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Paper 10
Date: January 9, 2024

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

GENZYME CORPORATION,
Patent Owner.

IPR2023-01044
Patent 10,429,288 B2

Before JEFFREY N. FREDMAN, SHERIDAN K. SNEDDEN, and JAMES A. TARTAL, *Administrative Patent Judges.*

SNEDDEN, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314, 37 C.F.R. § 42.4

I. INTRODUCTION

A. Background and Summary

Novartis Gene Therapies, Inc. and Novartis Pharmaceuticals Corporation (collectively, "Petitioner") filed a Petition requesting an *inter partes* review of claims 1–3 and 17–34 of U.S. Patent No. 10,429,288 B2 ("the '288 patent," Ex. 1001). Paper 1 ("Pet."). Genzyme Corporation ("Patent Owner") filed a Preliminary Response to the Petition. Paper 9 ("Prelim. Resp.").

To institute an *inter partes* review, we must determine that the information presented in the Petition shows "a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a) (2018). The Supreme Court has held that a decision to institute under 35 U.S.C. § 314 may not institute on less than all claims challenged in the petition. *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1359–60 (2018). After considering the evidence and arguments presented in the Petition and Preliminary Response, we determine that Petitioner has demonstrated a reasonable likelihood of success in proving that at least 1 of the challenged claims of the '288 patent is unpatentable.

B. Real Parties in Interest

Petitioner asserts that Novartis Gene Therapies, Inc. and Novartis Pharmaceuticals Corporation are the real parties in interest. Pet. 68. Patent Owner asserts that "Sanofi, the ultimate parent company of Genzyme Corporation, Genzyme Corporation, and Aventis, Inc. are the real parties-in-interest." Paper 8, 2.

C. Related Matters

The parties indicate that the '288 patent is asserted against Petitioner in *Genzyme Corporation and Aventis Inc. v. Novartis Gene Therapies, Inc. et al.*, Case No. 1:23-cv-00554-RGA, (D. Del), filed May 19, 2023. Pet. 68; Paper 8, 2.

Petitioner has also filed a petition for *inter partes* review in IPR2023-01045 against the claims of the '288 patent. Paper 2, 1; Paper 8, 2.

D. The '288 patent (Ex. 1001)

The '288 patent discloses "methods to characterize preparations of recombinant viral particles using analytical ultracentrifugation." Ex. 1001, Abstract. The '288 patent explains that "generation of recombinant viral vectors for the clinic requires an analytical method that monitors drug product quality with regard to homogeneity, purity and consistency of manufacturing." *Id*. at 1:38–41. In particular, analytical ultracentrifugation ("AUC") is used to assess "vector genome integrity of recombinant adeno-associated viral (rAAV) particles in preparations of rAAV particles" by distinguishing viral particles with full, intact genomes, empty viral capsids and viral particles with variant viral genomes. *Id.* at 19:7–16.

The '288 patent further explains as follows:

> By subjecting preparations to analytical ultracentrifugation (AUC) under boundary sedimentation velocity conditions, the sedimentation of viral particles can be monitored at time intervals (e.g., one or more times). The differential sedimentation coefficient distribution value (C(s)) versus the sedimentation coefficient in Svedberg units (S) is then plotted and the area under each peak in the C(s) distribution is integrated to determine the relative concentration of each peak. Each peak represents a species of viral particle reflective of its molecular weight.

Id. at 11:8–18.

"In some embodiments of the invention, extinction coefficients are used to calculate molar concentration and the actual percent value of the intact vector peak from absorbance data." *Id.* at 24:20–23. In other embodiments, "it is 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)." *Id.* at 24:35–38. Accordingly, the '288 patent describes comparing the unknown species against a standard curve generated using viral vector preps with encapsulated viral genomes of known nucleotide size with corresponding S values. *See id.* at 24:38–46; 49:9–39, Fig. 8.

E. Challenged Claims

Petitioner challenges claims 1–3 and 17–34. Representative independent claims 1 and 2 are reproduced below.

> 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.
>
> 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.

Ex. 1001, 54:20–51.

F. Evidence

Petitioner relies upon information that includes the following.

Ex. 1003, Le Bec et al., WO 2014/125101 A1, published Aug. 21, 2014 ("Le Bec").

Ex. 1004, Berkowitz, et al., "Monitoring the homogeneity of adenovirus preparations (a gene therapy delivery system) using analytical ultracentrifugation," 362 ANAL. BIOCHEM. 16–37 (2007) ("Berkowitz").

Ex. 1005, Cole et al., "Analytical Ultracentrifugation: Sedimentation Velocity and Sedimentation Equilibrium," *in* METHODS CELL BIO., VOL. 84, 143–179 (2008) ("Cole").

Ex. 1007, Schuck, "Size-Distribution Analysis of Macromolecules by Sedimentation Velocity Ultracentrifugation and Lamm Equation Modeling," 78 BIOPHYSICAL J. 1606–1619 (2000) ("Schuck").

Ex. 1015, Colosi, US 2009/0017542 A1, published Jan. 15, 2009 ("Colosi").

Ex. 1016, Zhao et al., "Overview of Current Methods in Sedimentation Velocity and Sedimentation Equilibrium

Analytical Ultracentrifugation," CURR. PROT. PROTEIN SCI. 20.12.1–20.12.49 (2013) ("Zhao").

Petitioner also relies on the Declaration of Steven A. Berkowitz, Ph.D. (Ex. 1020) to support its contentions.

Patent Owner relies on the Declaration of Jeffrey C. Hansen, Ph.D. (Ex. 2001) to supports its contentions.

G. Asserted Grounds of Unpatentability

Petitioner asserts that claims 1–3 and 17–34 would have been unpatentable on the following grounds:

Ground	Claim(s) Challenged	35 U.S.C. §[1]	Reference(s)/Basis
1	1, 17, 18, 20, 21, 23, 32, 33	102	Le Bec
2	1, 17, 18, 20, 21, 23, 32, 33	103	Le Bec
3	1–3, 17–26, 31–33	103	Le Bec, Berkowitz, Cole
4	27–30	103	Le Bec, Berkowitz, Schuck, Zhao
5	34	103	Colosi, Le Bec

H. Claim Construction

We interpret a claim "using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. 282(b)." 37 C.F.R. § 42.100(b) (2019). Under this standard, we construe the claim "in accordance with the ordinary and customary meaning of such

[1] The Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112-29, 125 Stat. 284, 287–88 (2011), amended 35 U.S.C. § 103, effective March 16, 2013. Because the application leading to the '288 patent was filed after the effective date of these AIA amendments, we apply the AIA version of 35 U.S.C. § 103.

claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent." *Id.*

Petitioner asserts that the claim terms require no express construction. Pet. 21. Patent Owner does not challenge Petitioner's position. Prelim. Resp. 30.

Having considered the parties' positions and evidence of record, we determine that no express construction of any claim term is necessary to determine whether to institute *inter partes* review. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co*., 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("[W]e need only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy.'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc*., 200 F.3d 795, 803 (Fed. Cir. 1999))). To the extent further discussion of the meaning of any claim term is necessary to our decision, we provide that discussion below in our analysis of the asserted grounds of unpatentability.

I. Level of Ordinary Skill in the Art

Petitioner proposes that a person of ordinary skill in the art ("POSA" or "POSITA") at the time of the invention

> would have possessed at least a B.S. in biology, chemistry, chemical engineering, biochemistry, biophysics, pharmaceutical science, or a related discipline, with two or more years of industry, laboratory, and/or clinical experience in analyzing or characterizing biomolecules, including viruses or viral vectors. Such a person may be familiar with, or consult with someone familiar with, the development, formulation, and/or administration of viral vectors for gene therapy and quality standards required to market such products.

Pet. 20–21 (citing Ex. 1020 ¶ 58). Patent Owner does not dispute Petitioner's proposal about the POSA's qualifications. *See generally*, Prelim. Resp.; Ex. 2001 ¶ 32.

For this Decision, we adopt and apply Petitioner's proposal for the person of ordinary skill in the art level, which appears to be consistent with the level of skill reflected in the asserted prior art.

J. Relevant Prosecution History

The '288 patent issued from Application No. 15/544,498, filed as PCT/US2016/013947, on January 19, 2016. The Examiner rejected the claims, *inter alia*, as anticipated and obvious over the cited art. *See* Ex. 1002, 482–495; 516–529.

In response to the Examiner's rejections, the Applicant amended the claims to recite a method of characterizing a preparation of recombinant "adeno-associated viral (AAV) particles," specifically. *See id.* at 539, 544–552. The Applicant argued that the art of record did not disclose "using analytical ultracentrifugation (AUC) as claimed to measure the relative amount of capsid particles comprising variant recombinant AAV genomes or empty AAV capsid particles in a preparation of recombinant AAV particles." *Id.* at 541. The Applicant argued that "[o]ne of skill in the art would not have assumed that the use of AUC would have allowed for the characterization of variant recombinant viral genomes or empty viral capsid particles in a preparation of recombinant AAV particles," and that there was no reasonable expectation of success in doing so. *Id.*

Following the Applicant's amendment, the Examiner issued a notice of allowance. *See id.* at 553–562. In the statement of reasons for allowance, the Examiner indicated that, although AUC was well-described in the art,

"AUC was not noted as having been applied to AAV separation routinely, and the general methods of separating AAV in the art were not very accurate or specific, especially when it came to variation within the AAV genome or the AAV subtype, and separation of empty AAV particles." *Id.* at 561. The Examiner found convincing "the argument that the results were surprising and/or unexpected" as compared to general methods of AUC taught by art of record. *See id.*

II. ANALYSIS

A. Legal Standards

"In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc*., 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring inter partes review petitions to identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim")). This burden of persuasion never shifts to the patent owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015). Moreover, a petitioner should not "place the burden on [the Board] to sift through the information presented by Petitioners, determine where each element [of the challenged claims] is found in [the cited references], and identify any differences between the claimed subject matter and the teachings of [the cited references.]" *Google Inc. v. EveryMD.com LLC*, IPR2014-00347, Paper 9 at 25 (PTAB May 22, 2014).

Petitioner relies on both anticipation and obviousness in its challenges. "Anticipation is a question of fact, as is the question of what a [prior art] reference teaches." *In re NTP, Inc*., 654 F.3d 1279, 1297 (Fed. Cir. 2011). To anticipate a claim under 35 U.S.C. § 102, "a single prior art

reference must expressly or inherently disclose each claim limitation." *Finisar Corp. v. DirecTV Group, Inc*., 523 F.3d 1323, 1334 (Fed. Cir. 2008). That "single reference must describe the claimed invention with sufficient precision and detail to establish that the subject matter existed in the prior art." *Verve, LLC v. Crane Cams, Inc*., 311 F.3d 1116, 1120 (Fed. Cir. 2002). That is, "the prior art reference—in order to anticipate under 35 U.S.C. § 102—must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements 'arranged as in the claim.'" *Net MoneyIN, Inc. v. VeriSign, Inc*., 545 F.3d 1359, 1369 (Fed. Cir. 2008) (quoting Connell v. Sears, Roebuck & Co., 722 F.2d 1542, 1548 (Fed. Cir. 1983)). Whether a reference anticipates a claim is assessed from the skilled artisan's perspective. *See Dayco Prods., Inc. v. Total Containment, Inc*., 329 F.3d 1358, 1368 (Fed. Cir. 2003) ('"[T]he dispositive question regarding anticipation [i]s whether one skilled in the art would reasonably understand or infer from the [prior art reference's] teaching' that every claim element was disclosed in that single reference." (quoting *In re Baxter Travenol Labs*., 952 F.2d 388, 390 (Fed. Cir. 1991))).

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time of the invention to a person having ordinary skill in the art. *KSR Int'l Co. v. Teleflex, Inc*., 550 U.S. 398, 406 (2007). "Obviousness is a question of law based on underlying facts." *MobileMedia Ideas LLC v. Apple Inc*., 780 F.3d 1159, 1167 (Fed. Cir. 2015). The underlying facts include (i) the scope and content of the prior art, (ii) any differences between the prior art and the claimed invention, (iii) the level of ordinary skill in the field of the invention, and (iv) any relevant objective considerations of nonobviousness.

Id. (citing *Graham v. John Deere of Kansas City*, 383 U.S. 1, 17–18 (1966)). An additional underlying fact is whether there was a reason to combine prior art teachings when so asserted. *Id*.

In analyzing the obviousness of a combination of prior art elements, it can be important to identify a reason that would have prompted one of skill in the art "to combine . . . known elements in the fashion claimed by the patent at issue." *KSR*, 550 U.S. at 418. A precise teaching directed to the specific subject matter of a challenged claim is not necessary to establish obviousness. *Id*. Rather, "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id*. at 420. Accordingly, a party that petitions the Board for a determination of unpatentability based on obviousness must show that "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *In re Magnum Oil Tools Int'l, Ltd*., 829 F.3d 1364, 1381 (Fed. Cir. 2016) (internal quotations and citations omitted).

We analyze the asserted grounds of unpatentability in accordance with these principles to determine whether Petitioner has met its burden to establish a reasonable likelihood of success at trial.

B. Summary of the Cited Prior Art

1. Le Bec[2]

Le Bec discloses methods for "producing a double-stranded recombinant rAAV vector, or self-complementary AAV (scAAV)." Ex. 1003, 6:14–16. The method results in a mixture of AAV viral particles including empty AAV particles (lacking a viral genome), full viral particles (containing a viral genome), and aggregate particles. *See id.* at 15:19–22, 18:1–6. Le Bec discloses that empty AAV particles and full AAV particles have different densities that are "sufficiently significant to distinguish [the particles] by centrifugation." *Id.* at 18:1–3. Le Bec notes that the literature reports empty AAV viral particles having a density that is "equivalent to 60S" and full AAV viral particles having a density that is "equivalent to 110S." *Id.* at 17:30–34. Applying this difference in densities, Le Bec discloses "a method . . . for analytically separating [the viral particles] by ultracentrifugation and quantifying the different species present in an AAV viral preparation." *Id.* at 18:1–6.

Specifically, Le Bec discloses

> The 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. Centrifugation of the samples was carried out at a speed of 16,000 rpm using 100 µl or 400 µl of undiluted pure vectors, sedimentation was followed by absorbance at the wavelength of 276 nm, and the sedimentation coefficient of the various populations was obtained using the software SEDFIT.

Id. at 15:19–28.

[2] Le Bec is a French language document. We rely on the certified English Translation. *See* Ex. 1003, 57.

In two examples, Le Bec discloses analytical ultracentrifugation analysis of specific recombinant scAAV vectors. *See id.* at 18:8–20, 19:7–15. The results are represented in Figures 2 and 3, shown below.

Figure 2 is reproduced below.

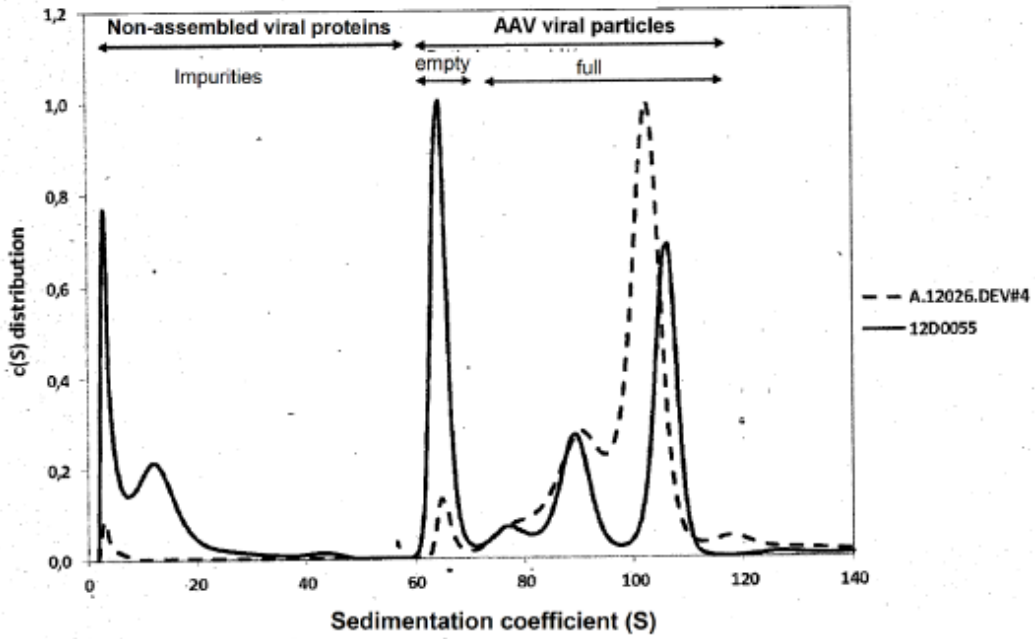

Figure 2

Figure 2 illustrates peaks at < 60S corresponding to non-assembled viral proteins and/or contaminants and peaks at 60S–110S corresponding to intact AAV particles. *Id.* at 18:8–20. "The 60S–110S population consists of 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.* at 18:21–25.

Figure 3 is reproduced below.

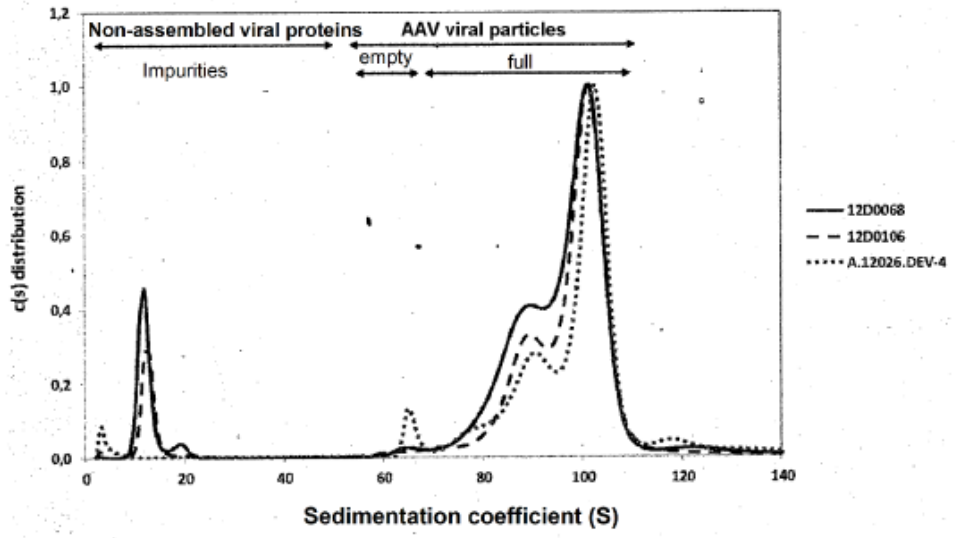

Figure 3

Figure 3 illustrates the results of analytical ultracentrifugation of "three batches of scAAV9-SMN vectors." *Id.* at 19:7–10. "These three batches all show a similar distribution and confirm that the [disclosed] 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%)." *Id.* at 19:11–15.

2. Berkowitz

Berkowitz "explores the capability of modern analytical ultracentrifugation (AUC) to characterize the homogeneity, under product formulation conditions, of preparations of adenovirus vectors used in gene therapy and to assess the lot-to-lot consistency of this unique drug product." Ex. 1004, Abstract. Berkowitz discloses that "single sedimentation velocity run on an adenovirus sample can detect and accurately quantify . . . (a) intact virus monomer particles, (b) virus aggregates, (c) empty capsids (ECs), and (d) smaller assembly intermediates or subparticles." *Id.* "This information,

which is collected on adenovirus samples under the exact formulation conditions that exist in the adenovirus vial, is obtained by direct boundary modeling of the AUC data generated from refractometric and/or UV detection systems using the computer program SEDFIT developed by Peter Schuck." *Id.* Berkowitz notes when engineering adenovirus drug products "[t]o achieve drug licensure, drug product quality (with regard to homogeneity and purity) and consistency of manufacturing are of key importance." *Id.* at 16.

Berkowitz discloses a method for analyzing band sedimentation velocity. *See id.* at 19. A virus sample was loaded in an AUC cell with CsCl sedimentation solution. *Id.* The band sedimentation velocity runs were conducted at a rotor speed of 10,000 rpm. *Id.* "The integration of individual bands to calculate the weight percentage of [empty cells (EC)] or aggregated material required correcting each [optical density (OD)] value for the baseline offset and the variation of the sector cross-sectional area with radial position." *Id.* Berkowitz discloses that simple peak integration "allows the percentage of EC material present in a virus preparation to be readily calculated." *Id.* at 21.

3. Cole

Cole describes AUC as "a versatile and powerful method for the quantitative analysis of macromolecules in solution." Ex. 1005, 144. "Three optical systems are available for the analytical ultracentrifuge (absorbance, interference, and fluorescence) that permit precise and selective observation of sedimentation in real time." *Id.* Cole explains that "[i]n sedimentation velocity (SV), the movement of solutes in high centrifugal

fields is interpreted using hydrodynamic theory to define the size, shape, and interactions of macromolecules." *Id.*

Cole teaches that basic AUC experiments measure sedimentation velocity (SV) or sedimentation equilibrium (SE). *Id.* at 162, Figure 1. "Velocity sedimentation is usually performed using a two-sector cell and scans are recorded at fixed intervals during the run." *Id.* "Equilibrium measurements usually employ a six-sector cell with three loading concentrations." *Id.*

Cole teaches computer programs for analyzing SV experiments. *See id.* at 165. For example, the SEDFIT program simulates sedimentation boundaries using a numerical solution of the Lamm equation. *See id.* at 166.

4. Schuck

Schuck describes "a method for direct boundary modeling for the size-distribution analysis in sedimentation velocity analytical ultracentrifugation." Ex. 1007, 1615. The method is implemented in the SEDFIT program. *See id.* at 1610.

5. Colosi

Colosi teaches methods for producing rAAV virions. Ex. 1015, Abstract. The rAAV virions include "AAV helper function constructs that provide for high-efficiency ra AV production but do not generate wild-type AAV." *Id.* ¶ 2. "The AAV genome generally comprises an internal non-repeating genome flanked on each end by inverted terminal repeats (ITRs)." *Id.* ¶ 8.

6. Zhao

Zhao teaches an overview of computational methods in analytical ultracentrifugation. Ex. 1016, 20.12.1. Zhao discloses that direct boundary modeling with size distributions may require regularization. *Id.* at 20.12.13. "Regularization is the selection, from all the distributions that fit the data statistically indistinguishably, of one particular solution that has the least information content." *Id.* Zhao discloses that SEDFIT implements Tikhonov and maximum-entropy regularization, which are methods often employed in biophysics. *Id.*

C. Ground 1: Anticipation of Claims 1, 17, 18, 20, 21, 23, 32, and 33 by Le Bec

Petitioner contends that claims 1, 17, 18, 20, 21, 23, 32, and 33 are anticipated by Le Bec. Pet. 22–32. Petitioner begins with its analysis of independent claim 1 (*id*. at 22–28), and then addresses the limitations added by dependent claims 17, 18, 20, 21, 23, 32 and 33 (*id*. at 28–32).

Patent Owner makes two main arguments in opposition to Petitioner's contentions with regard to independent claim 1, element c. Prelim. Resp. 31–45. First, Patent Owner contends that Petitioner fails to establish that Le Bec discloses integrating peaks to determine concentrations of partial or fragmented genomes. *Id.* at 34–42. Second, Patent Owner contends that Le Bec fails to anticipate because its method would have had to have been impermissibly modified to meet element 1c. *Id.* at 42–45. In particular, Patent Owner contends that "Le Bec's disclosure of a qualitative comparison between empty and full capsids . . . did not indicate the concentrations of different rAAV species containing partial or fragmented genomes." *Id.* at 44.

We preliminarily address Patent Owner's arguments for purposes of this Decision below.

1. Claim 1

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

Petitioner contends that Le Bec describes a method of characterizing rAAV particles by subjecting an rAAV preparation to sedimentation velocity analytical ultracentrifugation ("SV-AUC") conditions to determine the sedimentation coefficients of various rAAV particles. *Id.* at 23–24 (citing Ex. 1003, 15:17–23; Ex. 1020 ¶ 72). Petitioner contends that Le Bec performed SV-AUC as evidenced by Le Bec determining and plotting sedimentation coefficients, which showed "that Le Bec was measuring the velocities at which different sedimentation boundaries were moving." *Id.* at 24 (citing Ex. 1020 ¶¶ 72–78). Further, Petitioner contends that Le Bec's disclosed AUC parameters "result in boundary sedimentation conditions for rAAV-sized particles." *Id.* at 24 (citing Ex. 1020 ¶¶ 75–76; Ex. 1001, 17:17–20). For example, Petitioner notes that Le Bec's rotor speed "falls within the range identified in the '288 patent." *Id.* at 24–25 (citing Ex. 1001, 29–30 (Table 1)). Petitioner contends that Le Bec discloses "acquiring data in 'real-time,' which means that the sedimentation of rAAV particles was monitored at time intervals." *Id.* at 25 (citing Ex. 1020 ¶ 79).

Based on Petitioner's argument and evidence, summarized above, we are persuaded that Petitioner sufficiently shows that Le Bec discloses this element of claim 1. Patent Owner does not separately dispute Petitioner's showing in this regard. *See generally* Prelim. Resp.

b. Plotting the differential sedimentation coefficient distribution value (C(s)) versus the sedimentation coefficient in Svedberg units (S)

Petitioner contends that Le Bec's Figures 2 and 3 show plotting a differential sedimentation coefficient distribution value (C(s)) versus the sedimentation coefficient in Svedberg units (S). *Id.* at 25–26 (citing Ex. 1003, 6:4–10, Figs. 2, 3; Ex. 1020 ¶¶ 80–81 ("It is common and routine to plot the differential sedimentation coefficient (c(s)) on one axis and the sedimentation coefficient (S) on the other axis, which facilitates additional analyses, including the determination of relative concentrations."). Petitioner contends that "Le Bec describes Figures 2 and 3 as 'a graph showing the analytical ultracentrifugation distribution profile.'" *Id.* at 25 (citing Ex. 1003, 6:4–10).

Based on Petitioner's argument and evidence, summarized above, we are persuaded that Petitioner sufficiently shows that Le Bec discloses this element of claim 1. Patent Owner does not separately dispute Petitioner's showing in this regard. *See generally* Prelim. Resp.

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.

(1) Petitioner's Contentions

Petitioner contends that

> Le Bec teaches use of AUC to determine the "quantification of empty and full viral particles" and reports the results of that quantification in the form of a percentage. For example, Le Bec explains that "[t]he distribution profile…confirms that the HEK293 system essentially produced very few full AAV particles (< 25%). Ex.1003, 19:1-5; *see also* 19:12-15 (sf9 system sample essentially composed of full AAV particles (> 80%)). Le Bec teaches 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. Ex.1003, 18:11-27; *see also* Figs. 2 and 3.

Pet. 27; *see also id.* at 14–15. Petitioner contends that "[a] POSA would understand the disclosed percentages to be relative concentrations of the corresponding rAAV particle species in the sample." *Id.* (citing Ex. 1020 ¶¶ 82–84; Ex. 1003, 8:10–13). In the cited paragraphs, Dr. Berkowitz states that

> Applying its SV-AUC data, Le Bec reports values of the relative amount of rAAV particles. *See*, *e.g.*, Ex.1003, 19:11-15 ("These three batches all show a similar distribution profile and confirm that 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%)."). A POSA would understand that quantitation of species in an SVAUC experiment like that disclosed in Le Bec would have been determined by integration of the area under the peak of a c(s) v. S plot due to Le Bec's disclosure of such plots and that it used SEDFIT to determine the sedimentation coefficients of the different species in its rAAV preparations. Ex.1003, 15:19-28; Figs. 2 and 3. Moreover, because Le Bec reported percentages, the data is a relative concentration.

Ex. 1020 ¶ 83.

Petitioner contends further that "[a] POSA would understand the disclosed percentages to be relative concentrations of the corresponding rAAV particle species in the sample," that are obtained by "integrating the area under the curve for the peaks of interest." *Id.* (citing Ex. 1020 ¶¶ 82–84; Ex. 1003, 8:10–13). Petitioner notes that the SEDFIT software "was publicly available and freely downloadable before the '288 patent's priority date and at the time of Le Bec." *Id.* at 28 (citing Ex. 1020 ¶¶ 27–40, 83). Specifically, Petitioner contends that Le Bec discloses using the SEDFIT

software to integrate the area under each peak in the C(s) distribution to determine the relative concentration of each peak—each peak representing a species of rAAV particles. *See id.* at 27–28 (citing Ex. 1003, 18:11–27, 19:1–5, 12–15; Ex. 1020 ¶¶ 27–40, 82–84). Further, Petitioner's declaramt, Dr. Berkowitz, notes that "[a]t a minimum, a POSA would have known how to integrate SV-AUC data of rAAV particles from the teaching of Le Bec using the standard functionality built into the SEDFIT software." Ex. 1020 ¶ 84.

(2) Patent Owner's Contentions

Patent Owner contends that Petitioner's arguments fail to demonstrate that Le Bec discloses "each and every limitation of the claimed invention" (Prelim. Resp. 34–35 (quoting *SRI Int'l, Inc. v. Cisco Sys*., Inc., 930 F.3d 1295, 1306 (Fed. Cir. 2019)) or "describe[s] the claimed invention with sufficient precision and detail to establish that the subject matter existed in the prior art" (*Id.* at 35 (quoting *Wasica Fin. GmbH v. Cont'l Auto. Sys., Inc*., 853 F.3d 1272, 1284 (Fed. Cir. 2017)). In particular, Patent Owner contends that Petitioner does not establish that Le Bec discloses claim 1, step (c), which requires "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." *Id.* at 33. Rather, Patent Owner contends that Le Bec is vague "on how it determines the concentration values" and lacks "disclosure relating to the concentrations associated with certain peaks." *Id.* at 36 (citation omitted). Patent Owner contends that an important distinction between claim 1's method and Le Bec is "the ability of the claimed method to determine the concentration peaks corresponding to partial or fragmented genome species." *Id.* at 36.

Furthermore, Patent Owner distinguishes Le Bec's Figures 2 and 3 from claim 1's method. *See id.* at 36–42. In Figure 2, Patent Owner contends that Petitioner "ignores that within Le Bec's 'full' viral particles subpopulation [there] were multiple peaks corresponding to species of rAAV particles." *Id.* at 38 (citing Ex. 1003, 18:21–25). In Figure 3, Patent Owner contends that Petitioner fails to address each peak including "the agglomeration of what appears to be multiple peaks ranging from about 75S to about 110S," and "the single stranded AAV peak at about 90S." *Id.* at 39–41 (quoting Ex. 2001 ¶¶ 105–108).

Patent Owner further contends that Le Bec does not "disclose[] determining the relative concentration of each species corresponding to a peak in its C(s) distribution without need for further modification." *Id.* at 33 (citing Ex. 2001 ¶¶ 110-113) ("the Petition never establishes how Le Bec alone would have permitted the POSA to determine concentrations of partial and fragmented rAAV species without relying on additional sources of information to modify its AUC analysis"). Patent Owner contends that Le Bec's method of determining concentration from AUC peaks obtained via absorbance spectroscopy at 276 nm would require an extinction coefficient for each peak. *Id.* at 33 (citing Ex. 1003, 15:23–28; Figs. 2-3). Patent Owner notes that Le Bec "is silent regarding the extinction coefficients of the partial and fragmented species at 276 nm in its C(s) distributions." *Id.* at 34. Thus, Patent Owner contends that Petitioner "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." *Id.*

Patent Owner contends that Le Bec's reference to SEDFIT does not disclose integration of each peak. *See id.* at 42; *see* Ex. 1003, 15:27–28

("the sedimentation coefficient of the various populations was obtained using the software SEDFIT"). Accordingly, Patent Owner contends that "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." *Id.* at 44–45.

(3) Discussion

The dispute between the parties is whether 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." Pet. 27–28; Prelim. Resp. 31–45; Ex. 1020 ¶ 82–84. Having considered the parties' positions and evidence of record, summarized above, we determine that the information presented in the Petition establishes that Petitioner has a reasonable likelihood of prevailing in showing that claim 1 is anticipated by Le Bec. In particular, we are persuaded on the current record by the testimony of Dr. Berkowitz that "Le Bec teaches a method for characterizing a viral preparation of rAAV particles that can analytically separate, detect, and quantify the presence of empty capsids, full capsids, and aggregates based on sedimentation coefficients." Ex. 1020 ¶ 72 (citing Ex. 1003, 16:25–29; 15:17–23; 18:1–6). Here, we note that Le Bec teaches that the "distribution profile of the species allows the identification of two categories of populations," which include species identified as 60S, 90S, and 105S, for example. Ex. 1003, 18:11–27; *see also* Figs. 2 and 3.

We have considered Patent Owner's arguments and the testimony of Dr. Hansen, and are not persuaded on the current record to deny institution.

Prelim. Resp. 31–45; Ex. 2001 ¶¶ 96–113. For example, we recognize Patent Owner's contention that Petitioner "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." Prelim Resp. 35; *see also id.* at 33 (The "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."). We recognize also Dr. Hansen's testimony that, even accepting Petitioner's argument that the SEDFIT software was available and could have been used to "calculate[] relative concentrations by integrating the area under the peaks of a sedimentation coefficient distribution profile," "the POSA would not have considered Le Bec to have provided any indication that the area under ***each peak*** was determined nor that the area under ***each peak*** was converted to concentrations by applying the extinction coefficients for the rAAV species corresponding to each peak." Ex. 2001 ¶ 97 (citing Pet. 27); *see also id.* at ¶ 100 ("Neither the Petition nor the Berkowitz Declaration address Le Bec's omissions of concentration values for ***each peak*** in its C(s) distributions in Figures 2 and 3"). Having considered that information presented by Patent Owner, however, we determine that the information presented by Patent Owner creates genuine issues of material fact about whether a person of ordinary skill in the art would have interpreted Le Bec to disclose "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."[3] *See* 37 C.F.R. § 42.108(c) (stating "a genuine issue of material fact created by [Patent Owner's] testimonial evidence will be viewed in the light most favorable to the petitioner solely for purposes of deciding whether to institute an inter partes review."). Those issues may be further briefed and developed during trial, and the parties are encouraged to do so.

At this preliminary stage, viewing factual disputes involving a genuine issue of material fact in the light most favorable to Petitioner, we have determined only that Petitioner's evidence is sufficient for institution.

2. Claims 17, 18, 20, 21, 23, 32, and 33

Claims 17, 18, 20, 21, 23, 32, and 33 depend from claim 1. Patent Owner at this stage does not offer any arguments addressing Petitioner's substantive showing for those dependent claims. *See generally* Prelim. Resp. We find Petitioner has shown sufficiently that Le Bec discloses the additional limitations of dependent claims 17, 18, 20, 21, 23, 32, and 33 for the reasons stated in the Petition, which we find sufficient and credible for purposes of our preliminary findings. Pet. 22–32. Therefore, we are persuaded that at this stage of the proceeding that Petitioner has shown a

[3] We note also that, while the parties' dispute centers on whether Le Bec discloses "integrating the area under each peak" as required by the claims, neither party has offered a claim construction of that phrase. We understand that phrase to refer to a known standard technique for determining relative concentrations in a sample by calculating the area under the curve. Here, we credit the testimony of Dr. Berkowitz that "the SEDFIT software referenced in Le Bec and available prior to January 2015 calculated relative concentrations by integrating the area under the peaks of a sedimentation coefficient distribution profile." Ex. 1020 ¶ 83.

reasonable likelihood that Le Bec anticipates claims 17, 18, 20, 21, 23, 32, and 33.

3. Conclusion

Based on the preliminary record, we find that Petitioner has shown that it is reasonably likely to prevail in establishing that claims 1, 17, 18, 20, 21, 23, 32, and 33 are anticipated by Le Bec.

D. Ground 2: Obviousness of Claims 1, 17, 18, 20, 21, 23, 32, and 33 over Le Bec

Petitioner asserts that, to the extent not anticipated, claims 1, 17, 18, 20, 21, 23, 32, and 33 would have been obvious over Le Bec. Pet. 33–37. To support its contentions, Petitioner provides a detailed discussion explaining how Le Bec discloses all elements of the claims, supported by the testimony of Dr. Berkowitz. Pet. 22–37; Ex. 1020 ¶¶ 27–40. Patent Owner opposes. Prelim. Resp. 45–55. For the reasons explained below, we determine that Petitioner has sufficiently shown for purposes of institution how claims 1, 17, 18, 20, 21, 23, 32, and 33 would have been obvious over Le Bec.

1. Claim 1

a. Petitioner's Contentions

The parties dispute whether a person of ordinary skill in the art would have been motivated to modify Le Bec to practice the element of claim 1[c]. Petitioner contends that, to the extent not anticipated, Le Bec teaches or suggests 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. Pet. 33–37. More specifically, Petitioner contends that "Le Bec commented on the then-current limitations in producing scAAV vectors, including the high percentage of empty AAV particles." Pet. 33. Noting others that identified this problem, Petitioner contends that "POSAs were motivated to assess virus preparations for such undesirable contaminants." *Id.* at 34.

Further, Petitioner contends that "[t]he art taught that SV-AUC was a powerful tool for assessing the homogeneity of viral vectors used in gene therapy applications." *Id.* (citing Ex. 1004, 17; Ex. 1008, 6; Ex. 1019, 5). For example, Petitioner notes a person of ordinary skill in the art's would be motivated by "(1) the importance of drug product quality (with regard to homogeneity and purity) to achieve licensure, and (2) the recognized benefits of using boundary sedimentation velocity analysis for analyzing such aspects of biological samples." *Id.* at 34–35 (citing Ex. 1004, 16; Ex. 1008, 1, 6; Ex. 1003, 17:30–18:27; Ex. 1005, 145, 149, 161–168). Petitioner also contends that "[a] POSA would have reasonably expected success in applying SV-AUC to rAAV particles because the sedimentation coefficients of empty and full rAAV particles were known and reported in the literature, and because Le Bec taught that rAAV particles (full, empty, and aggregate) could be effectively separated, characterized, and quantified by analytical ultracentrifugation." *Id.* at 35 (citing Ex. 1003, 15:19-23; Ex. 1020 ¶ 181). Thus, Petitioner contends that "a POSA would have been motivated to choose SV-AUC when seeking to characterize a preparation of rAAV particles to assess homogeneity." *Id.* at 35 (citing Ex. 1020 ¶ 180; Ex. 1019, 4–5).

Next, Petitioner contends that even if "Le Bec does not describe integrating the area under each peak to determine the relative concentration

of each particle, doing so would have been obvious." Pet. 36. Petitioner contends that "a POSA would have been motivated to use SV-AUC to assess homogeneity of rAAV preparations and accurately quantify the rAAV species … [because] [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." *Id.* (citing Ex. 1008, 1; Ex. 1020 ¶¶ 180, 182. Petitioner contends that Le Bec "provides motivation to integrate peak areas of C(s) v. S plots: to assess levels of impurities such as empty particles and aggregates as well as particles containing single- and double-stranded genomes, and to compare the efficiency of different rAAV manufacturing platforms." *Id.* (citing Ex. 1003, 3:16–22, 15:27–28, 17:29–18:6). Additionally, Petitioner contends that SEDFIT software, as disclosed in Le Bec, included "the ability to calculate concentration information based on integration of peaks selected by the user," such that a person of ordinary skill in the art would have been motivated to use the software to determine relative concentrations with a reasonable expectation of success. *Id.* at 36–37 (citing Ex. 1003, 15:18–28; Ex. 1020 ¶¶ 27–40, 182).

b. Patent Owner's Contentions

Patent Owner contends that Petitioner "fails to identify how Le Bec's disclosure would have been modified to meet Element 1[c]," and instead merely refers to integration as a standard technique. Prelim. Resp. 47–48. More specifically, Patent Owner contends that Petitioner

> 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.

Id. at 52. As to those "challenges surrounding extinction coefficients," Patent Owner contends that Berkowitz describes "the need to account for differing extinction coefficients between species," and the difficulty of doing so for unknown variants. *See id.* at 50–51 (citing Ex. 1004, 21, 34; Ex. 1001, 24:35–38). Patent Owner asserts that Petitioner does not account "for differing extinction coefficients among different rAAV species analyzed at 276-nm in Le Bec, particularly unknown partial and/or fragmented genome species at 77S and 90S." *Id.* at 51 (citing Ex. 2001 ¶¶ 120–121).

Patent Owner's expert Dr. Hansen asserts that "[b]ecause 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]." Ex. 2001 ¶ 120. Further, Patent Owner contends that, "[b]y finding a way to calculate extinction coefficients of variant rAAV species, the inventors were able to determine the relative concentrations of these species [and] [t]his innovation helped lead to the invention of claim 1." Prelim. Resp. at 51.

In addition to challenging Petitioner's motivation to modify Le Bec, Patent Owner contends that Petitioner did not 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." *Id.* at 53–54 (citing Ex. 2001 ¶¶ 122–123). Patent Owner argues that "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." *Id.* at 54 (citing Ex. 2001 ¶ 123).

c. Discussion

Having considered the parties' positions and evidence of record, summarized above, we determine that the information presented in the Petition establishes that Petitioner has a reasonable likelihood of prevailing in showing that claim 1 would have been obvious in view of Le Bec. In particular, we are persuaded that Le Bec discloses the separation, characterization, and quantification of rAAV particles by analytical ultracentrifugation. Pet. 35; Ex.1003, 15:19–23; Ex.1020 ¶ 181. We are persuaded also, for the purposes of this Decision, by Petitioner's arguments and evidence that a person of ordinary skill in the art would have been motivated to use SV-AUC to assess viral particles in order to evaluate particles for drug product quality and that a POSA would have reasonably expected success in applying SV-AUC to rAAV particles in view of the teaching in Le Bec and state of the prior art. Pet. 34–35 (citing Ex. 1003, 15:19–23; Ex. 1004, 16–17; Ex. 1005 145, 149, 161–168; Ex. 1008, 1, 6; Ex. 1019, 4–5; Ex. 1020 ¶¶ 180–181). Here, we credit the testimony of Dr. Berkowitz that

> integrating the area under the peaks revealed in an c(s) vs S (distribution of sedimentation coefficient) plot generated in an SV-AUC experiment is a standard technique used to determine the relative concentrations of components in the analyzed sample (where relative refers to either the total area of the distribution plot or to some defined range of its x-axis, sedimentation coefficient expressed in unit of S). Ex.1004, 25. [P]eak integration was available in the SEDFIT software, and a POSA would have found it obvious to utilize the peak integration

> function to quantify peak size, as this lends necessary precision to the assessment of the viral preparation. Le Bec's own use of the SEDFIT software and reporting of relative concentrations of AAV particles would have indicated to a POSA that AAV particles could be effectively separated by SV-AUC and that relative concentrations could be determined by integrating the areas under the peaks using the SEDFIT software functionality, the same way it has been applied in other SV-AUC experiments.

Ex. 1020 ¶ 182.

We recognize Patent Owner's contention that Le Bec would need to be modified to identify partial or fragmented rAAV species, and that a "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." Prelim. Resp. 44–46 (citing Ex. 2001 ¶ 115); *see also* Ex. 2001 ¶ 120 ("Given the absence of information regarding extinction coefficients in Le Bec regarding any of the species at 276 nm, 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."). Although Patent Owner's arguments, supported by the declaration of Dr. Hansen, may have merit, those arguments raise a genuine issue of material fact that we decline to resolve on the current record. 37 C.F.R. § 42.108(c).

2. Dependent claims 17, 18, 20, 21, 23, 32, and 33

Claims 17, 18, 20, 21, 23, 32, and 33 depend from claim 1. We find Petitioner has established a reasonable likelihood of showing that Le Bec renders obvious the additional limitations of dependent claims 17, 18, 20, 21, 23, 32, and 33 for the reasons stated in the Petition, which we find sufficient and credible for purposes of our preliminary findings. Pet. 33–37.

Patent Owner at this stage does not offer any arguments addressing Petitioner's substantive showing. *See generally* Prelim. Resp. Therefore, we are persuaded that at this stage of the proceeding that Petitioner has shown a reasonable likelihood that Le Bec renders obvious claims 17, 18, 20, 21, 23, 32, and 33.

3. Conclusion

Based on the preliminary record, we find that Petitioner has shown that it is reasonably likely to prevail in establishing that claims 1, 17, 18, 20, 21, 23, 32, and 33 would have been obvious in view of Le Bec.

E. Ground 3: Obviousness of Claims 1–3, 17–26, and 31–33 over Le Bec, Berkowitz, and Cole

Petitioner asserts that claims 1–3, 17–26, and 31–33 would have been obvious over Le Bec in view of Berkowitz and Cole. Pet. 37–52. Patent Owner opposes. Prelim. Resp. 55–66. To support its contentions, Petitioner details that Le Bec in view of Berkowitz and Cole would have motivated the person of ordinary skill in the art to generate a standard curve and that the person of ordinary skill in the art would have had a reasonable expectation of success using the standard curve. See Pet. 45. For the reasons explained below, we determine that Petitioner has demonstrated by a preponderance of the evidence that claims 1–3, 17–26, and 31–33 would have been obvious over Le Bec in view of Berkowitz and Cole.

1. Claim 1

With regard to claim 1, Patent Owner contends that "[t]he 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." Prelim. Resp. 55. Patent Owner contends also that

> 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." [Ex. 2001], Hansen, ¶¶ 124-125. Le Bec fails to demonstrate concentration determination for certain peaks and Berkowitz 2007 does not cure Le Bec's omission. [Ex. 2001], Hansen, ¶¶ 124-129.

Prelim. Resp. 56.

As in Grounds 1 and 2, we find Petitioner has established a reasonable likelihood of showing that the combination of Le Bec and Berkowitz renders claim 1 obvious for the reasons stated in the Petition, which we find sufficient and credible for purposes of our preliminary findings. Pet. 37–39. Although Patent Owner's arguments, supported by the declaration of Dr. Hansen, may have merit, those arguments raise a genuine issue of material fact that we decline to resolve on the current record. 37 C.F.R. § 42.108(c). We, nevertheless, look forward to further development of this issue at trial.

2. Claim 2

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

Petitioner contends that "[t]his limitation is anticipated in Le Bec as described above for claim 1." Pet. 44. Patent Owner does not separately dispute Petitioner's showing in this regard. *See generally* Prelim. Resp.

Based on Petitioner's argument and evidence, summarized above in Section C.1.a., we are persuaded that Petitioner sufficiently shows that Le Bec discloses this element of claim 2.

b. Plotting the differential sedimentation coefficient distribution values C(s) versus the sedimentation coefficient in Svedberg units (S),

Petitioner contends that "[t]his limitation is anticipated in Le Bec as described above for claim 1." Pet. 45. Patent Owner does not separately dispute Petitioner's showing in this regard. *See generally* Prelim. Resp.

Based on Petitioner's argument and evidence, summarized above in Section C.1.b., we are persuaded that Petitioner sufficiently shows that Le Bec discloses this element of claim 2.

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 size

(1) Petitioner's Contentions

Petitioner contends that it would have been obvious to a person of ordinary skill in the art to apply Berkowitz's teachings to Le Bec, thereby using "SV-AUC to characterize viral preparations for gene therapy applications, including to identify and quantify empty capsids, intact monomers, aggregates, and incompletely formed species." Pet. 37–38 (citing Ex.1004, 17; Ex.1020 ¶¶ 199–200). Petitioner further contends that "Berkowitz expressly teaches that 'quantification' of each particle would be accomplished by integration: 'simple peak area integration . . . allows the percentage of EC [empty capsid] material present in a virus preparation to be readily calculated.'" *Id.* at 38 (citing Ex. 1004, 20).

Petitioner contends that "[a] POSA would have been motivated to apply Berkowitz's teachings to Le Bec's SV-AUC data to accurately

quantify the rAAV species in a consistent and reliable way for clinical lots of drug product." *See id.* at 38–39 (citing Ex. 1008, 1; Ex. 1020 ¶¶ 180, 199–201). Petitioner also contends that "[a] POSA would have been motivated to generate a standard curve and would have reasonably expected success using such a curve, in view of the teachings of Le Bec, Cole, and Berkowitz, and the general knowledge in the field." Pet. 45. Petitioner notes that "[t]he use of reference standards or standard curves was routinely applied to sedimentation coefficients and AUC experiments." *Id.* (citing Ex. 1020 ¶¶ 209–210). For example, Petitioner contends that Cole's article, which describes a hypothetical system, posits that when "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)." *Id.* at 46 (citing Ex. 1013, 9–10; Ex. 1020 ¶¶ 211–214).

Petitioner also notes that Le Bec reports "a higher sedimentation coefficient for full viral particles than for empty viral particles." *Id.* (citing Ex. 1003, 15:17–28; 17:20–19:15). Thus, Petition asserts that "[f]ull capsids-having greater mass-have higher sedimentation coefficients than empty capsids." *Id.* at 46–47. Finally, Petitioner contends that "[a] POSA, understanding the complications arising from nonfunctional rAAV particles and the desire for high-quality drug product (Ex. 1004, 16; Ex. 1008, 1, 6) would see the benefit of using a standard curve to identify the genome size of a particular species of recombinant AAV particles, and would be able to predictably utilize a standard curve to assess purity." *Id.* at 47 (citing Ex. 1003, 16; Ex. 1008, 1, 6; Ex. 1020 ¶ 214).

(2) Patent Owner's Contentions

Patent Owner contends that "applying Berkowitz's quantification techniques to Le Bec's AUC method for rAAV preparation would not address . . . integrating the area under each peak to determine the relative concentration of each peak, including peaks corresponding to partial and/or fragmented rAAV species." Prelim. Resp. 57 (citing Ex. 2001 ¶¶ 126–127). Rather, Patent Owner contends that "Le Bec uses absorbance detection at 276 nm 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." *Id.* (citing Ex. 1004, 21; Ex. 2001 ¶ 128).

Patent Owner further contends that "[t]he Petition never indicates that the asserted prior art references taught or suggested the 'standard curve' recited in Element 2[c]." Prelim. Resp. 59 (citing Pet. 45). Patent Owner asserts that "neither the Petition nor Berkowitz Declaration provides a single example of a standard curve applied to sedimentation coefficients or AUC experiments." *Id.* Further, Patent Owner contends that Petitioner "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.'" *Id.* at 60 (citing Pet. 46). In response to Petitioner's argument concerning a hypothetical system, Patent Owner contends such an "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)." *Id.*

Patent Owner also contends that "[n]either 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." *Id.* at 61.

Patent Owner relies on its expert to explain why the POSA would not have assumed frictional coefficients for rAAV species to be identical. *Id.* For example, Patent Owner's expert, Hansen, concludes that

> [t]he POSA would have been aware of the possibility that not all rAAV particles would have been assumed to have identical surfaces. … The POSA would have understood that changes to the rAAV surface (e.g., the spikes on the AAV surface) would have been expected to result in frictional changes to the rAAV surface, and thus impacted its sedimentation … [and] alter the protein mass.

Ex. 2001 ¶¶ 46–47.

Patent Owner contends that according to Berkowitz's 2007 publication, "different [rAAV] species did indeed have different frictional coefficients attributable to spike features on the surface of adenovirus particles." Prelim. Resp. 62 (citing Ex. 1004, 18, 321-32; Ex. 2001 ¶¶ 46–47, 136–137).

Patent Owner contends that "[f]or 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." *Id.* at 63 (citing Ex. 1001, 49:17–18). Patent Owner asserts that "[f]rom 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." *Id.* at 64 (citing Ex. 2001 ¶¶ 47, 138–139). Additionally, Patent Owner contend that "Berkowitz 2007 and Cole make clear that the POSA would not have expected a linear relationship between *S*-values and genome molecular weight." *Id.* at 65 (citing Ex. 2001 ¶ 140). Therefore, Patent Owner contends that "the POSA would not have been motivated to design a method that determines genome molecular weight from

sedimentation coefficient" and "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." *Id.* (citing Ex. 2001 ¶ 141) ("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 expected based on the prior art such as Cole and particularly Berkowitz 2007.").

(3) Discussion

Similar to the situation in Grounds 1 and 2 with regard to claim 1, Dr. Berkowitz and Dr. Hansen provide conflicting testimony for whether the combination of Le Bec, Berkowitz, and Cole teach or suggest 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 size, as required by claim 2. Ex. 1020 ¶¶ 208–214; Ex. 2001 ¶¶ 130–141. Patent Owner summarizes one aspect of the conflicting testimony arguing the following:

> [Petitioner] 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. [Ex. 2001], Hansen, ¶¶ 46-47, 132-135. [Petitioner] simply

> disregards the parts of these disclosures that contradict its position. . . .
>
> 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. [Ex. 2001], 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. [Petitioner] 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; [Ex. 2001], Hansen, ¶ 140.

Prelim. Resp. 61–62; *compare* Ex. 1020 ¶¶ 213 ("a POSA would consider for an rAAV particle's expected S-value is the frictional force, *f*."). Because the conflicting testimony creates a genuine issue of material fact, we view the material fact in the light most favorable to Petitioner solely for purposes of deciding whether to institute an *inter partes* review. *See* 37 C.F.R. § 42.108(c).

Having considered the parties' positions and evidence of record, summarized above, we find Petitioner has established a reasonable likelihood of showing that the combination of Le Bec, Berkowitz, and Cole renders obvious the additional limitations of dependent claim 2 for the reasons stated in the Petition, which we find sufficient and credible for purposes of our preliminary findings. Pet. 44–47.

3. Dependent Claims 3, 17–26, and 31–33

Claims 17–26, and 31–33 depend, directly or indirectly, from claim 1. Claim 3 depends from claim 2. We find Petitioner has established a reasonable likelihood of showing that the combination of Le Bec,

Berkowitz, and Cole renders obvious the additional limitations of dependent claims 3, 17–26, and 31–33 for the reasons stated in the Petition, which we find sufficient and credible for purposes of our preliminary findings. Pet. 39–43, 47. Patent Owner at this stage does not offer any arguments addressing Petitioner's substantive showing. *See generally* Prelim. Resp. Therefore, we are persuaded that at this stage of the proceeding that Petitioner has shown a reasonable likelihood that Le Bec renders obvious claims 3, 17–26, and 31–33.

F. Remaining Ground 4 and 5

Petitioner asserts that claims 27–30 of the '288 patent would have been obvious over the combination of Le Bec, Berkowitz, Schuck, and Zhao. Pet. 52–58. Petitioner also asserts that claim 33 would have been obvious over the combination of Colosi and Le Bec. *Id*. at 58–63. We have reviewed Petitioner's contentions as to the remaining grounds (Pet. 51–78) and, on this record, we are persuaded that Petitioner's arguments and evidence are sufficient to show a reasonable likelihood Petitioner would prevail in proving unpatentability of at least one claim in challenged in each of Grounds 4 and 5. Patent Owner at this stage does not offer any arguments addressing Petitioner's substantive showing. *See generally* Prelim. Resp. However, the burden always remains on Petitioner to prove unpatentability of each challenged claim. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc*., 800 F.3d 1375, 1378 (Fed. Cir. 2015).

III. CONCLUSION

Petitioner has, at this stage, established a reasonable likelihood of prevailing in showing that at least one of the challenged claims is unpatentable. This determination is, however, based on a preliminary

record. We will make a final determination on the patentability of the challenged claims, as necessary and applying the preponderance of the evidence standard, based on a fully developed record through trial. *See In re NuVasive,* 842 F.3d 1376, 1380–81(Fed. Cir. 2016) (noting in the context of an *inter partes* review that "there is a significant difference between a petitioner's burden to establish a 'reasonable likelihood of success' at institution, and actually proving invalidity by a preponderance of the evidence at trial") (quoting 35 U.S.C. § 314(a) and comparing § 316(e)).

Any argument not raised in a timely Patent Owner Response to the Petition, or as permitted in another manner during trial, shall be deemed waived even if asserted in the Preliminary Response. *See In re NuVasive,* 842 F.3d at 1380–81 (holding Patent Owner waived an argument addressed in the Preliminary Response by not raising the same argument in the Patent Owner Response). In addition, nothing in this Decision authorizes Petitioner to supplement information advanced in the Petition in a manner not permitted by the Board's Rules.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claims 1–3 and 17–34 of the '288 patent is hereby instituted on the grounds set forth in the Petition, commencing on the entry date of this Order, and pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial.

FURTHER ORDERED that the trial will be conducted in accordance with a separately issued Scheduling Order.

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