

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NOVARTIS GENE THERAPIES, INC. &
NOVARTIS PHARMACEUTICALS CORPORATION,
Petitioner

v.

GENZYME CORPORATION,
Patent Owner.

Case: IPR2023-01044
Patent No. 10,429,288

PATENT OWNER'S PRELIMINARY RESPONSE

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TABLE OF EXHIBITS

Exhibit	Description
2001	Declaration of Jeffrey C. Hansen in Support of Patent Owner's Preliminary Response ("Hansen")
2002	Jeffrey C. Hansen, Curriculum Vitae
2003	Burnham <i>et al.</i> , Analytical Ultracentrifugation as an Approach to Characterize Recombinant AAV Vectors, 26 <i>Human Gene Therapy Methods</i> 228 (2015) ("Burnham 2015")
2004	F. Collaud <i>et al.</i> , Preclinical Development of an AAV8-hUGT1A1 Vector for the Treatment of Crigler-Najjar Syndrome, 12 <i>Molecular Therapy: Methods & Clinical Development</i> 157, 166-67 (March 2019)
2005	E. Spies, Assessing the Quality of Adeno-Associated Virus Gene Therapy Vectors by Sedimentation Velocity Analysis, <i>AUC Insights</i> (March 2020)
2006	Q. Xie <i>et al.</i> , The Atomic Structure of Adeno-Associated Virus (AAV-2), a Vector for Human Gene Therapy, 99 <i>PNAS</i> 10405-410 (Aug. 6, 2002)
2007	J.M. Sommer <i>et al.</i> , Quantification of Adeno-Associated Virus Particles and Empty Capsids by Optical Density Measurement, 7 <i>Molecular Therapy</i> 122-28 (January 2003)
2008	T. Matsushita et al., Adeno-Associated Virus Vectors Can Be Efficiently Produced Without Helper Virus, 5 <i>Gene Therapy</i> 938-45 (February 10, 1998)
2009	J.F. Wright, Product-Related Impurities in Clinical-Grade Recombinant AAV Vectors: Characterization and Risk Assessment, 2 <i>Biomedicines</i> 80-97 (March 3, 2014)

I. INTRODUCTION

Clinical application of recombinant adeno-associated virus (“rAAV”) vector-based gene therapy requires quantifying the different species of rAAV particles, which may include empty, intact, and variant viral particles. The invention underlying U.S. Patent No. 10,429,288 (Ex. 1001, the “’288 patent”) provides a breakthrough application of analytical ultracentrifugation (“AUC”) to quantitatively characterize rAAV preparations as part of the manufacturing and purification process. Prior to this invention, there was no adequate technique that, in a single experiment, could achieve these necessary analytical results. This unsolved need presented significant impediments to the characterization and overall viability of gene therapy treatments that depend on accurate purity and potency.

Petitioners, Novartis Gene Therapies, Inc. and Novartis Pharmaceuticals Corporation (“Novartis”) filed *Inter Partes* Review (“IPR”) petition IPR2023-01044 (the “Petition” or “1044IPR”) challenging claims 1-3 and 17-34 (the “challenged claims”) of U.S. Patent No. 10,429,288 (Ex. 1001, the “’288 patent”) as anticipated and obvious.¹ The Petition fails to demonstrate by a

¹ Novartis also filed a parallel petition, IPR2023-01045 (the “1045IPR”), challenging claims 4-16 of the ’288 patent.

reasonable likelihood that the prior art disclosed or rendered obvious the challenged claims.

Prior to the '288 patent, it was known that the preparation of rAAV vectors often results in heterogenous mixtures containing “empty viral particles, full genome-containing viral vectors, and vectors with fragmented genomes or non-transgene-related DNA contaminants.” Ex. 2003, 228; *see also, e.g.*, Ex. 2009, 81, 86-89; Ex. 1001, 47:49-56; Ex. 2001 (“Hansen”); ¶¶ 35-41. The “generation of AAV vector products requires an analytical method that monitors product quality with regard to homogeneity, purity, and consistency of manufacturing,” yet prior to the '288 patent methods, “no method to support AAV vector characterization ha[d] been established.” Ex. 1001, 43:10-14.

To this day, the AUC method claimed in the '288 patent represents an important advance in the manufacturing process for rAAV preparations, the industry standard for detection of rAAV species and a practical and useful release assay. The prior method for detecting rAAV species, Southern blot, used a specific complimentary DNA probe sequence to detect rAAV species, but these probes could miss the presence of key species. *Id.*, 51:42-63. In a single experiment, the AUC method enables the detection and quantification of multiple rAAV species that either evaded detection or required multiple Southern blot experiments with different probes for accurate detection. *Id.*

The only independent claims challenged by this Petition, claims 1 and 2, are the result of the inventors' pioneering the use of sedimentation distribution plots to determine the relative concentrations of partial or fragmented genomes in rAAV preparations. *Id.*, 48:63-50:17. Claim 1, Element 1[c] recites "integrating the area under ***each peak*** in the C(s) distribution to determine the relative concentration of ***each peak***..."

In Ground 1, Novartis alleged that claim 1 was anticipated by Le Bec. Petition, 22-28. Le Bec, however, fails to disclose at least Element 1[c] of claim 1, particularly with respect to peaks not corresponding to empty capsids or fully intact rAAV particles. *Infra* Section IV.A. Novartis's anticipation Ground fails because it provides no argument for how Le Bec integrates and determines the area of each peak to determine the relative concentration of each peak, here, including partial and fragmented species. Le Bec would have to be modified to change the detection technique and provide a means to identify partial and modified genome species and thus cannot anticipate the challenged claims. *St. Jude Med., LLC v. Snyders Heart Valve LLC*, 977 F.3d 1232, 1239 (Fed. Cir. 2020) (finding a "fundamental problem" with an anticipation argument that "simply does not address" a claim element).

Novartis's Ground 2 argument, alleging Le Bec alone renders claim 1 obvious based on the POSA's general knowledge, fails to identify specifically how

Le Bec's disclosure would have been modified to meet the above denoted Element 1[c]. *Infra* Section IV.B. Without this explanation, Ground 2 "stymies a proper obviousness analysis." *Teradata Corp. v. SAP SE*, No. IPR2020-00942, Paper 10 at 14-15 (PTAB Nov. 24, 2020).

Ground 3's introduction of Berkowitz 2007's disclosure of "simple peak area integration... [that] allows the percentage of **EC [empty capsid]** material ... to be readily calculated" (Petition 16, 38 (citing Ex. 1004, 21)) still fails to provide Element 1[c]'s requirement of "determin[ing] concentrations for each peak," including for partial or fragmented rAAV genome peaks. *Infra* Section IV.C.1. Berkowitz 2007's use of interference optics simply does not inform the measure of absorbance optics as used by Le Bec. *Id.* Neither obviousness Ground 2 or 3 explains "how or why" the POSA would have modified Le Bec to determine concentrations for each peak, indicating "hindsight reconstruction of these references" to reach claim 1. *TriVascular, Inc. v. Samuels*, 812 F.3d 1056, 1066 (Fed. Cir. 2016).

For Ground 3's arguments for claim 2, Novartis fails to identify any prior art example where the size of any biologic compound, much less a viral particle, "is calculated by comparing the S value of the species to a standard curve." Petition, 45-46. Novartis resorts to arguing that in "a hypothetical system where the rAAV particles are uniform and have an identical frictional coefficient, the sedimentation

coefficient (s) will be proportional to the effective particle mass (M_b).” Petition 46. This argument also flounders, because viral particles are not a hypothetical system, and Novartis does not show, and neither Berkowitz nor Cole teaches, that the POSA would have assumed “all the species have equal frictional ratios.” Ex. 1005, 166; *see also* Ex. 1004, 18, 31-32 (describing unpredictable frictional behavior changes in adenoviral particles); *infra* Section IV.C.2. The ’288 patent inventors surprisingly found that sedimentation coefficients were linearly related to genome mass for rAAV particles, and that unlike adenovirus particles (Ex. 1004, 31-32), the frictional coefficient appeared to remain constant among rAAV particles. It is a “longstanding principle that the prior art must be considered for all its teachings, not selectively.” *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019). Rather than consider these references as a whole, Novartis “selectively culled from the prior art to fit the parameters of the patented invention.” *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534, 546 (Fed. Cir. 1998); *see also Arendi S.A.R.L. v. Apple Inc.*, 832 F.3d 1355, 1361 (Fed. Cir. 2016) (The Board “must avoid ‘hindsight bias and must be cautious of arguments reliant upon ex post reasoning.’”)

Novartis fails to establish a reasonable likelihood of succeeding in this Petition for challenged independent claims 1 and 2, as well as claims 17-34, which

depend from claim 1, and claim 3, which depends from claim 2. The Board should deny institution.

II. THE '288 PATENT

The '288 patent (Ex. 1001), titled “Analytical Ultracentrifugation for Characterization of Recombinant Viral Particles,” represents an important advance in the manufacture and purification of rAAV preparations, by providing the gene therapy field with a method to reliably identify and quantify concentrations of each species (e.g., empty capsids, capsids containing partial or fragmented genomes, and fully intact capsids) present in an rAAV preparation. Hansen, ¶ 55. Because of the inventors’ innovative application of AUC to analyzing rAAV preparations, AUC has become a critically important tool for the development of rAAV-based gene therapies.

A. The Importance of Genzyme’s Innovative AUC Method

A 2015 peer-reviewed publication co-authored in-part by the inventors of the '288 patent, Burnham and O’Riordan, and colleagues (Ex. 2003), publicized experiments disclosed in the '288 patent, including much of Examples 1-6. *See, e.g.*, Ex. 2003, 232, Figure 1 (Ex. 1001, Example 1 (FIGS. 1A, 1B, 2A, 2B)), 233, Figure 2 (Ex. 1001, Example 2, Table 4, FIGS. 3A-3B), 234, Figures 3A, 3B (Ex. 1001, Example 3, FIGS. 6B, 6C), 235, Figure 4 (Ex. 1001, Example 4, FIG. 7A-7C), 236, Figure 5 (Ex. 1001, Example 5, FIGS. 8, 9A-9C), 237, Figure 6D (Ex.

1001, Example 6, FIGS. 11A); Hansen, ¶ 56. A 2020 white paper by Beckman Coulter GmbH, the manufacturer of instruments for AUC analysis highlighted the importance of the Burnham's contribution, stating:

Burnham and colleagues showed that sedimentation velocity ... [AUC] experiments are able to characterize the quality of viral vector productions. ***A single AUC experiment provides insights into the composition of the encapsulated DNA, the success of the purification, the presence of aggregates and the ratio between empty, partially filled and filled viral particles....*** Taken together, the AUC is a valuable tool to analyze rAAV vectors notwithstanding the composition and length of the transgene or the viral serotype.

Ex. 2005 (citing Burnham 2015) (emphasis added).

A 2018 publication co-authored by an inventor of the Petitions' primary prior art reference (Ex. 1003), Christine Le Bec, and others, stated that "for the determination of empty-to-full capsid ratio, here we used AUC, a method that has been demonstrated to provide a reliable readout." Ex. 2004, 166-67 (citing Ex. 2003). It is not surprising the rAAV field, including Le Bec, would rely on the AUC inventors' method. Hansen, ¶ 58. As explained herein, the Le Bec prior art reference relied on by the Petition (Ex. 1003) did not provide a method that could quantify the ratio of different rAAV species within an rAAV preparation.

Indeed, the method disclosed and claimed in the '288 patent was the innovation that made AUC a valuable tool to identify the species present in rAAV compositions and measure the “the ratio between empty, partially filled and filled viral particles.” Ex. 2005; Hansen, ¶¶ 57-60. Novartis neither demonstrates that AUC was used in the prior art to identify each species present in a rAAV composition, nor that it could quantify those rAAV species, particularly partially filled rAAV species.

B. Disclosed Innovation of the '288 Patent

“[A] major problem in producing pure AAV vector preparations is the presence of capsids with *partial or fragmented genomes*.” Ex. 1001, 47:49-51 (emphasis added). “[T]he variant genomes” include partial or fragmented genome that “are smaller than the intact recombinant viral genome (e.g., truncated genomes).” *Id.*, 24:65-25:2.

The '288 patent provides a single method, using AUC boundary sedimentation under velocity conditions, which can analyze a sample in a matter of hours and provide quantitative characterization of rAAV preparations. *Id.*, 43:42-48. During rAAV production, for example, AUC facilitated “monitor[ing] [rAAV preparation] at time intervals (e.g., one or more times).” *Id.*, 11:7-12. Multiple innovations contributed to the inventors’ success. Hansen, ¶¶ 61-63.

The '288 patent discloses and claims “plotting the differential sedimentation coefficient distribution value ($C(s)$) versus the sedimentation coefficient in Svedberg units (S).” *See, e.g.*, Ex. 1001, 1:64-67; claim 1. The “distribution of sedimentation coefficients’ [] looks like a chromatogram.” *Id.*, 24:6-10. The inventors identified sedimentation velocity conditions that resulted in a plot where each individual rAAV species was present as a separate and distinct peak, each containing varying levels of genome encapsidation. *Id.*, 53:27-36. This peak separation allowed for integration of the peaks to determine each peak’s area (*id.*, 12:16-30), enabling relative quantification of each species present—including capsids comprising partial or fragmented genomes. Hansen, ¶ 62.

1. Overcoming the Challenge of Determining rAAV Species Concentration by AUC

The POSA understood that integrating peak area may not always be enough on its own to quantify the concentration of each rAAV species. Hansen, ¶¶ 48-54, 63. To determine the relative concentrations of species within a heterogeneous AAV preparation using AUC, the POSA may correlate peak area (determined by peak integration) to concentration. Ex. 1001, 24:6-10. When absorbance spectroscopy at certain wavelengths (e.g., 280 nm) is applied in AUC methods to monitor sedimentation of viral particles, knowing the proportion of peak area to concentration requires knowing the extinction coefficient (ϵ) of each species,

because different rAAV species will absorb certain wavelengths of light to different degrees. *Id.*, 24:20-23 (“[E]xtinction coefficients are used to calculate molar concentration and the actual percent value of the intact vector peak from absorbance data.”); *see also* Hansen, ¶¶ 52-54. Extinction coefficients had been determined for empty capsids and fully intact rAAV particles at an absorbance wavelength of 260 nm. Ex. 1001, 24:23-26 (citing Ex. 2007, 127) (“Molar absorbance extinction coefficients for both empty capsids ($\epsilon_{260/\text{capsid}}=3.72\text{e}6$) and intact vector ($\epsilon_{260/\text{vector}}=3.00\text{e}7$) can be calculated based on published formulae.”). However, “it [was] not possible to determine empirically the extinction coefficient of fragmented genomes,” because they are “of unknown size and sequence” *Id.*, 24:35-38; 44:25-32; 49:9-12; Hansen, ¶ 64.

“An alternative optical detection method for AUC” to absorbance spectroscopy was Rayleigh Interference Optics, which “measures the sample concentration based on refractive index differences between a reference solution and the AAV containing sample.” *Id.*, 46:58-67 (Example 2). Although “interference detection yields integrated peaks that are directly proportional to concentration” (*id*) it was understood to have significant drawbacks that hindered its application. Hansen, ¶¶ 50-51, 65-66. For example, interference detection required “a high concentration of sample” and its results could “be affected by a mismatch between the reference and AAV sample buffer.” Ex. 1001, 47:31-35.

For studying rAAV preparations, the sample concentration issue would have been understood by the POSA to have been particularly problematic because “AAV samples ... typically contain a low protein concentration.” *Id.*, 47:35-38.

Additionally, the need to “completely match the AAV sample and reference buffers” presented another drawback to interference optics that was not presented by absorbance spectroscopy. *Id.* Thus, absorbance spectroscopy was understood to be a preferred method for the detection of rAAV species, particularly species that may be less abundant than others, including partial or fragmented species.

Hansen, ¶ 52. Absorbance was therefore the method applied to most examples of the '288 patent.

Despite its superior practicability, however, a barrier to the application of absorbance spectroscopy to characterizing rAAV preparations, was that for some rAAV species, “it [was] not possible to determine empirically the extinction coefficient of particular species of recombinant viral particles (e.g., viral particles with fragmented genomes of unknown size and sequence).” Ex. 1001, 24:35-38.

To overcome this obstacle, the inventors determined that:

[A] relationship between S value and genome size may be established by analyzing recombinant viral vector preps with encapsidated viral genomes of known nucleotide size and a corresponding S value.... The calculated S values can be plotted to generate a standard curve to which recombinant viral species of unknown molecular weight or genome size

can be compared to determine the molecular weight of the unknown species.

Id., 24:38-46; *see also id.*, 44:25-32.

The application of this innovative method is illustrated in Example 5, which demonstrates the implementation of “AUC ... as a tool to quantify the aberrant packaging of fragmented genomes in rAAV vector preps.” *Id.*, 48:60-50:17; Hansen, ¶¶ 67-69. To generate an exemplary standard curve, “rAAV vector preps with encapsidated viral genomes of known size were analyzed by AUC, and their corresponding S values were determined, as shown in Table 5.”

TABLE 5			
S values for rAAV vectors with known genome size.			
Predicted Trend Line			
Sedimentation		Calculated values	
coefficient (S) (y)	Genome size (# NT) (x)	MW	Extinction coefficient (260 nm)
Empty capsid	N/A		3.72E+06
74	880	2.7E+05	9.17E+06
78	1421	4.4E+05	1.25E+07
82	1961	6.1E+05	1.59E+07
84	2232	6.9E+05	1.75E+07
88	2772	8.6E+05	2.09E+07
92	3313	1.0E+06	2.42E+07
96	3853	1.2E+06	2.76E+07
100	4394	1.4E+06	3.09E+07
104	4934	1.5E+06	3.43E+07
108	5475	1.7E+06	3.76E+07

Ex. 1001, 49:12-39.

Figure 8, which “shows the linear relationship between sedimentation coefficient and vector genome size,” provides the standard curve of Example 5, correlating genome size and S value. *Id.*, 9:28-32. Data plotted and fit in Figure 8

surprisingly “demonstrated a highly linear relationship ($R^2=0.9978$) between sedimentation coefficient and genome size.” *Id.*, 49:9-19.

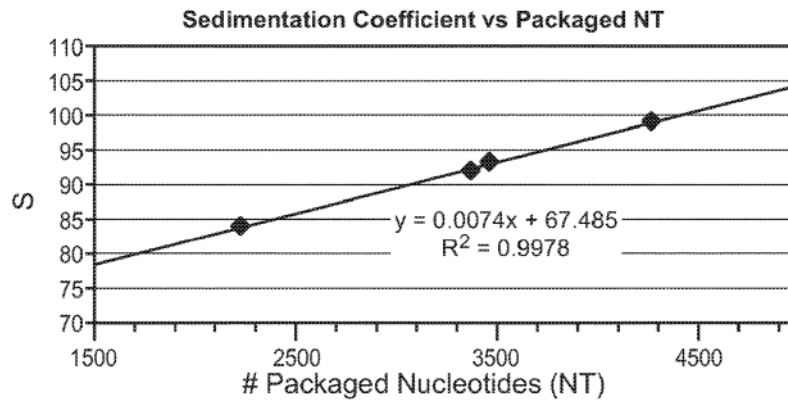


FIG. 8

Id., Fig. 8.

Generating the standard curve allowed the inventors to determine the molecular weight, genome size, and extinction coefficient at 260 nm of unknown rAAV species, for example, partial or fragmented species. *Id.* 48:60-50:17 (Example 5, Table 5); Figs. 8, 9A. Once the standard curve was generated, a study was conducted to show “that assessment of capsid genome size using AUC data correlates with assessment of genome size by Southern blot.” *Id.*, 9:33-35; 49:40-64.

2. One-Step rAAV Preparation Analysis by AUC

The inventors applied their method to quantitatively analyze the compositions of several samples to demonstrate how the method identified peaks

corresponding to rAAV species containing partial or fragmented genomes and could determine their concentrations. Hansen, ¶¶ 70-90.

a. Example 5

“To demonstrate the utility of AUC to detect genome fragments, a self-complementary vector comprising AAV2 ITRS, a minimal CBA promoter, and an EGFP transgene was packaged into an AAV9 capsid.” *Id.*, 49:40-44. After purifying the preparation to eliminate empty capsids, the remaining vector particles were “analyzed by AUC” and “[t]he standard curve was then used to assign genome size to each of the resolved genome containing capsids.” *Id.*, 49:44-47.

In Figure 9A, a “plot of differential sedimentation coefficient distribution value, $c(s)$, vs sedimentation coefficient in Svedberg units (S), yields the distribution of sedimentation coefficients for a [self-complimentary] scAAV9 EGFP vector preparation. Single stranded monomeric (82S) and double stranded dimeric (101S) species are labeled with the corresponding sedimentation coefficients and relative abundance values (%).”

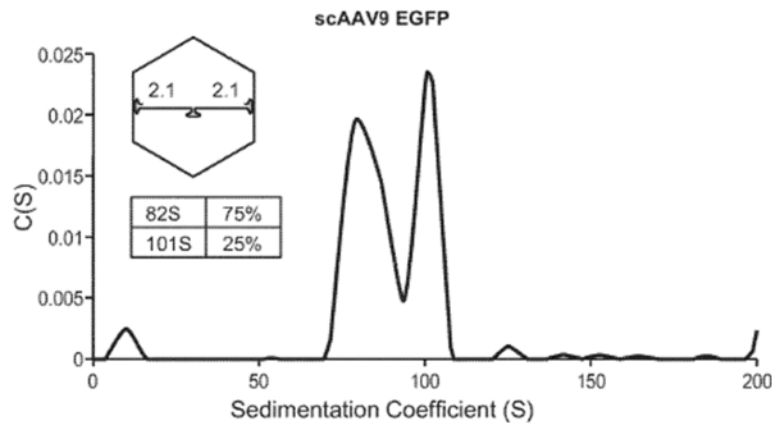


FIG. 9A

Id. at 9:35-42; 49:40-49; FIG. 9A.² Applying the standard curve, the inventors determined that 101S peak corresponded to an rAAV vector of ~4.3 kb (kb=kilobases), while the 82S peak corresponded to a vector genome size of ~2kb. *Id.*, 49:47-55. With the molecular weights of the two components determined, it was possible to calculate their extinction coefficients at 260 nm and, therefore, their relative concentrations of 25% for the 101S peak double-stranded species and 75% for the 82S peak single stranded species. *Id.*, 49:47-55; FIG. 9A. The AUC results showed good agreement with Southern blot results, which identified both

² The POSA would have understood that C(s) distribution peaks having lower sedimentation values than peaks for empty capsids do not correspond to rAAV species. Hansen, ¶ 73; Ex. 1004, 27 (The “slow-migrating material most likely corresponds to smaller fragments of [empty capsid or ‘EC’] and virus particles and possibly aggregates of viral proteins....”).

the single-stranded monomeric species (***) and dimeric double stranded species (*) in lane 1, shown below.

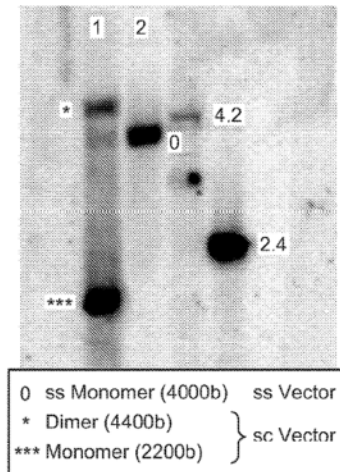


FIG. 9B

Id., 49:61-64; FIG. 9B.

Applying the innovative AUC method, Example 5 further disclosed “AUC analysis of a single stranded AAV9 EGFP vector” preparation which resulted in a “predominant peak with a measured S value of 99 S, corresponding to approximately 4.1 kb by the standard curve and 84% of capsid abundance” and a second peak single stranded rAAV vector peak at 85S having a relative concentration of 16%.

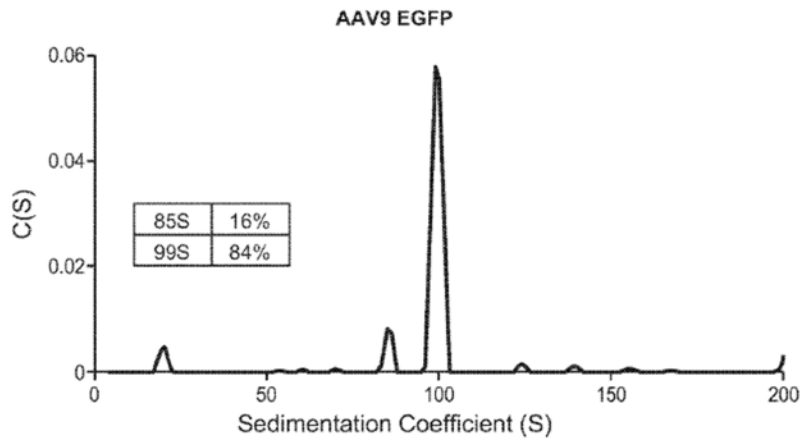


FIG. 9C

Id., 49:66-50:3; FIG. 9C. This result also agreed with the Southern blot analysis, showing this species in lane 2 (0) of FIG. 9B. *Id.*, 50:6-9; FIG. 9B.

b. Example 3

The inventors compared the heterogenous rAAV preparations produced by two AAV production methods, which both resulted in the production of empty capsids, partially and/or fragmented capsids, and fully intact capsids. *Id.*, 47:40-48:16; FIGs. 6B-C (reproduced below).

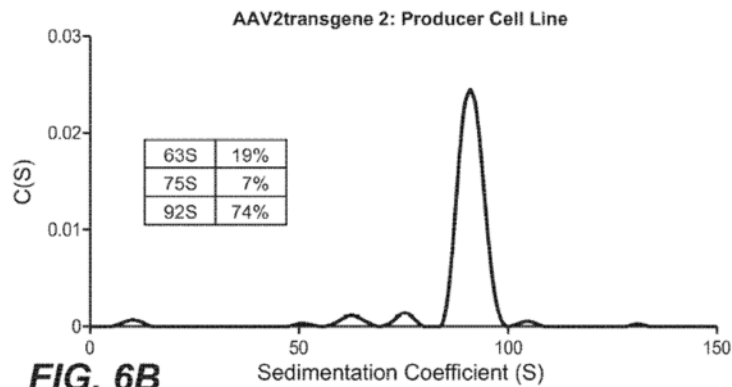
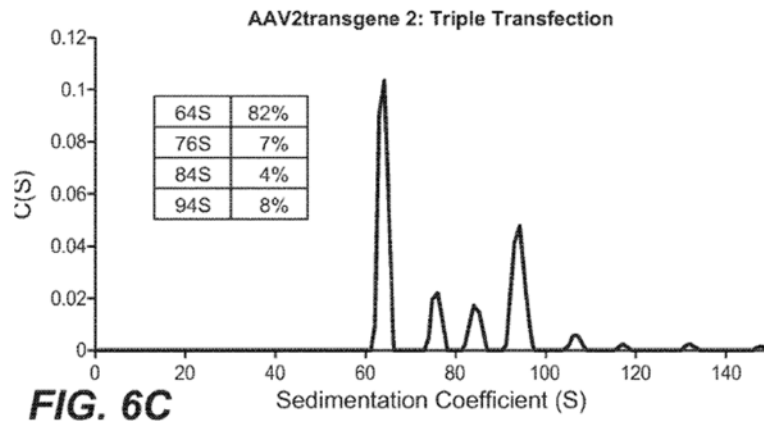


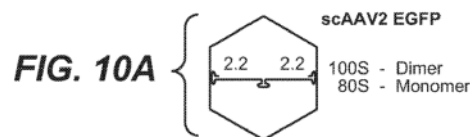
FIG. 6B



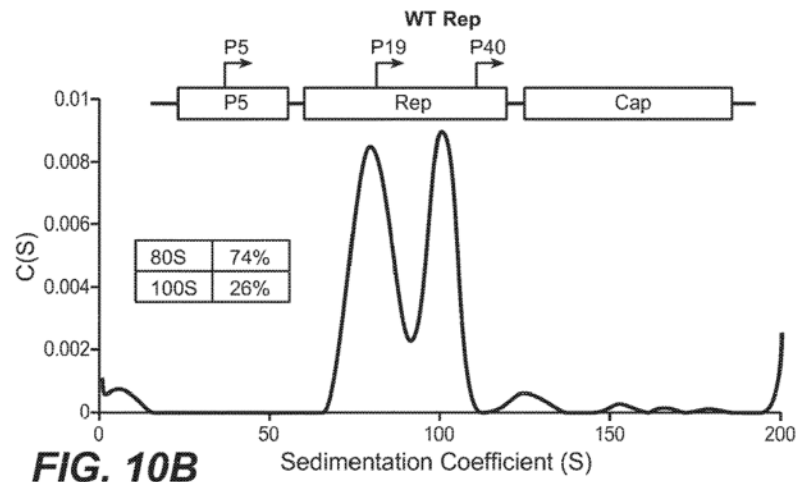
The fragmented genomes were identified to have peaks at 75S (FIG. 6B) 76S and 84S (FIG. 6C). *Id.*, 47:64-48:5. The inventors determined the concentrations of the fragmented species identified in their experiments, observing that “[t]he AUC profiles of vector preps produced by these methods were remarkably different.” *Id.*, 47:62-63. “Using the producer cell line method, 74% of capsids contained a full genome, represented by the 92 S species (FIG. 6B). 19% were empty capsids, with the remainder containing a fragmented genome species (75S species, 7%).” *Id.*, 47:64-48:1. The “triple transfection method” resulted in a less successful outcome: “82% of the capsids ... were empty, 64S species (FIG. 6C), with 11% of capsids containing a fragmented genome (76S and 84S species) and only 8% of capsids having a full genome (94S).” *Id.*, 48:1-5. The identification and quantification of each species illustrates the value of the inventive method and its utility for determining the quality of rAAV preparation and manufacturing procedures. Hansen, ¶ 77.

c. Example 6

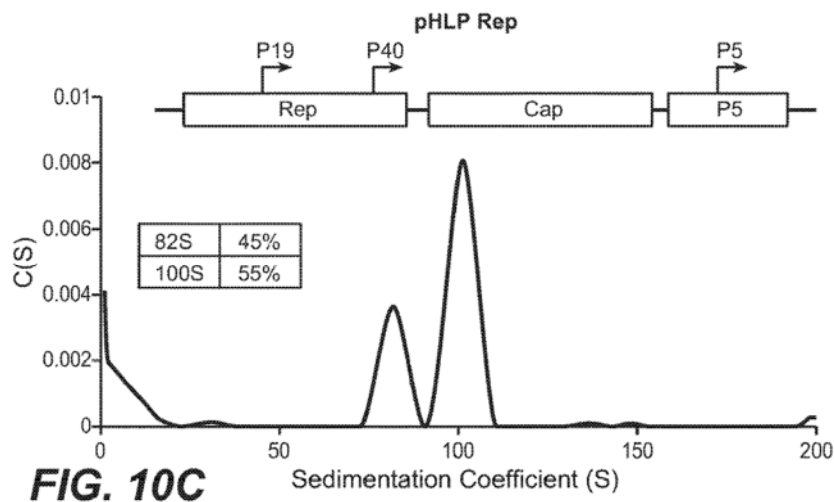
Example 6 demonstrates the application of the AUC method to identify and quantify unknown rAAV species containing partial or fragmented genomes that eluded the detection of the established Southern blot analytical method. Hansen, ¶¶ 78-87. The method was used to analyze how modification to the helper factor in a vector prep for the “self-complementary AAV vector harboring an EGFP transgene” impacted rAAV production. Ex. 1001, 50:29-42. The experiments compared a “first method (FIG. 10B)” for rAAV preparation employing an unmodified “helper plasmid” (the “WT Rep” construct) and a “second method (FIG. 10C)” where “the helper was modified” (the “pHLP Rep” construct). *Id.*, 50:33-39. “The full scAAV2 EGFP capsid was predicted to have a sedimentation coefficient of 100S in dimeric genome form and 80S in monomeric genome form (FIG. 10A).” *Id.*, 50:39-42.



For the unmodified helper of the WT Rep construct, the resulting packaging of the rAAV genome dimeric genomes (~100S peak) unexpectedly decreased to 26% relative to those containing monomeric genomes (~80S peak) at 74%.



Id., 50:49-53, Fig. 10B. In contrast, the modified helper of the pHLP Rep construct resulted in a ratio of rAAV particles containing dimeric genomes (~100S peak) at 55% versus monomeric particles (~82S) at 45%.

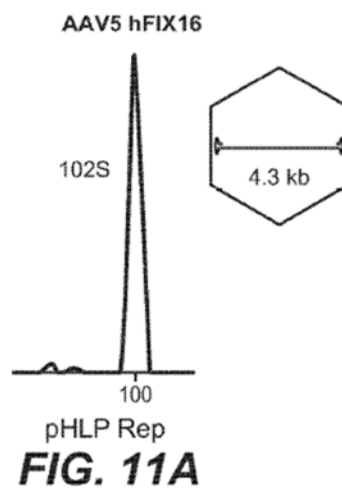


Id., 50:43-47. “These results uncovered a significant difference in genome packaging induced by” modifying “the helper plasmid.” *Id.*, 50:53-56. Detection of this result was facilitated by the AUC analysis differentiating between rAAV species containing different levels of genome encapsidation.

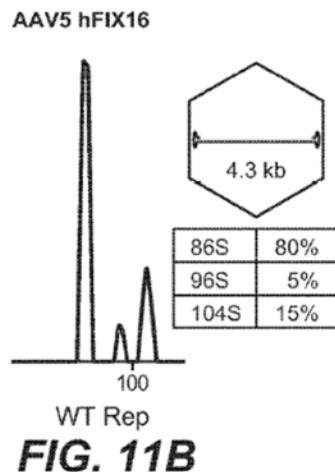
d. The Superiority of the Innovative AUC Method to Southern Blot

The power of the disclosed AUC method was further revealed through a comparison of AUC with Southern blot analysis. Hansen, ¶¶ 80-87. In another experiment of Example 6, a “single stranded AAV5 Factor IX vector, AAV5FIX, (FIG. 11A-B) and a single stranded AAV5hSMN vector (FIG. 11C-D) were generated using” the modified helpers, pHLP Rep, “as described above, but cap sequences of AAV2 were replaced by cap sequences of AAV5.” Ex. 1001, 50:57-62.

“Based on the nucleotide size of the FIX expression cassette (4.3 kb), the predicted sedimentation coefficient for the AAV5 FIX vector capsid was approximately 101S. AUC analysis of AAV2/SFIX made in the presence of” the modified pHLP Rep helper “revealed a homogenous profile with the majority of the vector (90%) sedimenting with an S value of the expected size.”



Id., 50:62-51:1, FIG. 11A. “In contrast, AAV5 FIX vector generated using [the unmodified wild-type, WT Rep,] generated a strikingly different AUC profile....Instead of a predominant peak at 101S, this profile revealed more capsid heterogeneity, with the majority of the AAV5 FIX (80%) sedimenting at a lower S value of 86 S, likely representing packaging of a fragmented genome” whereas “only 15% of the AAV5 FIX vector capsids sedimented at the correct S value of ~104S.”



Id., 51:1-11, FIG. 11B.

AAV5SMN vectors made using these same wild-type and mutated helpers also had different profiles. Hansen, ¶ 83. “AAV5 SMN vectors generated in the presence of” the modified pHLP Rep helper “showed less heterogeneity by AUC analysis, with a single capsid species sedimenting at the S value of 101S consistent with packaging of a genome of the predicted size of ~4.4 kb.”

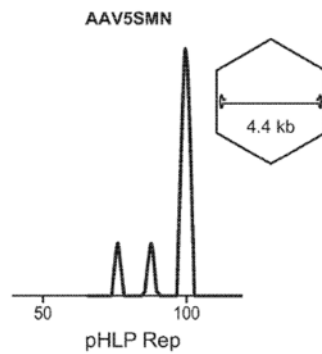


FIG. 11C

Ex. 1001, 51:12-19, FIG. 11C. “In contrast, the AUC profile for the same vector genome packaged using ‘wild-type’” WT Rep helper “revealed three distinct AAV vector species, with sedimentation coefficients of 100 S...92 S (representing a fragmented genome of approximately 3300 [nucleotides]) and 80 S (representing a fragmented genome of 2000 nucleotides).”

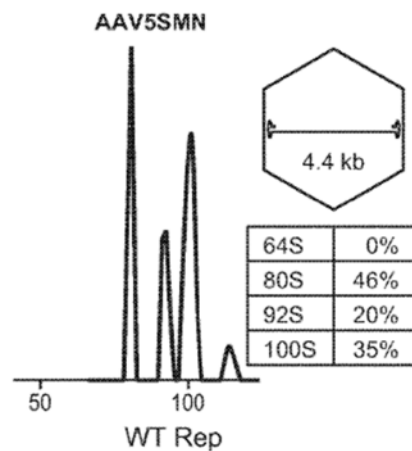


FIG. 11D

Id., 51:19-28, FIG. 11D.

Southern blot analysis of the AAV5SMN preparations were consistent with the AUC results for the pHLP helper (FIG. 11A) showing a homogenous profile of

the full-length vector (FIG. 12A, lane 2) compared with packaging of full-length and fragmented SMN genomes (FIG. 12A, lane 1). *Id.*, 51:29-37.

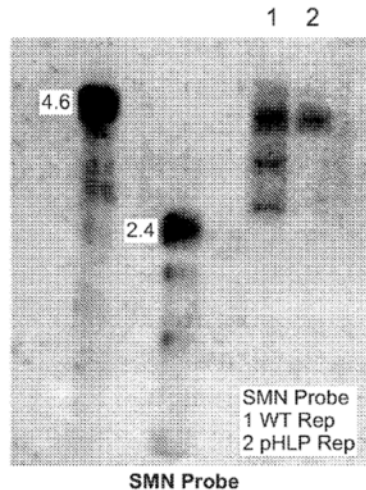
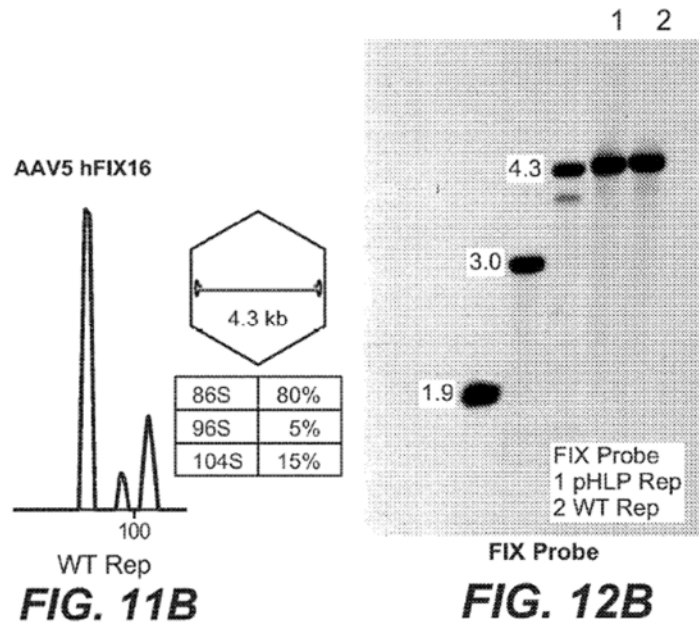
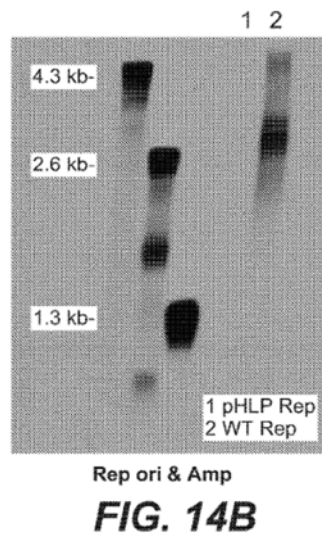


FIG. 12A

Southern blot analysis of the FIX vector preparation made with the pHLP modified helper agreed with the AUC result (FIG. 11A), showing predominantly full-length AAV (FIG. 12B, lane 1). In contrast, “AUC analysis of this AAV5FIX vector (FIG. 11B)” made with the WT-Rep helper “showed that 80% of the capsids contained a fragmented genome (~3000 nucleotides)” but these fragments “were **undetected** by the FIX probe” in a Southern blot experiment. *Id.*, 51:42-45 (emphasis added).



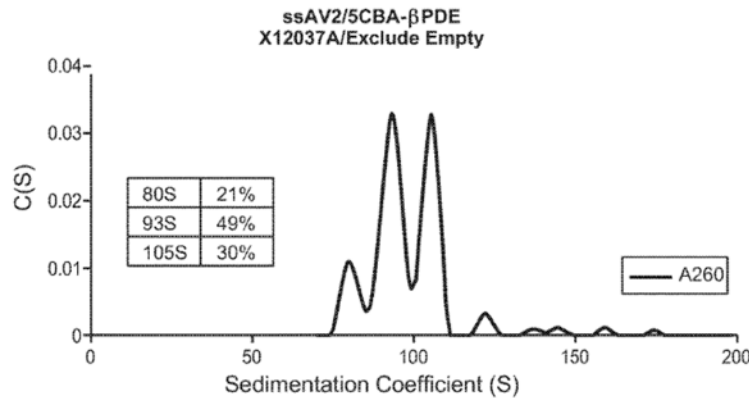
When an Amp^R specific probe was used in a Southern blot experiment, the vector genome species from the FIX vector preparation sedimenting at 86S containing a ~3 kb fragment (FIG. 11B) was detected.



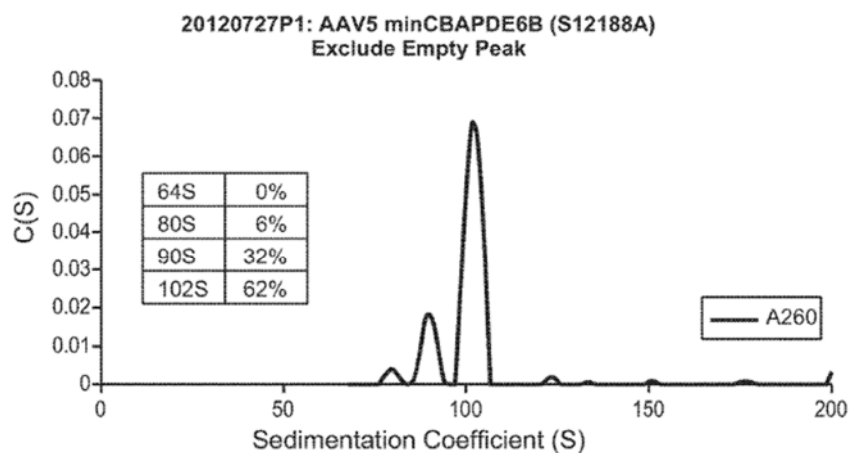
Id., 51:54-63, FIG. 14B. But the Amp^R probe did **not detect** the fully intact genome in the rAAV5 FIX vector prep generated with the modified pHLP Rep helper. *Id.* Thus, multiple experiments were required to identify the species in the

preparation by Southern blot. These comparative experiments illustrate the power of the inventors' AUC method. Unlike Southern blot, AUC is not sequence dependent, so the claimed AUC method allows for the detection and quantification of rAAV species, including partial or fragmented genomes, in a single experiment. Hansen, ¶ 87.

The '288 patent also applies the AUC method to analyze "the heterogeneity of AAV vectors produced using oversized genomes." *Id.*, 52:11-14; Hansen, ¶¶ 88-89. "An expression cassette harboring the full length CBA promoter driving expression of the β -phosphodiesterase transgene was packaged as an oversized genome of 5.4 kb (FIG. 15A) or as a wild type size genome of 4.6 kb (FIG. 15B)." *Id.*, 52:14-18. Oversized rAAV genomes "have been shown to be fragmented into subgenomic-length DNA." *Id.*, 52:7-11. Indeed, "the AUC profile of the AAV vector prep generated using the oversized vector genome demonstrated that nearly half of the vector prep sedimented as a [fragmented] 93S species ... of approximately 3.5 kb. 30% of the preparation was represented by another sub-genomic vector species of approximately 4.9 kb sedimenting at 105S. There was no evidence of packaging of a full-length 5.4 kb genome, which was predicted to sediment at 108-109 S."



Id., 52:22-30; FIG. 15A. “In contrast, AUC analysis revealed that the same transgene under control of the abbreviated CBA promoter” of wild-type size “sedimented predominantly as a vector species of 102 S, consistent with packaging of the predicted, full-length vector genome of 4.6 kb.”



Id., 52:30-34; FIG. 15B. “These results demonstrate the utility of AUC analysis in profiling AAV vectors with oversized genomes, and this profiling is critical, given the observed incidence of genome fragmentation.” *Id.*, 52:35-38.

C. Challenged Claims

Claim 1 recites:

1. A method of characterizing a preparation of recombinant adeno-associated viral (AAV) particles comprising the steps of

a) subjecting the preparation to analytical ultracentrifugation under boundary sedimentation velocity conditions wherein the sedimentation of recombinant AAV particles is monitored at time intervals,

b) plotting the differential sedimentation coefficient distribution value (C(s)) versus the sedimentation coefficient in Svedberg units (S), and

c) integrating the area under ***each peak*** in the C(s) distribution to determine the relative concentration of ***each peak***, wherein ***each peak represents a species of recombinant AAV particle.***

Ex. 1001, 54:30-33. Element 1[c], therefore, requires integrating the area under ***each peak*** in the C(s) distribution to determine the relative concentration of ***each peak***—not only empty capsids and fully intact viral particles, but also partial or fragmented species that may be present in the rAAV preparation. Claims 17-34 depend from claim 1, and thereby incorporate Element 1[c].

Claim recites:

2. A method to assess vector genome integrity of recombinant AAV particles in a preparation of recombinant AAV particles comprising

- a) subjecting the preparation to analytical ultracentrifugation under boundary sedimentation velocity conditions wherein the sedimentation of recombinant AAV particles is monitored at time intervals,
- b) plotting the differential sedimentation coefficient distribution value $C(s)$ versus the sedimentation coefficient in Svedberg units (S), and
- c) **identifying species** of recombinant AAV particles in the preparation **by presence of peaks** on the plot corresponding to an S value, wherein the **genome size** of a particular species of recombinant AAV particles **is calculated by comparing the S value of the species to a standard curve** generated by S values of recombinant AAV particles comprising encapsidated AAV genomes of known nucleotide sizes.

Id., 54:44-51. Element 2[c] requires generating a standard curve correlating S value with a measure of genome size (e.g., number of nucleotides) and using the standard curve to calculate the genome size of a particular rAAV species based on its S value. *See, e.g., id.*, 49:16-39 (Table 5), FIG. 8; *supra* Section II.B.1.

Claim 3 depends from claim 2, and thereby incorporates Element 2[c].

Claim 3 also recites “integrating the area under each peak in the $C(s)$ distribution to determine the relative concentration of each species of recombinant AAV particles.” *Id.*, 54:52-55. Therefore claim 3, like Element 1[c], requires determining the concentration of the species corresponding to **each peak**—not only

empty capsids and fully intact viral particles, but also partial or fragmented species present in the rAAV preparation.

III. CLAIM CONSTRUCTION

For this Preliminary Response only, Genzyme does not challenge the Petition's alleged "plain and ordinary meaning" constructions. Petition, 17-18.

IV. NOVARTIS HAS NOT DEMONSTRATED A REASONABLE LIKELIHOOD THAT CLAIMS 1-3 AND 17-34 ARE UNPATENTABLE AS ANTICIPATED OR OBVIOUS

For institution, Novartis bears the burden of proving that there is a reasonable likelihood that the challenged claims are unpatentable as anticipated and/or obvious based on the art and arguments set forth in its Petitions. *In re Magnum Oil Tools Int'l Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) ("[T]he Board must base its decision on arguments that were advanced by a party ..."). Because its Petition must form the basis of Novartis's challenge, and because the inadequacies in the Petition's proofs identified herein are so significant, Novartis's failures on the merits cannot be remedied. This failure therefore warrants denying institution. *Id.* at 1380 (To meet its burden the "petitioner must instead articulate specific reasoning, based on evidence of record, to support the legal conclusion of obviousness."); *see also* PTAB Consolidated Trial Practice Guide (Nov. 2019) ("TPG"), 73 ("Petitioner may not submit new evidence or argument in reply that it

could have presented earlier, e.g. to make out a prima facie case of unpatentability.”)

Novartis’s Petition does not prove anticipation (Ground 1) nor obviousness for claim 1 (Grounds 2 and 3), or claim 2 (Ground 3), the only independent claims challenged. Accordingly, the remaining claims which all depend, directly or indirectly, from claim 1 (claims 17-34) or claim 2 (claim 3) are also not anticipated or obvious. Because Novartis fails to demonstrate a reasonable likelihood that any of the challenged claims are unpatentable, institution should be denied.

A. Ground 1 Does Not Establish Le Bec Anticipates Element 1[c]

Element 1[c] recites “integrating the area under each peak in the C(s) distribution to determine the relative concentration of each peak, wherein each peak represents a species of recombinant AAV particle.” Ex. 1001, 54:30-33. The Petition fails to establish that Le Bec disclosed Element 1[c] “within the four corners of the document,” and thus has failed to demonstrate claim 1 is anticipated by Le Bec. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008).

The Petition states that “a POSA would understand that obtaining the percentages/relative concentrations disclosed in Le Bec using a distribution profile involves integrating the area under the curve for the peaks of interest.” Petition, 27 (citing Ex. 1003, 8:10-13, 18:11-27, Figs. 2-3; Ex 1020, ¶¶82-84).

In two clauses, Le Bec says that “the HEK293 system essentially produced very few full AAV particles (< 25%), with only 10% of viral particles containing the genome in double-stranded form” and “the sf9 system makes it possible to produce AAV viral particles essentially composed of full AAV particles (>80%), with a very high percentage of viral genome in double-stranded form (>50%).”

Ex. 1003, 19:1-15. Le Bec is silent as to how it arrived at those percentages. Le Bec does not describe integrating the area under peaks to arrive at those percentages. Nor, as discussed in more detail below (*infra* Section IV.A.2), does Le Bec describe the use of extinction coefficients at 276 nm to arrive at those percentages. Indeed, Le Bec does not describe that those rough percentages (“<25%,” 10%, “>80%” and “>50%”) were anything more than an imprecise estimate. Hansen, ¶¶ 98-99. Le Bec’s single reference to SEDFIT software (Ex. 1003, 15:26-28) is only in the context of obtaining the sedimentation coefficient, not determining the relative concentration of each species, and certainly not for integrating the area under each peak.

Assuming *arguendo* that Le Bec conducted peak area integration to obtain the concentration ranges it does disclose, as Novartis alleges (Petition, 27-28), Ground 1 is still inadequate to establish anticipation of Element 1[c] for at least the following reasons.

First, Novartis does not establish that Le Bec discloses “integrating the area under *each peak* in the C(s) distribution to determine the relative concentration of *each peak*, wherein *each peak* represents a species of recombinant AAV particle.” Element 1[c]. Hansen, ¶¶ 96-97, 100-109. Novartis’s Petition is understandably silent on Le Bec’s lack of disclosure of concentrations for each peak in its C(s) distributions that correlate to, for example, partial or fragmented genomes. *Infra* Section IV.A.2. Novartis’s proof relies on Le Bec’s disclosure of concentrations, but Le Bec’s does not contain any disclosure relating to the concentrations of partial or fragmented rAAV species. This omission, which Novartis’s Petition and the supporting Berkowitz Declaration (Ex. 1020) ignore, is a fatal deficiency to Ground 1.

Second, Novartis does not establish that Le Bec discloses determining the relative concentration of each species corresponding to a peak in its C(s) distribution without need for further modification. Hansen, ¶¶ 110-113. Le Bec used absorbance at 276 nm to analyze its rAAV preparation by AUC. Ex. 1003, 15:23-28 (“sedimentation was followed by absorbance at the wavelength of 276 nm.”). Therefore, determining the concentration for peaks corresponding to partial and fragmented rAAV species in Le Bec’s C(s) distributions (*Id.*, Figs. 2-3) would have required applying extinction coefficients for each species at the wavelength of 276 nm. Indeed, the ’288 patent details the challenge extinction coefficients had

posed for determining the concentrations of partial or fragmented species at similar wavelengths and identified an innovative way to overcome this challenge. *Supra* Section II.B.1 (citing Ex. 1001, 24:35-38); *see also* Ex. 1005, 152 (explaining absorbance is dependent upon a solute's extinction coefficient.) In his 2007 publication, Dr. Berkowitz explained that "AUC experiments can provide accurate and useful results ***when appropriate steps are taken*** to deal with the variability in signal response (***extinction coefficient***) for different adenovirus species." Ex. 1004, 17 (emphasis added). Le Bec, however, is silent regarding the extinction coefficients of the partial and fragmented species at 276 nm in its C(s) distributions, as are the Petition and Berkowitz Declaration. Thus, the Petition fails to establish how Le Bec would have permitted the POSA to determine concentrations of partial and fragmented rAAV species without relying on additional sources of information.

Each of these failures of proof provides an independent basis for why the Board should find that Novartis has failed to establish a reasonable likelihood that Le Bec anticipates claim 1.

1. Novartis Does Not Establish that Le Bec Discloses Integrating Peaks to Determine Concentrations of Partial or Fragmented Genomes

"Anticipation requires that a single prior art reference disclose ***each and every limitation*** of the claimed invention, either expressly or inherently." *SRI*

Int'l, Inc. v. Cisco Sys., Inc., 930 F.3d 1295, 1306 (Fed. Cir. 2019) (emphasis added). Novartis's anticipation arguments fail to address all terms within Element 1[c], which recites “**integrating the area under each peak** in the C(s) distribution to **determine the relative concentration of each peak**, wherein each peak represents a species of recombinant AAV particle.” It is not enough to merely integrate the area of “the peaks of interest” as Novartis argues. Petition, 27. If partial or fragmented genome-containing rAAV species yield peaks on the C(s) distribution, then the area under those peaks should be integrated to determine their relative concentrations. Le Bec, however, does not do so and neither the Petition nor Berkowitz Declaration address this glaring deficiency.

Anticipation requires that a single reference “describe the claimed invention *with sufficient precision and detail* to establish that the subject matter existed in the prior art.” *Wasica Fin. GmbH v. Cont'l Auto. Sys., Inc.*, 853 F.3d 1272, 1284 (Fed. Cir. 2017) (quoting *Verve, LLC v. Crane Cams, Inc.*, 311 F.3d 1116, 1120 (Fed. Cir. 2002)) (emphasis original). Novartis fails to identify where Le Bec discloses integrating and determining the area of specific peaks in its distribution, particularly those relating to partial and fragmented genome species, for example at 77S and 90S. Ex. 1003, 18:21-19:15, Figures 2-3; Hansen, ¶ 104. Therefore, the Petition does not establish how Le Bec would alone anticipate Element 1[c]. *Wasica*, 853 F.3d at 1284. (Explaining that “it has long been understood that

ambiguous references do not, as a matter of law, anticipate a claim.”) Given Le Bec’s vagueness on how it determines the concentration values, and the lack of disclosure relating to the concentrations associated with certain peaks, Novartis has failed to establish that Le Bec anticipates claim 1. *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1554 (Fed. Cir. 1983) (Finding a reference’s teaching “so unacceptably vague ... as not to support an anticipation rejection.”)

In contrast to Le Bec, the ’288 patent provides several examples of integrating peaks associated with partial or fragmented species, including Example 3 (FIGs. 6B-C), Example 5 (FIGs. 9A-B), and Example 6 (FIGS. 10B-C, 11A-11D, and 15A-15B). *Supra* Section II.B.2. The ’288 patent demonstrates the power of the ’288 patent’s AUC method by comparing it to Southern blot experiments, which often missed certain partial or fragmented genome-containing rAAV species if the probe did not bind to such species. *Supra* Section II.B.2.d . Therefore, the ability of the claimed method to determine the concentration peaks corresponding to partial or fragmented genome species is an important distinction between claim 1’s method and Le Bec’s disclosure. For this reason alone, Le Bec fails to anticipate claim 1.

To prove that Le Bec anticipates ***integrating each peak***, the Petition relies on Le Bec’s alleged “teach[ing] that the ‘distribution profile of the species allows the identification of two categories of populations’ and differentiates peaks as

corresponding to empty or full particles.” Petition, 27 (citing Ex.1003, 18:11-27; Figs. 2 and 3.). But Le Bec’s disclosure does not differentiate *each* peak. Hansen, ¶ 100-102. For example, Le Bec’s category of “full AAV viral particles” includes multiple peaks as shown in Le Bec’s Figure 2:

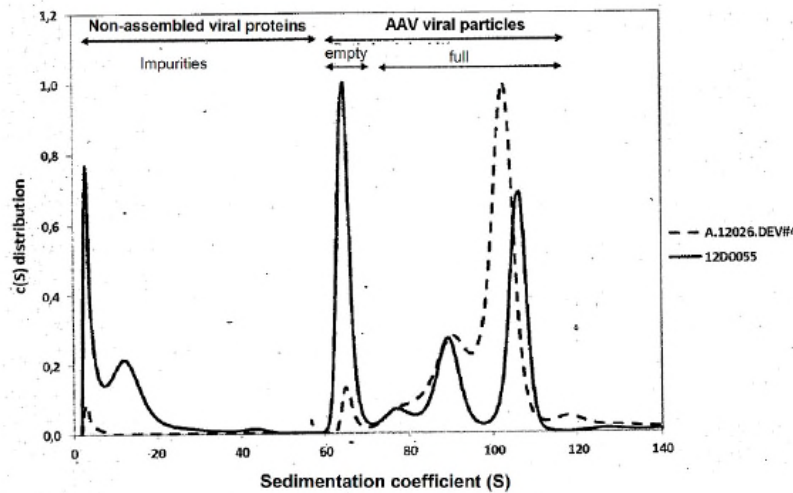


Figure 2

Ex. 1003, 6:3-7; 18:8-11; Fig. 2. Le Bec explains that “[t]he distribution profile of the species allows the identification of two categories of population: a) <60S corresponding to non-assembled viral 15 proteins and/or contaminants” and “b) 60S-110S corresponding to intact AAV viral particles” and “two subpopulations with empty AAV viral particles at 65S and full AAV viral particles between 80S and 110S, with the viral genome in single-stranded form at 90S and double-stranded form at 105S.” *Id.*, 18:11-25.

As support for anticipation of Element 1[c], the Petition quotes Le Bec’s statement that Le Bec’s C(s) “distribution profile...confirms that the HEK293

system essentially produced very few full AAV particles (< 25%)” (Petition, 27 (quoting Ex. 1003, 19:1-5), with “only 10% of viral particles containing the genome in double-stranded form.” Ex. 1003, 19:1-5, *see also* Petition at 15. The Petition, however, ignores that within Le Bec’s “full” viral particles subpopulation were multiple peaks corresponding to species of rAAV particles, including at the peaks at 90S and 105S. Ex. 1003, 18:21-25. The Berkowitz Declaration highlighted another “peak at approximately 77S that does not correspond to the peak for empty particle.” Ex. 1020, ¶¶ 108, 122, 130, 132, 211 (citing Ex. 1003, Fig. 2). The Petition, however, fails to identify where Le Bec “integrat[ed] the area under each peak in the C(s) distribution to determine the relative concentration of” the peaks specifically at 77S and 90S in Le Bec’s Figure 2. Hansen, ¶¶ 102-104.

The Petition’s reliance on Le Bec’s Figure 3 (Petition, 13-15, 27-28) is similarly unavailing for proving anticipation.

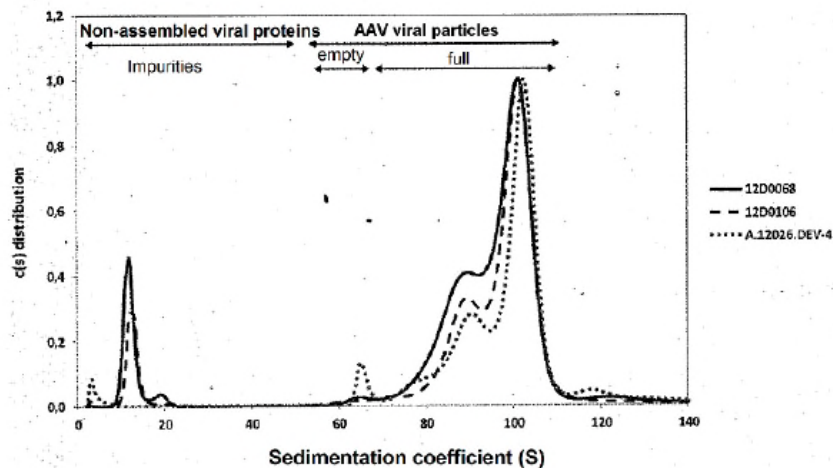


Figure 3

Ex. 1003, Fig. 3.

First, the Petition and Berkowitz Declaration never address the agglomeration of what appears to be multiple peaks ranging from about 75S to about 110S in Figure 3. Hansen, ¶¶ 105-106. This agglomeration indicates, but masks, the presence of multiple peaks and the POSA would have understood that for heterogeneous mixtures of particles, the use of AUC under boundary sedimentation conditions depends on resolving peaks of different species. See Ex. 1006, 169 (“This method can be used to study ... heterogeneous noninteracting and interacting systems provided that, in the latter cases, the **multiple components separate sufficiently during sedimentation to form distinct peaks** in the $g(s^*)$ versus s^* plots.”) (emphasis added); Ex. 1007, 1606-08 (When “diffusion broadens the sedimentation boundary, [it] makes it more difficult to resolve subpopulations of the distribution”); Hansen, ¶¶ 106-107.

Although not prior art, shortly after the 2015 priority date of the '288 patent, Dr. Berkowitz co-authored a publication on AUC that explained that “diffusional broadening results in low resolution (fairly poor separation of different species), making detection and quantitation of minor species rather limited, especially for protein species that migrate with sedimentation coefficient values that are close to the other peaks and/or are present at low levels.” Ex. 1011, 230. Consistent with the references filed by Novartis in this Petition, the '288 patent explains that “if multiple species of solute are present, this may lead to the formation of multiple sedimenting boundaries, each corresponding to a resolvable species.” Ex. 1001, 19:57-60. But “the presence of multiple species with similar sedimentation coefficients will cause the boundary to be broader than expected on the basis of diffusion alone.” *Id.*, 17:29-31. Thus, the record indicates that the POSA would have considered the broad peaks in Figure 3 to have been concealing peaks that correspond with partial or fragmented species. Hansen, ¶¶ 106-107. Novartis, however, fails to address the poor quality of the distribution plot in Figure 3 in its Petition and the Berkowitz Declaration is also silent on this issue.

Second, the Petition ignores that Le Bec’s description of the C(s) distribution in Figure 3 fails to account for the single stranded AAV peak at about 90S. At most, Le Bec provides a rough qualitative assessment of the relative amounts “of full AAV particles (>80%),” and “viral genome in double-stranded

form (>50%).” Ex. 1003, 19:11-15; Hansen, ¶108. This disclosure fails to meet Element 1[c]’s requirement of “integrating the area under each peak in the C(s) distribution to determine the relative concentration of each peak, wherein each peak represents a species of recombinant AAV particle.”

Le Bec states that “[t]he sedimentation coefficient of the various AAV viral particles (empty, full, aggregate) and other present populations (subparticles, contaminant proteins, aggregate) in the purified products was determined by real-time centrifugation.” Ex. 1003, 15:19-28; Petition 13. The Petition, however, does not provide any evidence of, for example, “integrating the area under each peak in the C(s) distribution to determine the relative concentration of each peak” corresponding to, for example, partial or fragmented species. Hansen, ¶ 109.

“[C]laims are interpreted with an eye toward giving effect to all terms in the claim.” *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 950 (Fed. Cir. 2006); *see also Pause Tech., LLC v. TiVo, Inc.*, 419 F.3d 1326, 1331 (Fed. Cir. 2005) (rejecting interpretation of claim element that ignored “other language appearing later in the claim.”) (quotations omitted). The “fundamental problem with [Novartis’s] basis for its argument” for Element 1[c] “is that it simply does not address” how Le Bec integrates and determine the area of each peak and the relative concentration of each peak, here, including partial and fragmented species. *St. Jude Med., LLC*, 977

F.3d at 1239. The failure of Ground 1 to account for the entirety of Element 1[c] “precludes anticipation by [Le Bec] on the record of” the Petition. *Id.* at 1241.

2. Le Bec Fails to Anticipate Because Its Method Would Have Had to Been Impermissibly Modified to Meet Element 1[c]

Because Le Bec clearly does not integrate certain peaks in its C(s) distributions to determine their relative concentrations, the Petition argued that “users [of SEDFIT] **could** determine relative concentrations by integrating areas under the curve.” Petition, 28 (citing Ex. 1020, ¶¶27-40, 83) (emphasis added). The fact that the POSA could conduct such integrations to determine the concentrations of partial and fragmented species does not meet the threshold for anticipation. *See Guangdong Alison Hi-Tech Co. v. Int’l Trade Comm.*, 936 F.3d 1353, 1364 (Fed. Cir. 2019). An element that is not expressly disclosed “may be inherently disclosed only if it is necessarily present, not merely probably or possibly present, in the prior art.” *Id.* The fact that Le Bec’s method, according to Novartis, *could* be used to determine the concentrations of peaks for which no concentrations are disclosed, does not mean that Le Bec necessarily discloses this step.

Further, the POSA would have understood that to determine concentration from AUC peaks obtained via absorbance spectroscopy at 276 nm, the method that Le Bec employs (see Ex. 1003, 15:25-26 (“sedimentation was followed by

absorbance at the wavelength of 276 nm”)), an extinction coefficient would have been required for each peak. This is because the correlation between peak area and concentration may depend upon use of the extinction coefficient of a species at a particular wavelength of light. *Supra* Section II.B.1. The Petition and Berkowitz Declaration fail to identify how Le Bec’s absorbance-based method determines the concentration of partial or fragmented genomes (e.g., peaks at 77S or 90S) when it fails to provide those concentrations (*supra* Sections IV.A-IV.A.1) or the extinction coefficient at 276 nm required to have determined those concentrations. Hansen, ¶ 110.

Indeed, Dr. Berkowitz’s 2007 publication (Ex. 1004, “Berkowitz 2007”) explains that to determine concentration of a viral particle using an absorbance-based AUC detection, the POSA may need to know the extinction coefficient for that species. Hansen, ¶ 111. Berkowitz 2007 states that “AUC experiments can provide accurate and useful results when appropriate steps are taken to deal with the variability in signal response (extinction coefficient) for different adenovirus species.” Ex. 1004, 17. In the studies documented in Berkowitz 2007, however, the authors “ha[d] not attempted to apply corrections to account for extinction coefficient differences.” Ex. 1004, 21. Berkowitz 2007 further raised “concerns about the accuracy of [] reported adenovirus UV extinction coefficient.” *Id.* at 34.

Another reference relied on in the Petition, Cole (Ex. 1005), states that “[u]nder conditions where the Beer–Lambert law holds, the absorbance signal is directly proportional to solute concentration: $A = \epsilon cl$, where ϵ is the solute’s weight extinction coefficient, c is the weight concentration, and l is the sample path length.” Ex. 1005, 152. Thus, to compare relative concentrations among species at wavelengths where the extinction coefficients vary between species, the POSA would have needed to determine the extinction coefficient for each species. Hansen, ¶ 112. Le Bec, however, provides no guidance on how to do so and the Petition and Berkowitz Declaration ignore this deficiency of Le Bec.

To practice the Element 1[c] with Le Bec’s data, the POSA would have had to obtain the necessary extinction coefficients viral particles for which Le Bec does not disclose concentrations (e.g., Le Bec’s single stranded genomes at 90S of the viral AAV particle species at 77S). *Supra* Section II.B.1; Hansen, ¶¶ 52-54, 110-113. There is no evidence that Le Bec did so, and indeed this would have been a significant departure from Le Bec’s disclosure of a qualitative comparison between empty and full capsids, that did not indicate the concentrations of different rAAV species containing partial or fragmented genomes. Ex. 1003, 18:10-19:15, Figures 2-3; Hansen, ¶ 113.

In order to disclose Element 1[c], Le Bec would have to be modified by either changing the detection technique or by disclosing a way by which the

extinction coefficients of partial and modified genome species could be identified. Le Bec did not do this and thus cannot be an anticipatory reference. *Enplas Display Device Corp. v. Seoul Semiconductor Co., Ltd.*, 909 F.3d 398, 405 (Fed. Cir. 2018) (“[p]rior art that must be modified to meet the disputed claim limitation does not anticipate the claim.”) Novartis fails to explain how Le Bec discloses “within [its] four corners” the information required to determine the concentration of partial or fragmented genomes present in its AAV preparations. *Net MoneyIN*, 545 F.3d at 1371. Thus, Novartis’s Ground 1 fails to establish anticipation of claim 1.

Because the other claims challenged in Ground 1, claims 17-18, 20-21, 23, and 32-33, all depend directly or indirectly from claim 1, Novartis has not established anticipation of these claims. Accordingly, Ground 1 fails to support a reasonable likelihood that Novartis has proven anticipation by Le Bec.

B. Ground 2: Novartis Fails to Establish Le Bec Rendered Claim 1 Obvious

Novartis further alleges that Le Bec alone rendered claim 1 obvious because “POSAs were motivated to assess virus preparations for such undesirable contaminants.” Petition, 33-34. For Element 1[c], Novartis argues that “[i]ntegrating the area under the peaks generated in an SV-AUC experiment is a

standard technique used to determine the relative concentrations of components in the analyzed sample.” Petition, 36.

As explained (*supra* Section IV.A), Le Bec discloses the use of AUC to obtain approximate concentration comparisons between empty capsids and fully intact capsids. Ex. 1003, 19:1-15. Le Bec, however, does not teach or suggest integrating the area under each peak in the C(s) distribution to determine the relative concentration of each peak in the distribution, including peaks corresponding to partial and fragmented rAAV species present in its disclosed rAAV preparations. *Supra* Section IV.A.1. The Petition also fails to establish that Le Bec alone would have motivated the POSA to use AUC to integrate the area under each peak in the C(s) distribution to determine the relative concentration of each peak of an rAAV preparation with a reasonable expectation of success in doing so. The POSA would have understood, for example, that the need to know the extinction coefficient of each rAAV species in Le Bec’s disclosure presented an obstacle to determining the concentrations of rAAV peaks associated with partial or fragmented genome and extinction coefficients were not readily obtained. Hansen, ¶ 115. Thus, Le Bec alone fails to render obvious claim 1.

1. Novartis Does Not Explain How the POSA Would Have Modified Le Bec to Arrive at Claim Element 1[c]

As an initial matter, the Petition’s Ground 2 obviousness argument based on Le Bec is legally deficient. The Petition fails to identify how Le Bec’s disclosure would have been modified to meet Element 1[c]. The Petition merely states that “[i]ntegrating the area under the peaks generated in an SV-AUC experiment is a standard technique used to determine the relative concentrations of components in the analyzed sample.” Petition, 36-37. As explained for anticipation, however, the Petition does not address claim 1’s requirement to integrate the area under each peak in the C(s) distribution to determine the relative concentration of *each* peak, including for partial or fragmented genome rAAV particles. *Supra* Sections IV.A.1-IV.A.2.

Ground 2 does not address this deficiency in Le Bec’s disclosure or explain why and how the POSA would have modified Le Bec with knowledge of the “standard technique” of integration to arrive at claim 1. Without this explanation, Ground 2 “stymies a proper obviousness analysis.” *Teradata Corp.*, No. IPR2020-00942, Paper 10 at 14-15 (denying institution because “the Petition neither identifies any difference between the teachings of the references and claim 1, nor identifies any specific allegedly obvious modification of either reference’s teachings”) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966)).

The Petition states that Le Bec discloses certain concentration values for populations of peaks in its C(s) distributions of Figures 2 and 3, and Novartis maintains that “obtaining the percentages/relative concentrations disclosed in Le Bec using a distribution profile involves integrating the area under the curve for the peaks of interest.” Petition, 27. The deficiency in Novartis’s anticipation Ground 1, however, is not merely whether Le Bec integrated the area under its peaks, but rather whether Le Bec “integrat[ed] the area under **each peak** in the C(s) distribution to determine the relative concentration of **each peak**....” Whether integration “is a standard technique used to determine the relative concentrations of components” (Petition, 36) does not address Le Bec’s deficiency in meeting Element 1[c]. Indeed, the Petition provides little in the way of substance to distinguish its obviousness Ground 2 based on Le Bec from its anticipation Ground 1, or to address what disclosure is missing from Le Bec to meet Element 1[c]. Thus, Novartis “advances analysis that merges anticipation and obviousness, which, on this record, signals a lack of the degree of particularity required under Section 312(a)(3).” *Sinjimoru Inc. v. Geneze Innovation Inc.*, IPR2021-00493, Paper 8 at 16 (PTAB July 28, 2021) (denying institution). For this failure alone, Ground 2 fails to establish a reasonable likelihood that Le Bec alone rendered claim 1 obvious.

2. Novartis Fails to Establish Why the POSA Would Have Been Motivated to Modify Le Bec to Arrive at Element 1[c]

Ground 2 fails to identify why the POSA would have been motivated to modify Le Bec to arrive at Element 1[c]. Hansen, ¶¶ 116-121. Novartis’s argument that “[i]ntegrating the area under the peaks generated in an SV-AUC experiment is a standard technique used to determine the relative concentrations of components in the analyzed sample” does not support how or why the POSA would have modified Le Bec’s method to integrate the area under each peak in the C(s) distribution to determine the relative concentration of each peak, including, partial and fragmented genome rAAV species. *TriVascular, Inc.*, 812 F.3d at 1066 (The Board must “be careful not to allow hindsight reconstruction of references . . . without any explanation as to *how* or *why* the references would be combined to produce the claimed invention.”) (emphasis in original; internal quotation marks and citations omitted).

In an obviousness analysis, “[e]vidence that supports, rather than negates, patentability must be fairly considered,” as the POSA has “knowledge of the entire body of technological literature, including that which might lead away from the claimed invention.” *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). The prior art as a whole taught the POSA that to determine the relative concentration of species within rAAV preparations by AUC using absorbance at

276 nm, the POSA would need to apply the extinction coefficient of each species to correlate peak area to concentration. *Supra* Section IV.A.2 (citing Exs. 1004, 1005); Hansen, ¶¶ 52-54, 117-121. The literature Novartis filed with its Petition, including a paper by its own expert, Dr. Berkowitz, explains that obtaining accurate extinction coefficients was often not readily possible.

The Berkowitz 2007 publication regarding the application of AUC to adenovirus particles (Ex. 1004) explains that “AUC experiments can provide accurate and useful results when appropriate steps are taken to deal with the variability in signal response (extinction coefficient) for different adenovirus species.” Ex. 1004, 17. Restated, depending on the wavelength different species absorb UV light to different degrees, so the correlation between peak area and concentration may be different for each species. The extinction coefficient adjusts for this difference between species. Ex. 1005, 152 (Explaining that “absorbance signal is directly proportional to solute concentration: $A = \epsilon cl$, where ϵ is the solute’s weight extinction coefficient, c is the weight concentration, and l is the sample path length.”). Hansen, ¶¶ 117-120.

Because of the need to account for differing extinction coefficients between species, Dr. Berkowitz “ha[d] not attempted to apply corrections to account for extinction coefficient differences” in his publication about applying AUC to adenoviruses. Ex. 1004, 21. The Berkowitz 2007 publication further noted

“concerns about the accuracy of [] reported adenovirus UV extinction coefficient” as a reason to avoid using absorbance in AUC experiments. Ex. 1004, 34.

Novartis falls prey to “hindsight syndrome by reasoning backward from the teaching of the patent itself.” *Creo Prod., Inc. v. Presstek, Inc.*, 166 F. Supp. 2d 944, 966 (D. Del. 2001) (internal quotation marks omitted), *aff’d*, 305 F.3d 1337 (Fed. Cir. 2002); *see also Rockwell Int’l Corp. v. U.S.*, 147 F.3d 1358, 1364 (Fed. Cir. 1998); *Jones v. Hardy*, 727 F.2d 1524, 1529 (Fed. Cir. 1984); *W.L. Gore*, 721 F.2d at 1553. Consistent with Berkowitz 2007, the inventors explain that at the time of the invention, “it [was] not possible to determine empirically the extinction coefficient of particular species of recombinant viral particles (e.g., viral particles with fragmented genomes of unknown size and sequence).” Ex. 1001, 24:35-38. By finding a way to calculate extinction coefficients of variant rAAV species, the inventors were able to determine the relative concentrations of these species. This innovation helped lead to the invention of claim 1. *Supra* Section II.B.1.

Neither the Petition nor the Berkowitz Declaration mention the need to account for differing extinction coefficients among different rAAV species analyzed at 276nm in Le Bec, particularly unknown partial and/or fragmented genome species at 77S and 90S. It follows, therefore, that neither the Petition nor the Berkowitz Declaration explain how to determine extinction coefficients for unknown partial and/or fragmented genome species. Hansen, ¶¶ 120-121. In fact,

the Berkowitz 2007 publication indicates that the POSA would have avoided relying on absorbance-based peak detection for AUC applied by Le Bec because of issues with extinction coefficients. *Id.*

Novartis does not establish why the POSA would have been motivated to use Le Bec's AUC method to integrate the area under each peak in the C(s) distribution to determine the relative concentrations of each species present in the rAAV preparation, for example partial and fragmented genome rAAV species, particularly given the challenges surrounding extinction coefficients. The POSA would have understood the need to know the extinction coefficients of individual species to accurately determine the relative concentration of each species present in an rAAV preparation using Le Bec's method at 276nm. Ex. 1004, 17; Ex. 1005, 152. Given the absence of information regarding extinction coefficients in Le Bec, the POSA had no guidance on how to apply Le Bec's AUC method to determine the relative concentration of each species in an rAAV preparation. Hansen, ¶¶ 120-121. The POSA would not have been motivated to determine the concentration of certain peaks, including peaks at 77S and 90S in Le Bec's Figures 2 and 3, because it would not have been possible to accurately determine their concentrations without their extinction coefficients at 276 nm. Hansen, ¶ 119.

Novartis's argument that "[i]ntegrating the area under the peaks generated in an SV-AUC experiment is a standard technique used to determine the relative

concentrations of components in the analyzed sample” (Petition, 36) ignores that the POSA would not have been motivated to do so for each peak in the C(s) distribution. Without extinction coefficients, merely integrating peak area in Le Bec’s C(s) distribution based on absorbance at 276 nm would not have alone provided a meaningful measure of concentration for *each* species in the distribution, such as partial or fragmented rAAV species. Hansen, ¶ 121.

“[O]bviousness concerns whether a skilled artisan not only *could have made* but *would have been motivated to make* the combinations or modifications of prior art to arrive at the claimed invention.” *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015)) (emphasis original). Because Le Bec does not disclose information required to accurately determine concentration of partial or fragmented rAAV species—or even how to obtain such information—the POSA would not have been motivated to practice Element 1[c].

3. Novartis Fails to Establish that the POSA Would Have Had a Reasonable Expectation of Success in Arriving at Element 1[c]

Novartis’s obviousness analysis, which merely presents Le Bec while alleging that “[i]ntegrating the area under the peaks generated in an SV-AUC experiment is a standard technique used to determine the relative concentrations of components in the analyzed sample” fails to consider the Element 1[c] in its entirety. Element 1[c] recites “integrating the area under *each* peak in the C(s)

distribution to determine the relative concentration of **each** peak.” Le Bec lacks guidance on extinction coefficients at 276 nm for any of its peaks, and Novartis does not explain how the POSA would have obtained the required extinction coefficients at 276 nm for partial or fragmented rAAV species, like those at 77S and 90S in Le Bec’s Figure 2. Without this information, Novartis cannot establish a reasonable expectation in successfully determining the relative concentrations of each peak, particularly peaks corresponding to partial or fragmented genomes, based on Le Bec alone. Hansen, ¶¶ 122-123.

“It was [Novartis]’s burden to demonstrate” that the POSA “would have had a reasonable expectation of success in” combining teachings “to achieve the claimed invention.” *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367–68 (Fed. Cir. 2016) (internal quotation marks and citations omitted). The Petition and accompanying Berkowitz Declaration do not provide any explanation for a why the POSA would have reasonably expected the claimed method to have worked without the application of extinction coefficients by Le Bec to partial or fragmented genome AAV species peaks. To the contrary, the references submitted with the Petition indicate that Le Bec’s failure to provide any hint of information relating to extinction coefficients would have led the POSA to conclude that it was not reasonably possible to determine relative concentrations for each peak. Hansen, ¶ 123. *In re Dow Chem.*, 837 F.2d at 473 (the POSA has

“knowledge of the entire body of technological literature, including that which might lead away from the claimed invention.”). Thus, Novartis fails to establish a reasonable expectation of success for Element 1[c].

Because the other claims challenged in Ground 2, claims 17-18, 20-21, 23, and 32-33, all depend directly or indirectly from claim 1, Novartis has not established the obviousness of these claims. Accordingly, Ground 2 fails to support a reasonable likelihood that Novartis has proven obviousness over Le Bec alone.

C. Ground 3: Novartis Fails to Establish that Le Bec In View of Berkowitz and/or Cole Rendered Claims 1 and 2 Obvious

1. Ground 3 Novartis Fails to Establish that Le Bec In View of Berkowitz Render Element 1[c] Obvious

The addition of the Berkowitz (Ex. 1004) and Cole (Ex. 1005) references to Le Bec in Novartis’s obviousness Ground 3 do not overcome the deficiencies of Ground 2 for claim 1. For Element 1[c], the Petition contends that “Berkowitz expressly teaches that ‘quantification’ of each particle would be accomplished by integration.” Petition, 38. The Petition relies on Berkowitz’s statement that “simple peak area integration, taking into account radial dilution effects ... allows the percentage of *EC [empty capsid]* material present in a virus preparation to be readily calculated.” Petition 16, 38 (citing Ex. 1004, 21) (emphasis added). The Petition’s Ground 3 argument based on Le Bec in view of Berkowitz is duplicative

of the Petition's Ground 2 argument that "[i]ntegrating the area under the peaks generated in an SV-AUC experiment is a standard technique used to determine the relative concentrations of components in the analyzed sample" in Ground 2.

Petition, 36. Novartis is merely providing a specific example of integrating an AUC peak. Neither argument, however, remedies the Petition's failure to address the absence of disclosure in Le Bec relating determining the concentration of peaks at, for example, 77S and 90S. *Supra* Section IV.A.1. The issue is not merely whether the POSA would have known how to integrate peaks; rather, the deficiency in all of Novartis's grounds is the second part of Element 1[c], "integrating the area under each peak ... to **determine the relative concentration of each peak.**" Hansen, ¶¶ 124-125. Le Bec fails to demonstrate concentration determination for certain peaks and Berkowitz 2007 does not cure Le Bec's omission. Hansen, ¶¶ 124-129.

For example, the quoted passage in Berkowitz (Petition, 38 (citing Ex. 1004, 21)) addresses the quantification of empty capsids for adenovirus compositions, rendering it cumulative with the Petition's Le Bec anticipation argument for Ground 1 (Petition, 27-28) and obviousness argument in Ground 2 (Petition, 36-37). Le Bec discloses approximate relative concentrations of "empty" and "full" capsids, but Le Bec does not address the concentration of peaks for other partial or

fragmented rAAV particle species in its C(s) distribution, for example the species at 77S and 90S. *Supra* Section IV.A.1.

Merely applying Berkowitz’s quantification techniques to Le Bec’s AUC method for rAAV preparation would not address Le Bec’s failure to render obvious Element 1[c]’s requirement of integrating the area under each peak to determine the relative concentration of each peak, including peaks corresponding to partial and/or fragmented rAAV species. Hansen, ¶¶ 126-127. “[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). The Petition never explains how or why the POSA would have modified Le Bec based on Berkowitz. For example, Le Bec uses absorbance detection at 276nm wavelength to obtain its C(s) distribution (Ex. 1003, 15:25-26), whereas Berkowitz 2007 describes avoiding absorbance detection because of issues obtaining accurate extinction coefficients. Ex. 1004, 21 (“At present we have not attempted to apply corrections to account for extinction coefficient differences.”); Hansen, ¶ 128.

Indeed, Novartis does not explain why the POSA would have been motivated to apply Berkowitz—which expressly avoids absorbance measurements because of issues obtaining extinction coefficients (Ex. 1004, 21, 34)—with Le Bec which uses absorbance measurements that require applying extinction

coefficients to determine concentration. Moreover, Novartis does not identify teachings in Berkowitz demonstrating the application of AUC to quantify partial or fragmented viral particles. Hansen, ¶¶ 128-129. The Petition states that “Berkowitz provides examples of these calculations for empty capsids and aggregates in Table 2.” Petition, 16 citing (Ex. 1004, 29 (Table 2)). Novartis, however, never addresses the quantification of partial and/or fragmented virus particles using either Le Bec or Berkowitz. Hansen, ¶ 128.

Novartis’s argument that Berkowitz teaches “‘quantification’ of each particle would be accomplished by “simple peak area integration” impermissibly applies hindsight to arrive at the conclusion of obviousness. *TriVascular*, 812 F.3d at 1066 (Fed. Cir. 2016) (The Board must “be careful not to allow hindsight reconstruction of references . . . without any explanation as to *how* or *why* the references would be combined to produce the claimed invention.”) (emphasis in original; internal quotation marks and citations omitted). For example, the inventors were able to rely on absorbance spectroscopy, and its incumbent advantages of permitting analysis of smaller sample size and the absence of a requirement to match exactly buffer systems between sample and reference, because they determined a way to calculate extinction coefficients for partial and fragmented genome particles at 260 nm. *Supra* Section II.B.1. Novartis has failed to identify any reference in the art that addresses the extinction coefficient issue

associated with the 276 nm absorbance detection applied in Le Bec. Thus, Ground 3 fails for claim 1 for similar reasons as Ground 2.

2. Ground 3 Fails to Establish that Le Bec, Berkowitz, and Cole Render Claim 2 Obvious

The Petition never indicates that the asserted prior art references taught or suggested the “standard curve” recited in Element 2[c]. Petition, 45. With this element absent from the art, Novartis resorts to relying on conclusory testimony from its expert, Dr. Berkowitz, that the “use of reference standards or standard curves was routinely applied to sedimentation coefficients and AUC experiments.” Petition, 45 (citing Ex. 1020, ¶¶209-210). But neither the Petition nor Berkowitz Declaration provides a single example of a standard curve applied to sedimentation coefficients or AUC experiments. *Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Paper 9 at 15 (PTAB Aug. 24, 2022) (precedential) (Expert testimony that “does not cite to any additional supporting evidence or provide any technical reasoning to support his statement ... is entitled to little weight.”)

In fact, it was the '288 patent's inventors' who developed a method including that the “calculated S values can be plotted to generate a standard curve to which recombinant viral species of unknown molecular weight or genome size can be compared to determine the molecular weight of the unknown species” or rAAV. Ex. 1001, 24:43-46; *supra* Section II.B.1. Novartis's inability to point to

any other examples in which sedimentation coefficients of partial or fragmented viral particles were used to identify viral particles by their genome size demonstrates the inventiveness of the '288 patent. Hansen, ¶¶ 130-131. Novartis resorts to hindsight-based reasoning to argue that “[w]ith a few reference points, a POSA would understand how to mathematically estimate the mass corresponding to a given sedimentation coefficient.” Petition, 46 (citing Ex. 1013, 9-10; Ex. 1020, ¶¶ 211-214.)

As the basis for its argument, the Petition cites the equation stating:

$$s \equiv \frac{v}{\omega^2 r} = \frac{M_b}{f}$$

“where s is the sedimentation coefficient, M_b is the effective or buoyant mass of the particle, and f is the frictional coefficient.” Petition, 46 (citing Ex. 1005, 146). Novartis further argues that “[i]n a hypothetical system where the rAAV particles are uniform and have an identical frictional coefficient, the sedimentation coefficient (s) will be proportional to the effective particle mass (M_b).” Petition 46 (citing Ex. 1013, 9-10; Ex. 1020, ¶¶ 211-214). Novartis’s entire argument is premised on the assumption that the sedimentation coefficient would vary linearly with genome size (i.e., the amount of DNA packaged within the capsid) in such a hypothetical system. The Berkowitz Declaration explains this broad assumption:

[F]or rAAV particles differing only by their genome size, a POSA would expect any changes would be internal and not affect the frictional force of the AAV capsid shell (to a good first approximation). Thus, a POSA would generally expect the S-value of an rAAV particle with a variant genome to vary linearly (to a good first approximation) with its buoyant mass M_b (with the amount of DNA inside the AAV capsid being the major controlling factor influencing the change in a AAV particle's s value).

Ex. 1020, ¶ 213.

Novartis argues that the POSA would have assumed that all rAAV particles, including partial and fragmented rAAV genome particles has the same frictional coefficient, f , such that the sedimentation varied linearly with rAAV species molecular weight. Neither the Petition nor Berkowitz Declaration provide support for why the POSA would have assumed that all rAAV particle species would have the same frictional coefficient. In fact, Berkowitz 2007 and Cole contradict this assumption. Hansen, ¶¶ 46-47, 132-135. Novartis simply disregards the parts of these disclosures that contradict its position. “It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill

in the art.” *In re Wesslau*, 353 F.2d 238, 241 (CCPA 1965); *see also Henny Penny*, 938 F.3d at 1332; *W.L. Gore*, 721 F.2d at 1551.

Cole and Berkowitz 2007 describe why the POSA would **not** have assumed that the frictional coefficients for all rAAV species in a preparation were identical. Hansen, ¶¶ 45-47, 135-139. Cole states that “[a]lthough the c(s) distribution can be converted to a distribution of molar masses [c(M) distribution], the derived masses will only be accurate if there is one dominant species present or if all the species have equal frictional ratios.” Ex. 1005, 166. Heterogeneous, rAAV preparations like Le Bec and those of the ’288 patent contain multiple species. Novartis does not provide any evidence for why a POSA would have assumed that the rAAV species would have had “identical frictional coefficient[s].” Petition, 46; Hansen, ¶ 140.

Berkowitz’s 2007 publication observed that for adenovirus preparations, different species did indeed have different frictional coefficients attributable to spike features on the surface of adenovirus particles. Ex. 1004, 18, 31-32; Hansen, ¶¶ 46-47, 136-137. Berkowitz 2007 states that the high frictional coefficient of adenovirus particles was surprising given that the “adenovirus capsid is well known to have an icosahedral shape that can be well approximated by a hydrodynamic sphere having a diameter that is 0.94 times the face-to-face distance of the icosahedron.” Ex. 1004, 18 (internal citation omitted). Berkowitz found

that the unexpected frictional behavior of adenovirus particles may have been caused by spike projections on the outer surface of the particles. *Id.* (“These spike projections must impart a significant amount of frictional drag on the overall adenovirus particle.”) AAV particles were also observed to have “three-fold proximal spikes” on their surface. Ex. 2006, 10408-409; Hansen, ¶¶ 42-43, 136. Berkowitz 2007 observes “adenovirus material migrating between 500 and 600 S as possibly representing adenovirus monomers that have lost their fiber spikes Such a particle would have nearly the same molecular mass as an intact virus monomer but significantly reduced hydrodynamic drag and therefore a higher sedimentation coefficient than the intact adenovirus particle.” Ex. 1004, 31. Thus, the POSA considering Berkowitz 2007 would have had concerns that certain rAAV species could exhibit similar frictional behavior, and such behavior would disrupt the linear relationship between *S* values and *M_b*. Hansen, ¶¶ 46, 136.

Additionally, claim 2 recites that the “the genome size of a particular species of recombinant AAV particles is calculated by comparing the *S* value of the species to a standard curve.” For there to be a “highly linear relationship ...between sedimentation coefficient and **genome size**” changes in mass must be attributable to genome changes (i.e, the amount of encapsidated DNA) and not changes to the mass of the capsid. Ex. 1001, 49:17-18 (emphasis added), FIG. 8; *supra* Section II.B.1. Berkowitz 2007 explains, however, why the POSA would

not have assumed changes in mass for rAAV species would be due only to changes in the amount of packaged genome. Berkowitz 2007 explains that changes to the spike proteins on the outside of the capsid have implications not only for frictional coefficient, but also for the ratio of genome to protein. Ex. 1004, 31-32 (“[P]articles with missing spikes would also have a slightly higher DNA to protein ratio and therefore have a slightly higher buoyant density than the intact adenovirus particle.”) From Berkowitz 2007, the POSA would have understood that changes to particle mass would not be limited to genome size, but could also be attributed to changes in the capsid protein. Hansen, ¶¶ 47, 138-139. This is another reason why “a POSA would generally” not “expect the S-value of an rAAV particle with a variant genome to vary linearly ... with its buoyant mass M_b (with the amount of DNA inside the AAV capsid being the major controlling factor influencing the change in a AAV particle’s s value).” *Contra* Ex. 1020, ¶ 213; Petition, 46-47.

Novartis uses the challenged claims as a roadmap to “selectively cull[] from the prior art to fit the parameters of the patented invention.” *ATD Corp.*, 159 F.3d at 546. In so doing, Novartis ignores that the teachings of Cole and Berkowitz 2007 in their entirety fail to support Novartis’s conclusions of obviousness. For example, Novartis and Dr. Berkowitz improperly cherry pick the parts of Berkowitz 2007 that support its arguments, while disregarding those parts that do

not. Berkowitz 2007 and Cole make clear that the POSA would not have expected a linear relationship between S-values and genome molecular weight. Hansen, ¶ 140. Thus, the POSA would not have been motivated to design a method that determines genome molecular weight from sedimentation coefficient, because references like Cole and Berkowitz 2007 taught that factors relating to changes in capsid frictional coefficient and capsid protein mass also likely impact sedimentation S values. Hansen, ¶ 141. Likewise, the POSA would not have reasonably expected, based on Cole and Berkowitz 2007, that a standard curve correlating sedimentation coefficients and genome mass would accurately project genome mass of unknown species, because changes in mass were thought to occur to capsid proteins as well. Hansen, ¶ 141.

An obviousness analysis requires examining what the POSA would have done without the guidance from the inventors. *Arendi* , 832 F.3d at 1361 (stating that “[i]n reaching this conclusion, the court must avoid ‘hindsight bias and must be cautious of arguments reliant upon ex post reasoning.’”); *TriVascular*, 812 F.3d at 1066 (the Board must “be careful not to allow hindsight reconstruction of references . . . without any explanation as to how or why the references would be combined to produce the claimed invention”); *InTouch Techs., Inc. v. VGO Commc’ns*, 751 F.3d 1327, 1352 (Fed. Cir. 2014) (finding that the “expert also succumbed to hindsight bias in her obviousness analysis.”).

The inventors of the '288 patent observed that changes in frictional coefficient did not change for rAAV. This was not something that the POSA would have known or expected based on the prior art such as Cole and particularly Berkowitz 2007. Hansen, ¶ 141. This new analytical step allowed the inventors to determine genome molecular weight based on sedimentation coefficient. The relied-upon prior art fails to support Novartis's obviousness theory of Ground 3 for claim 2.

V. NOVARTIS HAS FAILED TO ESTABLISH A NEED FOR MULTIPLE PARALLEL PETITIONS

By filing two Petitions against the '288 patent, Novartis has abused the IPR process. “[M]ultiple petitions by a petitioner are not necessary in the vast majority of cases.” TPG, 59. Novartis's challenge of the '288 patent is not one of the “rare” cases where “two petitions ... may be needed.” *Id.*

As explained herein, the number of challenged claims is not “large,” because of the many overlapping elements shared between the challenged claims, and Novartis does not allege any “dispute about priority date.” *Id.* Novartis's two Petitions merely allow Novartis to get multiple bites at the apple by presenting multiple unpatentability grounds for nearly every claim. *Global Tel*Link Corp. v. HLFIP Holding, Inc.*, No. IPR2021-00445, Paper 14 at 18 (PTAB June 22, 2021) (“There is no entitlement to assert . . . more than one ground . . . against each

challenged claim.”). Novartis had the burden to demonstrate why two Petitions were necessary, but Novartis “has not shown that it was necessary to distribute its challenges across [two] petitions.” *Fantasia Trading LLC v. Cognipower, LLC*, IPR2021-00068, Paper 22 at 10 (PTAB May 12, 2021). Should the Board decide to institute either Novartis Petition challenging the ’288 patent, it should exercise its discretion to deny institution of the other Petition.

A. The Number of Challenged Claim Is Not Large Because of Significant Overlap Among the Claim Elements

Novartis complains that “[t]here are thirty-four challenged claims in total, seven of which are independent claims.” Paper 2, 1-3. The number of claims asserted in litigation is only a threshold fact that does not alone justify two petitions. The Board has denied petitions challenging *fifty-three* claims because of “a great deal of repetition or overlap among the different petitions that could have been avoided had each petition been directed to grounds that rely on one primary prior art reference.” *Fantasia*, IPR2021-00068, Paper 22 at 12.

Novartis had the burden to explain why it needed two Petitions. *Comcast Cable Commc’ns, LLC v. Rovi Guides, Inc.*, IPR2020-00796, Paper 8 at 10-11 (PTAB Oct. 21, 2020); *Fantasia*, IPR2021-00068, Paper 22 at 10 (It is “petitioner’s burden under § 314(a)” to explain why multiple petitions are necessary). Novartis, however, fails to “explain sufficiently how the two Petitions

at issue ... collectively challenge the claims in a materially different manner that justifies multiple proceedings.” *Comcast*, IPR2020-00796, Paper 8 at 10-11 (denying institution on multiple petitions challenging a total of 56 claims.)

In its bare bones, two-and-a-half-page brief to support multiple Petitions, Novartis explains that “the claims have been divided into two distinct claim sets, with the claims of Petition 1 [1044IPR] relating primarily to claimed parameters of performing SV-AUC and the claims of Petition 2 [1045IPR] relating primarily to analyses of SV-AUC data.” Paper 2 at 2-3. This statement merely states how Novartis chose to divide claims between Petitions *without explaining why* the division of claims between two Petitions was necessary. *See Infinera Corp. v. Oyster Optics, LLC*, IPR2020-00326, Paper 12 at 12 (PTAB June 26, 2020) (“[A]lthough Petitioner correctly argues that the petitions in the two proceedings challenge different claims, Petitioner chose that claim allocation without persuasively explaining the ‘need’ to do so.”). The repetition of many elements among multiple claims combined with the repetitive arguments supplied by Novartis belies a legitimate basis for two Petitions.

Novartis considers claim 1 (1044IPR), as related “to claimed parameters of performing SV-AUC,” and claim 4, challenged in the 1045IPR, as related “to analyses of SV-AUC data.” Paper 2 at 2-3. Independent claims 1 and 4 differ in their preambles, with claim 1 reciting a “method of characterizing a preparation of

[rAAV] particles” and claim 4 reciting a “method to determine the presence of empty capsids or capsid particles comprising variant sized [rAAV] genomes.”

Ground 1 of both Petitions challenge claims 1 and 4 as anticipated by Le Bec.

Ground 1 in both Petitions challenge claims 1 and 4 as obvious over Le Bec. But each Petition contains only a single sentence in Ground 1 addressing the preambles of claims 1 and 4 with nearly identical cites to Le Bec. *Compare* 1044IPR, 23 (citing Ex. 1003 15:17-23, 16:26-29, 18:1-6); 1045IPR, 19-20 (citing Ex. 1003, 15:17-23, 16:25-29, 18:1-6).

Elements (a) and (b) of claims 1 and 4 are effectively identical. In fact, all the challenged independent claims, i.e., claims 1 and 2 (challenged in IPR2023-01044) and 4-8 and 12 (challenged in IPR2023-01045) recite the elements:

subjecting the preparation to analytical ultracentrifugation under boundary sedimentation velocity conditions wherein the sedimentation of [rAAV] particles is monitored at time intervals,

plotting the differential sedimentation coefficient distribution value (C(s)) versus the sedimentation coefficient in Svedberg units (S)

Ex. 1001, 54:23-29 (claim 1); 54:37-43 (claim 2); 54:60-66 (claim 4); 55:7-13 (claim 5); 55:28-34 (claim 6); 55:49-55 (claim 7); 56:1-7 (claim 8); 56:50-56 (claim 12). But these are not the only elements present in several claims.

Independent claims 1 and 5-8 and dependent claims 3 and 15 each recite:

integrating the area under each peak in the C(s) distribution to determine the relative concentration of each species of recombinant AAV particles....

Ex. 1001, 54:30-33 (claim 1); 54:52-55 (claim 3); 55:14-16 (claim 5); 55:35-37 (claim 6); 55:56-59 (claim 7); 56:8-10 (claim 8); 57:1-4 (claim 15).

Because of the substantial overlap between the claims, the total number of claims does not support multiple Petitions. In contrast to the Board decisions that Novartis cites (Paper 2, 2), Novartis’s challenges are not directed to “non-overlapping in their subject matter.” *Contra Google LLC v. Hammond Dev. Int’l, Inc.*, IPR2020-00413, Paper 16 at 42 (PTAB July 14, 2020) (Instituting after Patent Owner “d[id] not request that we exercise our discretion to deny institution under § 314(a)”). Novartis repeatedly relied on the “normal efficiencies of referring back or consolidating arguments.” *Contra Google LLC*, IPR2020-00413, Paper 16 at 42 (quotation marks omitted).

B. Novartis Challenged Most Claims with Multiple Grounds

Similarities between the challenged claims permitted Novartis to challenge most claims with two and often three separate Grounds “with significant repetition of argument among the various petitions.” *Fantasia*, IPR2021-00068, Paper 22 at 11-12. Of the eight independent claims, seven were challenged by multiple

grounds, with six claims challenged with three grounds each. The table below illustrates which claims were challenged by multiple Grounds.

Grounds Per Claim	Challenged Claims	Independent Claim(s)	Total Claims
Three	1, 4-8, 17-18, 20-21, 23, 32-33	1, 4-8	13
Two	10-15	12	6

As an example of significant repetition (*id.*), the text in Ground 1 of the each Petition for Elements 1[a]-1[b] (1044IPR) and Elements 4[a]-4[b] (1045IPR) is nearly verbatim (*compare* 1044IPR, 23-26; 1045IPR, 20-22), Ground 2 (1044IPR, 33-35; 1045IPR 43-46), and Ground 3 (1044IPR, 37-38; 1045IPR, 48-49).

Novartis raises nearly identical Le Bec anticipation and obviousness arguments in Grounds 1 and 2 of both Petitions. “If [Novartis] had been more selective in presenting its arguments, it may have been possible to challenge all claims within the word limits for a single Petition.” *Samsung Electronics Co., Ltd. v. Lynk Labs, Inc.*, IPR2022-00150, Paper 15 at 10 (PTAB Jul. 5, 2022). Instead, Novartis’s repetitive arguments in the Petitions are in sharp contrast to *Apple Inc. v. Seven Networks, LLC* (cited Paper 2 at 2), where there were “separate material issues in a majority of grounds across both petitions.” IPR2020-00157, Paper 10 at 27 (PTAB June 15, 2020).

The circumstances here are dissimilar to *Marvell Semiconductor*, another case Novartis cites to support its “non-overlapping” claims argument (Paper 2, 2). There, “the Office published [the TPG] containing the admonition that two petitions are rarely needed, ***less than one week*** before Petitioner filed its petitions.” *Marvell Semiconductor, Inc. v. Uniloc 2017 LLC*, IPR2019-01349, Paper 9 at 13-14 (PTAB Feb. 4, 2020) (emphasis added). Nearly four years later Novartis should have been aware of the requirement to “explain sufficiently how the two Petitions at issue ... collectively challenge the claims in a materially different manner that justifies multiple proceedings,” but failed to do so. *Comcast*, IPR2020-00796, Paper 8 at 10-11. Thus, consistent with Board precedent, if either the 1044IPR or 1045IPR is instituted, the Board should exercise its discretion and deny the second Petition.

VI. CONCLUSION

For the foregoing reasons, the Petition should be denied, and no proceeding instituted.

Respectfully submitted,

Dated: October 11, 2023

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WORD COUNT CERTIFICATION

Pursuant to 37 C.F.R. § 42.24(d), I certify that this Preliminary Response contains 13,835 words (excluding the title page, table of contents, table of exhibits, claim listing, this certificate, and the certificate of service), as determined by Microsoft Word.

Dated: October 11, 2023

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CERTIFICATE OF SERVICE

I certify that today in:

*Novartis Gene Therapies, Inc. & Novartis Pharmaceuticals Corporation v.
Genzyme Corporation, IPR2023-01044 (U.S. Patent 10,429,288)*

I caused to be served a copy of:

PATENT OWNER'S PRELIMINARY RESPONSE
EXHIBITS 2001-2009

upon:

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