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Paper 10
Date: January 17, 2024

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

GENZYME CORPORATION,
Patent Owner.

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IPR2023-01045
Patent 10,429,288 B2

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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 4–16 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."). Patent Owner disclaimed claims 4 and 10–14. Prelim. Resp. 1; Ex. 2010. Claims 5–9, 15, and 16 of the '288 patent remain at issue. Prelim. Resp. 2.

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 remaining at issue 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. 66.

Petitioner also filed a petition seeking *inter partes* review of claims 1–3 and 17–34 of the '288 patent in IPR2023-01044. Paper 2, 1; Paper 7, 2. Based on that petition, *inter partes* review of the '288 patent was instituted in IPR2023-01044 on January 9, 2024.

*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. 67; Paper 7, 2.

Petitioner has also filed a petition for *inter partes* review in IPR2023-01044 against the '288 patent. Paper 2, 1; Paper 7, 2.

*D. Ranking Petitions*

Petitioner filed a supplemental paper ranking the two petitions it filed challenged claims of the '288 patent, and providing an explanation of the differences between the petitions, why the differences are material, and why the Board should exercise its discretion to institute both petitions. Paper 2 (citing Consolidated Trial Practice Guide 59–60).[1] Petitioner ranks the petition in IPR2023-01044 first and thePetition in this proceeding second. Petitioner asserts that two petitions are needed because Patent Owner has alleged infringement of thirty-four claims in the related litigation, of which seven are independent. *See id.* at 1. Petitioner asserts that the claims challenged in the two petitions do not overlap, as the claims challenged in IPR2023-01044 relate to parameters for performing a method and the claims of challenged in this proceeding relate to analysis of data. *See id.* at 1–2. Petitioner asserts that "[t]he thirty-four challenged claims of the '288 patent cannot be addressed in one petition because of the word-count limit and non-overlapping scope of the challenged claims." *Id.* at 2. Accordingly,

[1] *Available at*: https://www.uspto.gov/sites/default/files/documents/tpgnov.pdf?MURL=TrialPracticeGuideConsolidated

Petitioner contends that "[t]he Board should exercise its discretion under § 314(a) to institute both petitions." *Id.*

Patent Owner opposes by highlighting a substantial overlap between the 34 challenged claims of the '288 patent. Prelim. Resp. 57–60. In particular, Patent Owner contends that claim 1, challenged in IPR2023-01044, and claim 4 "differ in their preambles" and further that each of independent claims 1 and 5–8 recite similar elements. *See* Prelim. Resp. 59–60 ("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 . . . .'"). Patent Owner concludes that, "[b]ecause of the substantial overlap between the claims, the total number of claims does not support multiple Petitions." *Id.* at 60.

Upon consideration of the specific circumstances under which Petitioner filed two petitions, we decline to exercise our discretion to deny institution in this proceeding. We agree with Petitioner that a large number of claims have been asserted against it in district court and that addressing those 34 claims may necessitate filing two separate petitions.[2] *See* TPG at 59 ("[T]he Board recognizes that there may be circumstances in which more than one petition may be necessary, including, for example, when the patent owner has asserted a large number of claims in litigation.") The fact that the same claims are not challenged between the two petitions weighs in favor of declining to exercise our discretion to deny institution. *See Gen. Plastic Co., Ltd. v. Canon Kabushiki Kaisha*, IPR2016-01357, Paper 19 at 16–17 (PTAB

[2] We recognize that Patent Owner has now disclaimed claim 4 and 10–14, however, that disclaimer was entered after the filing date of the Petition. Ex. 2010.

Sept. 6, 2017) (precedential as to § II.B.4.i). If we "discretionarily dismissed one petition or the other, some claims of the ['288] patent would be left uncovered by any ground alleged by Petitioner." *Marvell Semiconductor, Inc. v. Uniloc 2017 LLC*, IPR2019-01349, Paper 9 at 14 (PTAB Feb. 4, 2020) (instituting review); Paper 2, 2.

*E. 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.

*F. Challenged Claims*

Petitioner challenges claims 5–9, 15, and 16. Claims 5–8 are independent. Representative independent claim 5 is reproduced below.

> 5. A method of measuring the relative amount empty capsids in a preparation of recombinant 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),
>
> c) integrating the area under each peak in the C(s) distribution to determine the relative concentration of each species of recombinant AAV particles, and
>
> d) comparing the amount of recombinant AAV particles having an S value corresponding to empty capsid particles to the amount of recombinant AAV particles having an S value corresponding to recombinant AAV particles comprising intact AAV genomes or the total amount of recombinant AAV particles in the preparation.

Ex. 1001, 54:56–55:23.

*G. Evidence*

Ex. 1003, Le Bec, 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").

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.

*H. Asserted Grounds of Unpatentability*

Petitioner asserts that claims 5–9, 15, and 16 would have been unpatentable on the following grounds:

| Grounds | Claim(s) Challenged | 35 U.S.C. §[3] | Reference(s)/Basis |
|---|---|---|---|
| 1 | 5–8, 15 | 102 | Le Bec |
| 2 | 5–8, 15 | 103 | Le Bec |
| 3 | 5–9, 15–16 | 103 | Le Bec, Berkowitz |

*I. 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

[3] 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. 17–18. 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.

*J. Level of Ordinary Skill in the Art*

The level of ordinary skill in the art usually is evidenced by the prior art references themselves. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001); *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995).

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. 17 (citing Ex. 1020 ¶ 58). We do not find a proposal by Patent Owner for a different level of skill in the preliminary response. *See* PO Resp. generally.

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'288 patent and the asserted prior art.

*K. 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." *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. Summary of the Cited Prior Art*

#### *1. Le Bec*[4]

Le Bec discloses methods for "producing a double-stranded recombinant rAAV vector or self-complementary AAV (scAAV)." Ex. 1003, 6:14–17. 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 15:17–23, 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 17:29–18:6. 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.

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

> 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 15:17–28.

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.

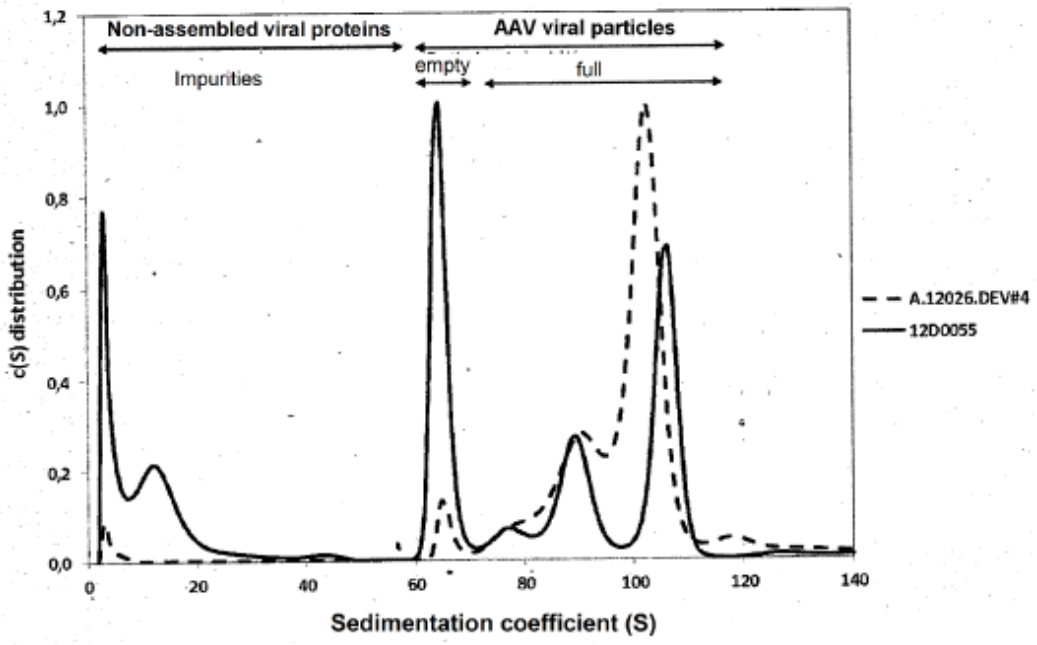


**Figure 2**

Figure 2 illustrates peaks at < 60S corresponding to non-assembled viral proteins and an/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.

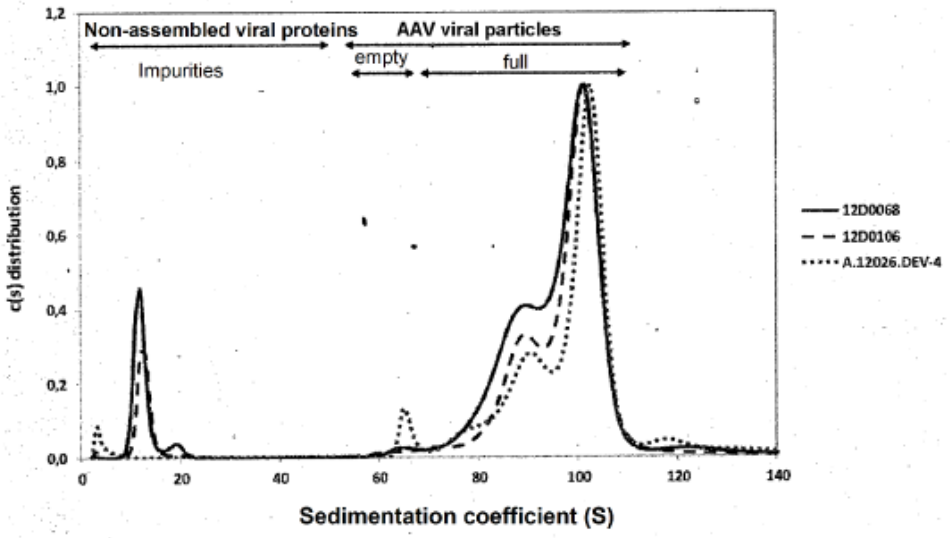


**Figure 3**

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 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.

*B. Ground 1: Anticipation of Claims 5–8 and 15 by Le Bec*

*1. Claim 5*

*a) [Preamble] A method of measuring the relative amount [of] empty capsids in a preparation of recombinant AAV particles comprising the steps of*

Petitioner contends that "[t]o the extent the preamble is construed to be limiting (citation omitted), it is taught by Le Bec." *Id.* at 26. Petitioner asserts that "Le Bec teaches that its method can detect and quantify the presence of empty capsids in rAAV preparations." *Id.* (citing Ex. 1003, 15:17–23, 17:12–15, 18:1–6; Ex. 1020 ¶ 91).

b) *[5a] subjecting the preparation to analytical ultracentrifugation under boundary sedimentation velocity conditions wherein the sedimentation of recombinant AAV particles is monitored at time intervals,*

Petitioner refers back to their earlier argument as described in Petitioner's argument for claim 4[a]. Patent Owner does not separately dispute this limitation. *See generally* Prelim. Resp.

c) *[5b] plotting the differential sedimentation coefficient distribution value (C(s)) versus the sedimentation coefficient in Svedberg units (S),*

Petitioner refers back to their earlier argument as described in Petitioner's argument for claim 4[b]. Patent Owner does not separately dispute this limitation. *See generally* Prelim. Resp.

d) *[5c] integrating the area under each peak in the C(s) distribution to determine the relative concentration of each species of recombinant AAV particles*

*(1) Petitioner's Contentions*

Petitioner contends "Le Bec teaches use of AUC to determine the 'quantification of empty and full viral particles' and reports the results of the that quantification in the form of a percentage." Pet. 26. Petitioner contends 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." *Id.* at 27. Petitioner asserts that the SEDFIT software, disclosed in Le Bec, would allow for a user to "determine relative concentrations by integrating areas under the curve." *Id.* (citing Ex. 1020 ¶ 27). Petitioner's expert, Dr. Berkowitz, notes that a "user employs their mouse to define a range of interest, and SEDFIT then calculates the area under the curve for the selected peak or range, the percent fraction of this peak area relative to the

total are of the plot and the average (weight-average) sedimentation coefficient for [a] peak." Ex. 1020 ¶ 38.

*(2) Patent Owner's Contentions*

Patent Owner contends that Petitioner "fails to establish that Le Bec disclosed" limitation 5[c], which describes "integrating the area under *each peak* in the C(s) distribution to determine the *relative concentration of each species* of recombinant AAV particles." Prelim Resp. 28 (citing Ex. 1001, 55:14–16). Patent Owner contends that "the ability of the claimed method to determine the concentration peaks corresponding to partial or fragmented genome species is an important distinction between the method of the challenged claims and Le Bec's disclosure." *Id.* at 34. Patent Owner contends that Petitioner's reliance on Le Bec's Figure 3 fails to prove anticipation because (1) "the Petition and Berkowitz Declaration never address the agglomeration of what appears to be multiple peaks ranging from about 75S to about 110S" and (2) "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." *Id.* at 36, 38 (citing Ex. 2001 ¶¶ 105–106).

Patent Owner also contends that Petitioner "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." *Id.* at 30 (citing Ex. 2001 ¶¶ 110–113). Patent Owner contends that "[t]he fact that the POSA *could* conduct such integrations to determine the concentrations of partial and fragmented species does not meet the threshold for anticipation." *Id.* at 39. Patent Owner contends that "the POSA would have had to obtain the necessary extinction coefficients viral particles for which Le Bec does not disclose concentrations" to practice

the limitation of 5[c]. *Id.* at 41. Patent Owner further contends that "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 42.

*(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 species of recombinant AAV particles." Pet. 26–27; Prelim. Resp. 26–42; Ex. 1020 ¶ 82–84; Ex. 2001 ¶¶ 52–54, 104–113. 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 5 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. 33 (citing Ex. 2001 ¶ 104; *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 Ex. 1020 ¶ 83; 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."[5] *See*

[5] 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

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.

> e) *[5d] comparing the amount of recombinant AAV particles having an S value corresponding to empty capsid particles to the amount of recombinant AAV particles having an S value corresponding to recombinant AAV particles comprising intact AAV genomes or the total amount of recombinant AAV particles in the preparation.*

Petitioner contends that "[t]he final limitation of claim 5 merely describes a mental comparison one could perform and should not be afforded any patentable weight." Pet. 28 (citing *Praxair*, 890 F.3d at 1031-1035). Alternatively, Petitioner contends Le Bec discloses a method to compare empty and full viral particles "by comparing the peak size at 65S representing the amount of empty capsid particles to the peaks at 90S and 105S, which [were] labeled 'full' in Figures 2 and 3." *Id.* at 29 (citing Ex. 1003, 18:11-27; Ex. 1020 ¶¶ 95-96; *Novo Nordisk*, 424 F.3d at 1355; *Kennametal*, 780 at F.3d at 1381).

Based on Petitioner's argument and evidence, summarized above, we are persuaded that Petitioner sufficiently shows that Le Bec discloses this element of claim 5. Patent Owner does not separately dispute Petitioner's showing in this regard. *See generally* Prelim. Resp.

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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.

*f) Conclusion*

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 6–8 and 15*

As noted by Patent Owner, Elements 5[c], 6[c], 7[c], 8[c], and claim 15 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, 55:14–16; 55:35–37; 55:56–58; 56:8–10; 57:1–4; Prelim. Resp. 28. Thus, our analysis of claim 5 applies equally to each of claims 6–8 and 15.

*3. Conclusion*

Based on the preliminary record, we find that Petitioner has shown that it is reasonably likely to prevail in establishing that claims 5–8 and 15 are anticipated by Le Bec.

*C. Ground 2: Obviousness of Claims 5–8 and 15 by Le Bec*

*1. Petitioner's Contentions*

Petitioner contends that claims 5–8 and 15 are obvious over Le Bec alone in view of the general knowledge of a person of ordinary skill in the art. Pet. 43. First, Petitioner contends that the application of sedimentation velocity analytical ultracentrifugation was obvious in view of Le Bec. *Id.* Petitioner contends that Le Bec "commented on the then-current limitations in producing self-complementary AAV vectors, including the high percentage of empty AAV particles 'with an inactive product.'" *Id.* at 44. As such, a person of ordinary skill in the art would have been "motivated to assess virus preparations for such undesirable contaminants." *Id.* Petitioner further contends a person of ordinary skill in the art "would have been

motivated to choose SV-AUC when seeking to characterize a preparation of rAAV particles to assess homogeneity." *Id.* at 45 (citing Ex. 1020 ¶¶ 180, 184–188; Ex. 1019, 4-5). Petitioner contends that

> [a] POSA would have had a reasonable expectation of 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 of Le Bec's teaching that rAAV particles (full, empty, and aggregate) could be effectively separated, characterized, and quantified by analytical ultracentrifugation.

*Id.* (citing Ex. 1003, 15:19-23; Ex. 1020 ¶¶ 181, 185–188).

Second, Petitioner contends that "[t]o the extent Patent Owner argues that 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." *Id.* at 46. Petitioner contends 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." *Id.* (citing Ex. 1020 ¶ 182). Petitioner further contends that "Le Bec itself provides motivation to integrate peak areas of C(s) v. S plots." *Id.* (citing Ex. 1003, 3:16–22; 15:27–28; 17:29–18:6). Using the SEDFIT software disclosed in Le Bec, Petitioner contends that "[a] POSA would have been motivated to use the integration function in the SEDFIT software to determine the relative concentrations of rAAV species in Le Bec's samples with a reasonable expectation of success in view of Le Bec's own use of the SEDFIT software to report relative concentrations." *Id.* at 46–47 (citing Ex. 1003, 15:18–28; Ex. 1020 ¶¶ 182, 185–188).

*2. Patent Owner's Contentions*

Patent Owner contends that Petitioner "fails to identify how Le Bec's disclosure would have been modified to meet Elements 5[c], 6[c], 7[c], 8[c], and claim 15," and instead merely refers to integration as a standard technique. Prelim. Resp. 44. 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 49. 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 47–48 (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 48 (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 claim elements 5[c], 6[c], 7[c], 8[c], and claim 15." Ex. 2001 ¶ 121. 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 claims 5-8 and 15." Prelim. Resp. 48.

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 51 (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 51–52 (citing Ex. 2001 ¶ 123).

*3. 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 claims 5–8 and 15 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. 45; 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 person of ordinary skill in the art 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. 44–45 (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. 43 (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).

*4. Conclusion*

Based on the preliminary record, we find that Petitioner has shown that it is reasonably likely to prevail in establishing that claims 5–8 and 15 would have been obvious in view of Le Bec.

*D. Ground 3: Obviousness of Claims 5–9, 15, and 16 over the Combination of Le Bec and Berkowitz*

*1. Petitioner's Contentions*

Petitioner contends that claims 5–9, 15, and 16 "would have been obvious to a POSA in view of Le Bec in combination with Berkowitz." Pet. 47. Petitioner contends that "[s]ubjecting Le Bec's preparation of rAAV particles to analytical ultracentrifugation 'under boundary sedimentation velocity conditions,' would have been obvious to a POSA based on the teachings of Berkowitz, which disclosed the use of SV-AUC to characterize adenovirus preparations for potential gene therapy applications." *Id.* at 49 (citing Ex. 1004, 17; Ex. 1020 ¶¶ 216–219). Petitioner further contends that "a POSA would have expected SV-AUC to be easier to apply to rAAV than the larger adenovirus particles examined in Berkowitz." *Id.* (citing Ex. 1001, 19:22–28; Ex. 1020 ¶ 200).

Petitioner then contends that "Berkowitz expressly teaches that 'quantification' of each particle would be accomplished by integration." *Id.* at 51. Petitioner directs us to Berkowitz, which provides "simple peak area integration … allows the percentage of EC [empty capsid] material present in a virus preparation to be readily calculated." Ex. 1004, 21. Petitioner argues 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." Pet. 51 (citing Ex. 1020 ¶¶ 199–202, 217–219; Ex. 1008, 1). Petitioner further argues that "a POSA would have had a reasonable expectation of success in doing so, based on Berkowitz's success in achieving such integration and the ready availability of the SEDFIT software." *Id.* (citing Ex. 1020 ¶ 202).

Petitioner contends that "[c]laims 5, 6, 7, and 8 each have a limitation regarding comparing the relative amounts of various species of particles in the viral preparations." *Id.* Petitioner contends that "[a] POSA would have been motivated to apply Berkowitz's teachings to Le Bec's analysis with a reasonable expectation of success, because Le Bec itself demonstrated that a heterogenous mixture of rAAV particles could be characterized and quantified by analytical ultracentrifugation." *Id.* at 52–53 (citing Ex. 1020 ¶¶ 199–202, 217–219). Petitioner then contends that "Berkowitz expressly discusses the types of information that can be obtained from an SV-AUC experiment." *Id.* at 54 (citing Ex. 1004, 17). Petitioner contends that "[a] POSA would have been motivated to apply Berkowitz's teachings to Le Bec's SV-AUC data to elicit information regarding heterogenicity of clinical lots of drug product in pursuit of a product with increased purity and homogeneity." *Id.* (citing Ex. 1020 ¶¶ 199–202, 217–219).

*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. 54 (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).

*3. Discussion*

Similar to the situation in Grounds 1 and 2, Dr. Berkowitz and Dr. Hansen provide conflicting testimony for whether Le Bec teaches or suggests "Elements 5[c], 6[c], 7[c], 8[c], and claim 15, 'integrating the area under each peak in the C(s) distribution to determine the relative concentration of each species of recombinant AAV particles.'" Prelim. Resp. 53; Ex. 2001 ¶¶ 124–125. As above, because the conflicting testimony with regard to those elements create 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).

With regard to Petitioner's reliance on Berkowitz, we agree with Patent Owner that, while Berkowitz provides a specific example of integrating an AUC peak, the issue is not whether a person of ordinary skill in the art would have known how to integrate peaks, rather the issue in this Ground is whether a person of ordinary skill in the art would had reason to modify Le Bec to integrate the area under each peak in the C(s) distribution to determine the relative concentration of each species of recombinant AAV particles as required by the challenged claims. To that point, we find some merit in Patent Owner's assertion 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. Ex. 1004, 21 ("At present we have not attempted to apply

> corrections to account for extinction coefficient differences."); [Ex. 2001], Hansen, ¶ 128.

Prelim. Resp. 48; Ex. 2001 ¶ 128 ("The Petition does not explain why the POSA would have had a reason to combine Berkowitz 2007—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.").

## 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 5–9, 15, and 16 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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