was also the bond-breaking agent used in the Reducing SDS-PAGE analysis summarized in Table 2, where Reducing SDS-PAGE observed two to three times less aggregated albumin than non-Reducing SDS-PAGE or SEC-HPLC. *See supra* § II.A.3; Appx3633.

(2-8° C).” Appx36-37. But these communications do not demonstrate that Healthgen’s clinical grade products contain less than 2% aggregated albumin after they are shipped to the United States.

For example, the Commission cited Healthgen’s communication to a customer stating that “long-term testing ‘indicated the OsrHSA has a stability property of 3 years in 2-8° C’” (Appx36 (quoting Appx3132)), and another communication to a customer that “concluded that stability testing of OsrHSA ‘indicated that OsrHSA is still stable in 40° C $\pm$ 2° C for 10 days, 25° C $\pm$ 2° C for 6 months and 2~8° C for 3 year[s]’” (Appx36 (quoting Appx3139)). These communications, however, simply confirm that Healthgen’s OsrHSA product remains “stable” within the specification of less than 4% aggregated albumin. *See* Appx3372.

The Commission also faulted Healthgen’s expert, Dr. DeFilippi, for having “no knowledge as to the way Healthgen ships or maintains the stability of its products.” Appx37. But it was not Healthgen’s burden to prove its products do not infringe; it was Ventria’s burden to prove that they do. *See Welker Bearing Co. v. PHD, Inc.*, 550 F.3d 1090, 1095 (Fed. Cir. 2008) (“[T]he burden remains with the patentee to prove infringement, not on the defendant to disprove it.”). And whatever steps Healthgen takes to keep the aggregates below 4%, there is no doubt that those

steps were not sufficient to prevent the aggregate content from increasing. *See supra* § II.C.1.b.

2. Reducing SDS-PAGE data cannot corroborate pre-import SEC-HPLC data because it artificially decreases the amount of aggregated albumin.

The Commission also found that the Reducing SDS-PAGE data Ventria presented at trial “further corroborated” Ventria’s infringement allegation that Healthgen’s clinical grade products are “within the scope of the claims’ ‘less than 2% aggregated albumin’ limitation.” Appx32-34. But the opposite is true. The Reducing SDS-PAGE data only underscore the Commission’s error.

a. Reducing SDS-PAGE cannot be used to measure whether Healthgen’s clinical grade products, as sold, contain “less than 2% aggregated albumin.”

Reducing SDS-PAGE cannot be used to quantify the total amount of albumin aggregates. It can only quantify aggregates linked by covalent bonds other than disulfide bonds, because disulfide-linked aggregates are broken apart during sample preparation. *See, e.g.*, Appx1858-1859[855:18-856:6]; Appx2206-2207[1181:17-1182:8]; Appx1468-1469[467:15-468:2]; Appx1504[503:14-19]; Appx3461.

Under the agreed-upon construction of “aggregated albumin,” all aggregates count. *See* Appx2892 (agreeing that construction of “aggregated albumin” is “[n]on-monomeric albumin (e.g., albumin dimers)”). Neither the ALJ nor the Commission sought to carve out any subset of aggregates from the term “aggregated albumin.”

Thus, the proper analysis requires determining whether a sample contains less than 2% aggregated (non-monomeric) albumin, not whether a sample contains less than 2% aggregated albumin linked by covalent bonds other than disulfide bonds. Yet, the latter is all that can be determined using Reducing SDS-PAGE. *See supra* § II.A.1.

It is undisputed that pre-treating a sample with a reducing agent—i.e., a bond-breaking agent—breaks up certain aggregates linked by covalent disulfide bonds. *See supra* § II.A.1. Reducing SDS-PAGE thus can and does provide an artificially low level of aggregated albumin in Healthgen’s clinical grade product, as aggregates that are linked by disulfide bonds are converted to single albumin units (e.g., monomers and fragments). *See supra* § II.C.1.a.

Therefore, this test cannot be used to prove infringement. *See High Tech Med. Instrumentation, Inc. v. New Image Indus., Inc.*, 49 F.3d 1551, 1555 (Fed. Cir. 1995) (“[A] device does not infringe simply because it is possible to alter it in a way that would satisfy all the limitations of a patent claim.”).

The inappropriateness of using Reducing SDS-PAGE to purportedly quantify aggregates in Healthgen’s clinical grade product is underscored by the availability of appropriate methods of quantification. For example, Ventria and Healthgen both use **test method** to quantify aggregates in their rHSA products. *See* Appx3372; *see supra* § II.D.1 (discussing Ventria’s use of **test method** to quantify aggregates in

Optibumin). And, as noted above, Ventria used Native-PAGE pre-litigation to analyze aggregation in Healthgen's medium grade products. *See supra* § II.A.2; Appx2187-2194[1162:17-1169:15]; Appx3748-3754. Additionally, Ventria's test laboratory SGS advertises its ability to quantify aggregates using appropriate techniques (not Reducing SDS-PAGE). Appx3628-3629.

Instead of selecting one of these appropriate methods of quantification, Ventria instructed its laboratory (SGS) to perform Reducing SDS-PAGE—a technique designed to decrease the level of aggregation in protein samples. *See* Appx3443 (noting that SGS “performed the assay as instructed by the sponsor”); Appx3293 (same). The only reason one would take the additional step of treating a sample with a reducing agent would be to break up aggregates linked by covalent disulfide bonds. *See* Appx2212-2213[1187:14-1188:6] (“[T]o the greatest extent possible, or to the extent possible, reducing SDS is breaking up these aggregates greater than – by greater than a factor of 2.”). Indeed, when carrying out Ventria's directive to use a reducing agent before analysis, SGS did not purport to quantify aggregated albumin. Rather, SGS captioned both its reports as “Study Report for Purity Analysis of rHSA Samples by SDS-PAGE under Reducing Condition.” Appx3441; Appx3291. Nothing in the text of the reports indicates that it was designed to quantify aggregated albumin—the word “aggregate” does not appear in either report. Appx3441-3448; Appx3291-3298.

The Commission erred by failing to confront these facts in its analysis.

b. The Commission's reasons for accepting Reducing SDS-PAGE data to measure aggregated albumin are flawed.

The Commission rationalized its reliance on Reducing SDS-PAGE data (Appx20-25), but each aspect of the Commission's discussion contradicts the evidence of record and is not supported by substantial evidence.

First, the Commission erred when it found that the '951 patent's disclosure of Reducing SDS-PAGE supports the use of Reducing SDS-PAGE to quantify whether a sample contains "less than 2% aggregated albumin." Appx20-21 (quoting Appx302[72:46-54]). The '951 patent does not disclose quantifying total aggregated albumin using Reducing SDS-PAGE. Rather, it states that the results of Reducing SDS-PAGE showed "significantly less aggregates *at around 250 KDa* than the old process samples have. (Average greater than 2% for the old process, and average less than 1% for the new process)." Appx302[72:51-54] (emphasis added). But this passage does not even specify that the aggregates are albumin (as opposed to impurity proteins). Moreover, aggregates at 250 kDa account for only a subset of the total present, i.e., aggregates with a mass at around 250 kDa remaining after treatment with a bond-breaking agent. Therefore, this example does not report the quantity of *total aggregated albumin* as the claims require. *See* Appx2892.

Next, the Commission found that Dr. DeFilippi “acknowledged” that the ’951 patent “reports aggregate quantification by reducing SDS-PAGE.” Appx21 (citing Appx2275-2276[1250:23-1251:4]). But while Dr. DeFilippi agreed that the Reducing SDS-PAGE analysis in the ’951 patent “reports *some* quantification” of aggregated albumin, he did not state that this analysis reported a quantity of *total* aggregated albumin. Appx2275-2276[1250:23-1251:4] (emphasis added). To the contrary, he explicitly testified that no technique in the ’951 patent was used to quantify the amount of total aggregated albumin. *Compare id.*, with Appx2219[1194:19-21] (Dr. DeFilippi answering “[n]ot quantifying, no” in response to being asked whether “the ’951 patent quantif[ied] the total aggregated albumin including dimers using any technique”). Indeed, Dr. DeFilippi explained that the ’951 patent reported observing dimers by SEC-HPLC, yet those dimers—aggregated albumin—were not quantified using any technique and may not have even been detected using Reducing SDS-PAGE. Appx2219[1194:2-18]; *see* Appx302[72:18-21] (noting the presence of a “Cellastim dimer peak” around 130 kDa by SEC-HPLC).

As discussed above, Reducing SDS-PAGE can only “quantify” what it observes, i.e., the aggregates that remain in samples after being treated with a bond-breaking agent under various conditions, where the conditions used to break up aggregation in the sample may change the purportedly “quantified” results.

See supra § II.A.1. The Commission erred by not asking what is being quantified. It is true that SDS-PAGE may be used to determine the percentages/quantities of the species observed, even for samples pre-treated with a reducing/bond-breaking agent. But no percentages/quantities can be generated for species that are destroyed during sample preparation.

The Commission also erred when it found that “the peer-reviewed literature of record discloses that *reducing* SDS-PAGE is a suitable, and recommended, analytical technique for quantifying aggregated albumin.” Appx22-23 (emphasis added). Here, the Commission erroneously relied on discussions of SDS-PAGE generally (where results both with and without a reducing agent are compared) as purported support for using Reducing SDS-PAGE in isolation, without SDS-PAGE on a non-reduced sample for comparison.

For example, the Commission quoted an article by den Engelsman stating that “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” and lists SDS-PAGE and CE-SDS as “robust, quantifiable methods for QC testing.” Appx22 (footnotes omitted) (quoting Appx3465). However, the cited passage does not mention Reducing SDS-PAGE or suggest that only Reducing SDS-PAGE could be used to quantify the amount of total aggregated albumin in a given product. Appx3465. It instead discusses SDS-PAGE. The

Commission also selectively excerpted den Engelsman's warning that SEC and SDS-PAGE involve "sample preparation methods which may *impact the result both qualitatively and/or quantitatively*." Appx3465 (emphasis added).

The Commission also cited other pages of den Engelsman as purportedly describing Reducing SDS-PAGE "as suitable for quantification of aggregates," but none of these additional pages say that. Appx22 (citing Appx3457; Appx3459; Appx3461). For example, den Engelsman describes the use of SDS-PAGE generally as a technique for "differentiation [of] disulfide mediated and non-disulfide mediated covalent aggregates." Appx3457. This differentiation is possible by comparing the results collected using non-Reducing SDS-PAGE—where no reducing agent was used—with results collected using Reducing SDS-PAGE—where the sample was altered with a reducing agent to break covalent disulfide bonds. Appx3461 ("If reducing conditions are used, SDS-PAGE can discriminate between aggregates held together by disulfide bonds and those held together by other (non-reducible) covalent bonds."). By comparing the results of SDS-PAGE (on a non-reduced sample) to the results of Reducing SDS-PAGE (on a reduced sample), the level of aggregates linked by disulfide bonds may be determined. *See* Appx3461. Thus, this section of den Engelsman is describing a comparative technique that discriminates between different *types of aggregates*; it is not quantifying *total aggregation*. Appx3461.

On another page cited by the Commission, den Engelsman indicates that quantification is “[p]ossible” with SDS-PAGE (Appx3459 (Table IV)), while simultaneously reporting that “[i]f reducing conditions are used, SDS-PAGE can discriminate between aggregates held together by disulfide bonds and those held together by other (non-reducible) covalent bonds” (Appx3461). It mentions nothing of using Reducing SDS-PAGE by itself to quantify the total amount of aggregated albumin in a sample.

The Commission further erred in its reliance on den Engelsman’s conclusion, and Mahler’s similar conclusion, that “*no single method covers the analysis of all aspects of aggregates*” and, “[*a*]*s each method covers different aggregate characteristics, the results obtained with a particular method are strictly linked to that method.*” Appx22 (quoting Appx3464); *see also* Appx22-23 (citing Appx3377-3402). But that no technique is perfect does not mean that one must resort to a technique known to artificially decrease the quantity of aggregates—i.e., Reducing SDS-PAGE—to determine whether a sample contains “less than 2% aggregated albumin.” Rather, if one is truly interested in quantifying the total level of aggregated albumin, den Engelsman and Mahler both recommend using more than one analytical method (“orthogonal methods”) to confirm that “the applied method, e.g.

SEC[-HPLC], provides adequate results.”⁹ Appx3465; Appx3381 (recommending the use of orthogonal methods, i.e., a “combination or a variety of different analytical methods, each having its own characteristic measuring principle, for example, by size, quantification or structure, etc.”). Notably, Ventria’s test laboratory, SGS, also recommends using “orthogonal analytical techniques,” including size-exclusion chromatography with multi-angle laser light scattering (“SEC-MALS”) to provide a quantitative assessment of aggregates. Appx3628-3629.

The Commission failed to appreciate that if a method (here, Reducing SDS-PAGE) provides results that vary by a factor of three (i.e., 0.64% to 1.8%), it is not an appropriate method. *Compare* Appx3447 (HB012 Lot# HGEN-RPX-001), *with* Appx3297 (HB012 Lot# HGEN-RPX-001). But using orthogonal techniques (as recommended by den Engelsman and Mahler), it is possible to quantify aggregates with precision. For example, data provided by Healthgen’s independent laboratory show that, with one exception, SEC-HPLC and *non-Reducing SDS-PAGE* provided results that were relatively consistent. *See supra* § II.A.3 (Table 2). By contrast, Reducing SDS-PAGE *on the same samples* showed two to three times less aggregated albumin than SEC-HPLC or non-Reducing SDS-PAGE. In all cases,

⁹ The potential disadvantage of SEC-HPLC is that it may not observe very large insoluble aggregates. Appx3382. However, SDS-PAGE (under any conditions) has the same shortcoming and is capable of observing an even narrower range of protein sizes than SEC-HPLC. Appx3383.

using orthogonal techniques (i.e., SEC-HPLC and non-Reducing SDS-PAGE) established that Reducing SDS-PAGE did not provide adequate results.

The Commission further erred when it found that Dr. DeFilippi's use of Reducing SDS-PAGE in his invalidity and noninfringement analyses suggests that Reducing SDS-PAGE is an appropriate method for determining whether Healthgen's clinical grade products contained "less than 2% aggregated albumin." *See* Appx23 (citing Appx2194-2195[1169:16-1170:15]). In the context of invalidity, Dr. DeFilippi explained that the prior-art reference in question (Van Urk) did not use Reducing SDS-PAGE to quantify aggregated albumin. Appx1858[855:5-7]. Rather, Dr. DeFilippi explained that Van Urk discloses a separate technique, gel permeation HPLC (which is the same as SEC-HPLC, *see* Appx2215[1190:17-22]), which is appropriate for quantifying aggregated albumin. Appx1860-1862[857:15-859:17]; Appx3694.

Additionally, in the context of noninfringement, Dr. DeFilippi relied on Reducing SDS-PAGE to show that certain accused products had *more than 2%* aggregated albumin. *See* Appx2194-2195[1169:16-1170:15] (Dr. DeFilippi testifying that "[e]ach band alone is greater than the 2 percent"). Reducing SDS-PAGE could be used to confirm that a product has *more than 2%* aggregated albumin because a product that has more than 2% aggregated albumin even *after* being treated with a reducing agent would necessarily have had more than 2% aggregated albumin

before being treated with a reducing agent. *See* Appx2207-2208[1182:19-1183:5] (Healthgen’s expert testifying that Reducing SDS-PAGE could be used to show more than 2% aggregated albumin). Conversely, it is inappropriate to use Reducing SDS-PAGE to confirm whether a product has *less than 2%* aggregated albumin because Reducing SDS-PAGE artificially decreases the amount of aggregated albumin in the sample. *See* Appx2207[1182:14-18] (Healthgen’s expert testifying that Reducing SDS-PAGE “would not be reliable” for showing that a product contains less than 2% aggregated albumin). Therefore, the Commission’s criticism of Dr. DeFilippi on these grounds is unfounded.

The Commission’s statement that “the use of analytical techniques measuring aggregated albumin that use a surfactant and a reducing agent provide largely similar results as techniques that do not use those reagents” (Appx23) defies logic. The Commission compared three different flawed test results (one SEC-HPLC performed before shipping and storage and two Reducing SDS-PAGE tests performed after the products were shipped to the United States and altered with bond-breaking agents that reduce aggregated albumin) without ever demonstrating that any of these test methods are appropriate.

The Commission’s statement about “similar results” across the techniques likewise is illogical. Its comparison of the SEC-HPLC data with the two additional tests using Reducing SDS-PAGE fails to account for the SEC-HPLC data having

been taken in China only one day after manufacture, i.e., at a time when albumin aggregation is at its lowest and before shipping and storage conditions would increase the amount of aggregated albumin. *See supra* § II.C.1. Therefore, that the SEC-HPLC test result taken in China is “in between the two [reducing] SDS-PAGE test results” and “does not show the highest amount of aggregated albumin of the three tests” is of no moment. Appx24. Had the samples that were analyzed by Reducing SDS-PAGE in May and June 2021—several months after manufacture and after shipping to the United States—been tested using an appropriate method such as SEC-HPLC, the amount of aggregated albumin would have been greater than 1.81% (the amount observed after treatment with a bond-breaking agent) and “very, very likely” would have been above 2%. *See* Appx2228[1203:11-19]; Appx2230[1205:8-14]. Moreover, as the Commission acknowledged, the Reducing SDS-PAGE data that resulted in 0.64% and 1.81% aggregated albumin used “markedly different” testing conditions, including bond-breaking/reducing agents of varying strengths. *See* Appx35. The May 2021 Reducing SDS-PAGE testing that resulted in 0.64% aggregated albumin used TCEP, a “relatively strong bond-breaking agent” (*see* Appx2224[1199:3-6]; Appx3441-3448), while the June 2021 Reducing SDS-PAGE testing that resulted in 1.81% aggregated albumin used DTT, another strong bond-breaking agent that is relatively weaker than TCEP (*see* Appx2224[1199:18-21]; Appx3291-3298). This relative difference in strength of the

bond-breaking agents between the two tests likely explains the difference in results: the stronger bond-breaking agent TCEP broke apart more aggregated albumin (resulting in the formation of over 3% albumin fragments) than did the relatively weaker bond-breaking agent DTT. That Reducing SDS-PAGE provides such starkly different results depending on the type of bond-breaking/reducing agent employed establishes that it cannot be an appropriate test for quantifying aggregated albumin in Healthgen's clinical grade product.

Finally, the Commission's statement that Healthgen's expert, Dr. DeFilippi, did not "criticiz[e] or disput[e]" the Reducing SDS-PAGE conditions or protocol, or that he "agreed during cross-examination that 'three test results on the same batch' of OsrHSA clinical grade product 'showed results of less than 2 percent aggregated albumin,'" is irrelevant and misses the point. Appx34 (quoting Appx2304-2307[1279:4-1282:14]). Dr. DeFilippi opined that all three test results were flawed—(1) the SEC-HPLC data taken in China failed to account for aggregation caused by shipping and storage, and (2) the Reducing SDS-PAGE data artificially lowered the amount of aggregated albumin due to the use of a reducing agent. *See* Appx2221-2222[1196:14-1197:18]. Dr. DeFilippi thus did not need to pick apart the individual conditions or protocols used in the testing to disagree with the appropriateness of the timing or type of test used to determine the total amount of aggregated albumin after the product is imported into the United States.

C. The Commission erred in finding that Ventria satisfied the domestic-industry requirement because Ventria's investments in the only product that practices the '951 patent are neither "significant" nor "substantial."

The domestic-industry requirement "includes an economic prong, which 'requires that there be an industry in the United States,' and a technical prong, which 'requires that the industry relate to articles protected by the patent,' both of which must be met." *Philip Morris Prods. S.A. v. Int'l Trade Comm'n*, 63 F.4th 1328, 1341 (Fed. Cir. 2023) (quoting *InterDigital Commc'ns, LLC v. Int'l Trade Comm'n*, 707 F.3d 1295, 1298 (Fed. Cir. 2013)). Only the economic prong is at issue in this appeal.

The economic prong considers whether "there is in the United States, with respect to the articles protected by the patent, . . . (A) significant investment in plant and equipment; (B) significant employment of labor or capital; or (C) substantial investment in its exploitation, including engineering, research and development, or licensing." 19 U.S.C. § 1337(a)(3); *Certain Variable Speed Wind Turbines and Components Thereof*, Inv. No. 337-TA-376, 1996 WL 1056330, at *13 (USITC Nov. 1, 1996). These activities "must pertain to products covered by the [asserted] patent." *Hyosung*, 926 F.3d at 1361 (alteration in original) (quoting *InterDigital*, 707 F.3d at 1297-98).

The Commission adopted the ALJ's finding that Ventria's investments in Optibumin alone satisfied the economic prong of the domestic-industry requirement. Appx54-55. But in endorsing the ALJ's Optibumin-only analysis, the Commission

erred either by approving investments that do not meet the statutory requirement of being “significant” or “substantial” or by violating this Court’s prohibition against substituting qualitative factors for quantitative significance or substantiality under Section 337. *Lelo*, 786 F.3d at 883-84 (“The plain text of § 337 requires a quantitative analysis in determining whether a petitioner has demonstrated a ‘significant investment in plant and equipment’ or ‘significant employment of labor or capital.’”); *see also Hyosung TNS Inc. v. Int’l Trade Comm’n*, 926 F.3d 1353, 1361 (Fed. Cir. 2019).

1. Ventria’s claimed investments in Optibumin are quantitatively small.

Ventria’s claimed investments in Optibumin are very low in both absolute and relative terms. For the words “significant” and “substantial” to have any meaning in the context of 19 U.S.C. § 1337, Ventria’s modest investments in Optibumin alone cannot satisfy the economic prong.

The facts underlying Ventria’s investments in Optibumin are undisputed: Ventria claimed approximately \$dollar amount in plant and equipment related to Optibumin out of \$dollar amount originally claimed for its six rHSA products, approximately \$dollar amount in labor related to Optibumin out of \$dollar amount originally claimed for its six domestic-industry products, and approximately \$dollar amount in research and development related to Optibumin out of \$dollar amount originally claimed for its six domestic-industry products. 19 U.S.C. § 1337(a)(3)(A)-(C); Appx219; Appx54-55;

see also Appx1738-1739[736:21-737:8]; Appx1739-1740[737:24-738:16]; Appx1744-1745[742:10-743:10]; Appx3327; Appx3333; Appx3338; Appx2341-2345[1316:16-1320:5]; Appx3632; Appx3823-3824. It was Ventria and its sales-based allocation formula that calculated these figures, which represent approximately % inv of Ventria's total investments over a six-year period. Appx1738-1739[736:21-737:8]; Appx1739-1740[737:24-738:16]; Appx1744-1745[742:10-743:10]; Appx3327; Appx3333; Appx3338; Appx2341-2345[1316:16-1320:5]; Appx3632.

Ventria's Claimed Domestic Investments (2015-2020)				
Type of Expenditure	Claimed Total Expenditures	Claimed Total DI Allocation	Claimed Optibumin Allocation	Optibumin's Share of Total/ Total DI
Plant and Equipment (A)	\$dollar amount	\$dollar amount	\$dollar amount	% inv. / % inv.
Labor Expenditures (B)	\$dollar amount	\$dollar amount	\$dollar amount	% inv. / % inv.
Research & Development (C)	\$dollar amount	\$dollar amount	\$dollar amount	% inv. / % inv.

Appx1668-1669[666:2-667:6]; Appx1676-1685[674:1-683:22]; Appx1738-1745[736:4-743:5]; Appx2341-2345[1316:16-1320:5]; Appx3632; Appx3152-3239; Appx3240-3241; Appx3242-3260; Appx3261-3267; Appx3268; Appx3270-

3278; Appx3427-3429; Appx3140-3142; Appx3143-3145; Appx3146-3148; Appx3149-3151; *see also* Appx3327; Appx3333; Appx3338; Appx3823; Appx219.

The Commission, via the FID, affixed the title of “significance” and “substantiality” to these investments—but in doing so removed any meaning from those words. Appx54-55; Appx219-222. The FID acknowledged Healthgen’s argument that Ventria’s “Optibumin® sales were actually meager” (Appx220), but it attempted to explain away this meagerness with flawed “quantitative” analyses and qualitative considerations (Appx219-222). Any attempt to label Ventria’s investments as “significant” or “substantial,” however, both ignores the paucity of Ventria’s investments and allows qualitative considerations to compensate for facially deficient investments.

2. The qualitative value of Ventria’s claimed investments in Optibumin cannot compensate for their quantitative deficiency.

The Commission attempted to undergird its finding that Ventria satisfied the economic prong by citing several tests: (a) a foreign-to-domestic investments comparison, (b) a revenue-to-investments comparison for research and development, (c) an attribution of uncontended and unallocated alleged investments, and (d) a comparison of research-and-development expenditure ratios with non-competitor companies. Appx54 (citing Appx211-222). None of these tests, however,

provided useful, quantitative contextual analysis in the context of the ITC's Investigation—and none of them supported a finding of domestic industry.

- a. The mere fact that investments are entirely within the United States, without more, cannot transform “small” investments into “significant” or “substantial” ones.**

The Commission held, “[I]t is notable that 100% of Ventria’s investments in Optibumin® occur in the United States. . . . [T]his weighs heavily in favor of finding that Ventria’s investments are significant and substantial.” Appx219-220. The Commission appeared to recognize that a complainant operating entirely within the United States does not automatically transform *any* investments (no matter how low) into “significant” or “substantial” investments. *See generally Certain Stringed Musical Instruments and Components Thereof*, Inv. No. 337-TA-586, 2008 WL 2139143 (USITC May 16, 2008) (complainant’s operations were located entirely in the United States but nonetheless found insignificant and insubstantial). The Commission, however, identified nothing more and the locus of operation improperly became dispositive in this instance. Appx219-222. 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, 2011 WL 7628059, at *20 (USITC Nov. 1, 2011).

Ventria’s extremely low sales of Optibumin underscores the limited probative benefit of a foreign-versus-domestic investments comparison in this context, particularly when other quantitative contextual tests are available. Finding investments significant or substantial merely because they 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.

b. Manufacturing an “investments-to-revenues” analysis to create a larger number from two smaller numbers cannot support a finding of “significant” or “substantial.”

The Commission also improperly gave credence to a contrived investments-to-revenues analysis, which compared the allocated dollar investments in a product to the actual dollar revenues from a product. Appx220. 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 alleged that its plant-and-equipment expenditures in Optibumin from 2018 to 2020 comprised % rev. of its revenue for Optibumin, its labor expenditures comprised % rev. of revenue, and its research-and-

development expenditures comprised % rev. of revenue. Appx220. But that contrived quasi-analysis may simply reflect that Ventria failed to sell much of its product. Moreover, applying this analysis across all six of Ventria's rHSA products for the 2015 to 2020 timeframe results in allocated expenditures in plant-and-equipment at % rev. of revenue, labor at % rev. of revenue, and research-and-development at % rev. of revenue. Ventria's investment-to-revenue ratio in Optibumin is thus unexceptional compared to the other alleged domestic-industry products, while its numerical investments compared to the other rHSA products are tiny in comparison. Ventria's argument also hides the economic reality that Ventria's allocated investments in Optibumin account for roughly just % inv of its total investments. *See* Appx219-222.

c. The Commission cannot rely on unidentified and unallocated investments to compensate for fatal deficiencies in Ventria's own claimed investments.

More problematic, the Commission improperly credited unidentified "investments" in research and development 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 supra* § II.E.1.b.(2); Appx1738, 736:7-20).

The ALJ acknowledged that Ventria did not provide any evidence of domestic-industry investments in Optibumin before 2018 (Appx221), but

nonetheless attributed some unknown and undisclosed portion of an alleged \$dollar amount increase in “product development” to Ventria’s Optibumin investments, alleging the spending was “due at least in part to investments in Optibumin®” (Appx222). If Ventria had actually made any of these expenditures for Optibumin, it could have and should have produced evidence of them during fact and expert discovery. Ventria instead presented no evidence (and the ALJ cited none) that any of those alleged investments related to the domestic-industry products generally or to Optibumin specifically—Ventria and the ALJ merely alleged some portion might relate to Optibumin. Under the Commission’s own precedent, a generic claim without any analysis is not—and cannot be—enough. *See Certain Electronic Stud Finders, Metal Detectors and Electrical Scanners*, Inv. No. 337-TA-1221, 2022 WL 834280, at *28-29 (USITC Mar. 14, 2022) (finding no domestic industry where the complainant failed to allocate alleged investments among different domestic-industry products).

Ventria’s own expert attributed less than \$dollar amount to research-and-development spending for Optibumin, and these were the *only* contentions of research-and-development investments in Optibumin that Ventria advanced during the entire Investigation. Appx1738-1739[736:21-737:8]; Appx1739-1740[737:24-738:16]; Appx1744-1745[742:10-743:10]; Appx2341-2345[1316:16-1320:5]; Appx3632; Appx3327; Appx3333; Appx3338; Appx3823. The ALJ’s attempts to

backfill Ventria's own claimed investments with some undisclosed and unallocated amount is inappropriate and constitutes clear error.

d. The Commission's reliance on comparative data from other, much larger, publicly traded companies was based on a logical fallacy that data is relevant because it is the only data available.

The Commission also concluded Ventria's investments were significant by comparing its research-and-development expenditures to revenue ratios to those of publicly traded "peers" suggested by Mr. Deeter. Appx218 n.36; Appx220 n.38. In addition to the Commission providing no explanation of the relevance for this ratio to a domestic-industry analysis, no witness ever explained why Ventria, a relatively young, privately held company, was a "peer" to Repligen and BioLife Solutions, two decades-old, publicly traded biotech companies with very different corporate structures, numbers of products, and numbers of employees; consequently, it lacks any meaningful comparison to aid context. *See* Appx1749-1751[747:1-749:6]. The Commission acknowledged that these two companies are "not competitors" of Ventria, but it employed the analysis regardless because "they are publicly-traded companies and thus, [Ventria's expert] had access to their publicly-available data." Appx218 n.36. This is a classic example of the *Streetlight Effect*: the logical error of

relying on data, not because it is relevant, but because it is easy to find.¹⁰ This logic is just as inappropriate here as it is everywhere else, and this Court should reject it.

3. Ventria’s failure to prove that its five other domestic-industry products practice the ’951 patent necessitates reversal on domestic industry instead of remand.

In adopting the ALJ’s finding that Ventria satisfied the economic prong of the domestic-industry requirement through its investments in Optibumin alone, the Commission took no position on the ALJ’s other basis for finding domestic-industry—that is, based on investments in all six Ventria domestic-industry products (including Optibumin). The Commission used the “single dispositive issue approach” afforded by this Court to rely only on Optibumin investments in deciding the economic prong. *Beloit*, 742 F.2d at 1423.

As this Court stated in *Beloit*, however, that approach “carries with it a risk—here the risk of a reversal, and a consequent need for the Commission to revisit one or more portions of the initial determination on which it had taken no position.” *Id.*

¹⁰ The *Streetlight Effect* is a frequent subject of economics and scientific literature, illustrated by the example of a man crawling on his hands and knees under a streetlight looking for his lost wallet. When asked by a police officer why he is not looking across the street where he dropped it, the man explains, “Because the light’s better here.” David H. Friedman, *Why Scientific Studies Are So Often Wrong: The Streetlight Effect*, Discover (Dec. 9, 2010) (“Researchers tend to look for answers where the looking is good, rather than where the answers are likely to be hiding.”) (<https://www.discovermagazine.com/the-sciences/why-scientific-studies-are-so-often-wrong-the-streetlight-effect> (last visited May 23, 2023)).

Such is the case here—or, rather, would be, if the other five-product option remained available to the Commission; however, because the ALJ relied on the wrong test to determine whether Ventria’s products practice the ’951 patent (*see supra* § II.E.1.b.(1)), the Commission’s “*Beloit-ing*” of the economic prong has greater consequences.

For the same reasons that Healthgen’s medium grade products do not practice the ’951 patent, as the Commission correctly found, so Ventria’s medium grade domestic-industry products also do not practice the ’951 patent, i.e., they have more than 2% aggregated albumin when analyzed using an appropriate test. Thus, Ventria’s five non-Optibumin domestic-industry products—Cellastim, Exbumin, OptiPEAK, OptiVERO, ITSE+A—would not be available for use in an alternate economic prong analysis.

V. CONCLUSION

For the foregoing reasons, the Commission’s determinations that Healthgen’s clinical grade products infringe and that Ventria established a domestic industry should be reversed.

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