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.

Case No. IPR2023-01045
Patent No. 10,429,288

PETITION FOR *INTER PARTES REVIEW*

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I. INTRODUCTION

U.S. Patent No. 10,429,288 ("the '288 patent") relates to analyzing recombinant adeno-associated virus ("rAAV") preparations using analytical ultracentrifugation ("AUC"). Critical to allowance of the '288 patent was Patent Owner's argument that the claimed invention was "surprising" and that "one of skill in the art would not have predicted with a reasonable expectation of success that methods described for a virus such as adenovirus could be applied to [rAAV] particles." Ex.1002, 541. That is, Patent Owner represented that AUC had not been used to analyze rAAV particles in a printed publication. As illustrated herein, the prior art objectively indicates that representation was incorrect.

A published patent application referred to herein as "Le Bec" describes using AUC to characterize rAAV preparations. Le Bec was not before the Examiner, and it shows conclusively that application of AUC to rAAV was not "surprising." Indeed, Le Bec used the same instrumentation, software, and analysis that researchers had relied on for decades to characterize heterogeneous compositions of biomacromolecules—a fact acknowledged in the patent and evidenced by the prior art. Moreover, Le Bec ascribes no particular fanfare to its use of AUC on rAAV preparations; instead Le Bec treats it as what it is—the routine use of a decades old technique to characterize rAAV preparations. The claims challenged in this petition recite various data comparisons that could be employed when performing AUC on

rAAV particles, but those comparisons were well known. Because the method was already known, there is nothing inventive about the claimed subject matter of the ’288 patent.

Accordingly, Petitioner respectfully submits the challenged claims are unpatentable. That position is supported by the art of record, the POSA’s knowledge, Patent Owner’s admissions, and the declaration of Dr. Steven Berkowitz (Ex.1020), an expert in AUC, including its application to viral preparations.

II. REQUIREMENTS FOR *INTER PARTES* REVIEW UNDER 37 C.F.R. §42.104

A. Grounds for Standing

Petitioners certify that (1) the ’288 patent is available for *inter partes* review (“IPR”) based on its January 20, 2015, priority date (Ex.1001, (60)), and (2) Petitioners are not barred or estopped from requesting review on the grounds identified.

B. Identification of Challenges

Pursuant to 37 C.F.R. §§42.104(b) and 42.22(a)(1), Petitioners request review and cancellation of the claims of the ’288 patent on the following grounds:

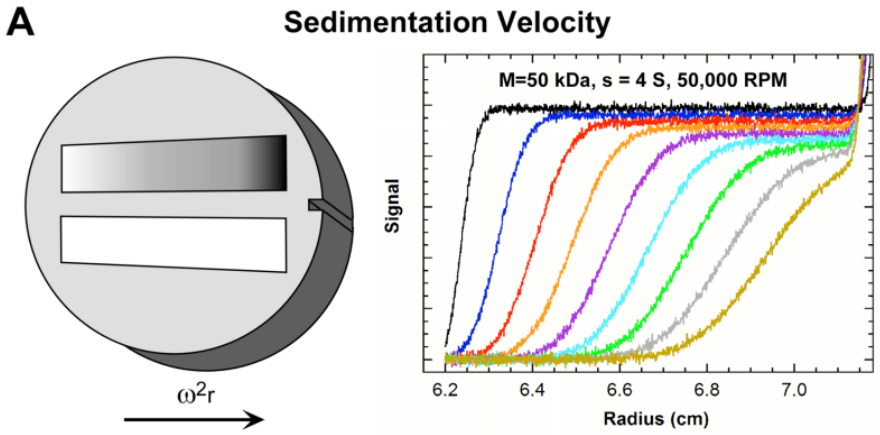
Ground	Claim(s)	Basis	References
1	4-8, 10-15	§102	Anticipated by *Le Bec*
2	4-8, 10-15	§103	Obvious over *Le Bec* alone
3	4-16	§103	Obvious over *Le Bec* in view of *Berkowitz*

III. BACKGROUND

A. Analytical Ultracentrifugation

Theodore Svedberg invented the analytical ultracentrifuge in 1925, and the fundamental principles of analytical ultracentrifugation have changed little since. Ex.1020, ¶¶9-13; *see also* Ex.1005, 144 ("For over 75 years, analytical ultracentrifugation [] has proven to be a powerful method for characterizing solutions of macromolecules."); Ex.1001, 19:22-28; Ex.1006, 163; Ex.1013, Ex.1018, 22 (referring to AUC as the "gold standard").

The claims of the '288 patent involve a type of AUC called sedimentation velocity analytical ultracentrifugation ("SV-AUC"). SV-AUC involves spinning a sample fast enough to force suspended particles or dissolved molecular species to migrate in solution while collecting data on their differing sedimentation velocities (i.e., rates of movement). Ex.1020, ¶¶13-21. A boundary of particles moving at the same rate forms in response to the gravitational force, and a series of scans are taken to measure the rate of movement (sedimentation velocity) of the boundaries over time. Ex.1020, ¶¶25-26; Ex.1006, 165.



Ex.1005, 162, Fig. 1 (depicting sedimentation velocity cells—a reference cell and a sample cell—and the data obtained from scans over time). Sedimentation velocity is a function of particle characteristics such as mass, shape, and density and is reported as a sedimentation coefficient (i.e., the rate at which a particle moves in response to acceleration) measured in Svedberg units, S (10^{-13} s). Ex.1005, 146; Ex.1020, ¶¶16-21. SV-AUC can separate, identify, and quantify different species of particles in a heterogenous mixture by their sedimentation coefficients. Ex.1020, ¶16.

The Lamm equation (which was derived in 1929 by Ole Lamm) describes the sedimentation and diffusion of a solute under ultracentrifugation and is used to determine sedimentation coefficients. Ex.1020, ¶139; Ex.1005, 146; Ex.1011, 228. In 2000, Peter Schuck created a publicly available, freely downloadable computer program called SEDFIT, which uses a distribution of Lamm equation solutions to directly model the sedimentation boundary, and greatly increased the information derivable from AUC experiments. Ex.1020, ¶171; *see also* Ex.1004, 17. SEDFIT

can graphically display sedimentation coefficient distribution profiles and determine relative concentrations of species in a sample. Ex.1020, ¶¶27-40. The SEDFIT software was widely used and frequently cited in publications. Ex.1020, ¶27; Ex.1005, 166-167, 173; Ex.1006, 167. It was also discussed in the '288 patent. Ex.1001, 21:4-19.

B. Using SV-AUC to Characterize Wide Varieties of Particle Sizes, Including Viral Preparations

After the release of SEDFIT and other, similar analysis tools, those in the field saw the benefits of AUC for a wide variety of applications. Ex.1020, ¶26. In the early 2000s, companies were developing gene therapy products comprising viral-based vectors, which required rigorous assessments of purity, potency, and safety during and after their manufacture. *See*, *e.g.*, Ex.1004, 16 ("To achieve drug licensure, drug product quality (with regard to homogeneity and purity) and consistency of manufacturing are of key importance."); Ex.1008, 1 ("[I]t has been speculated that nonfunctional empty virions in clinical vector lots may reduce efficiency of therapeutic gene transduction in the liver by competing with the fully packaged therapeutic vector particles for receptor uptake."). SV-AUC was seen as a powerful and useful tool for assessing the homogeneity of viral vectors used in gene therapy applications. Ex.1004, 17; *see also* Ex.1005, 145 ("The range of molecular weights suitable for AUC exceeds that of any other solution technique from a few

hundred Daltons (e.g., peptides, dyes, oligosaccharides) to several hundred-million Daltons (e.g., viruses, organelles).").

Moreover, SV-AUC had been identified as a useful tool for characterizing rAAV particles before the priority date for the '288 patent. Ex.1020, ¶¶41-44, 64-71; Ex.1019, 4-5; Ex.1006. An article from 1999 compared sedimentation coefficients of AAV virus-like particles determined by analytical ultracentrifugation. Ex.1009, 373-374, Fig. 3. A 2012 Assessment Report from the European Medicines Agency identified analytical ultracentrifugation as a method used to "determine mass, density and distribution profiles" for Glybera, a gene therapy product comprising a replication deficient AAV vector. Ex.1010, 15. Distribution profiles are a hallmark of SV-AUC (*see, e.g.*, Ex.1003, 6:3-10), indicating characterization of rAAV particles in pharmaceutical compositions via SV-AUC was known. An article from 2014 commented that "analytic ultracentrifugation technology is a powerful tool for quantitative characterization of structural heterogeneity of rAAV preparations, allowing precise and selective observation of viral capsid sedimentation in real time…. For future studies, it may be necessary to use analytic ultracentrifugation for further characterization of compositions of clinical rAAV lots." Ex.1008, 6.

Indeed, the use of SV-AUC with rAAV particles was not just theoretical, it had already been performed and reported in a published patent application ("Le

Bec"). *See* Ex.1003. Before the '288 patent application was filed, the field was aware of SV-AUC, its usefulness in characterizing biomolecules of different types, and its actual application to the development of gene therapy technologies by identifying and quantifying rAAV particles.

IV. THE '288 PATENT

The '288 patent purports to have developed "methods to characterize preparations of recombinant viral particles using analytical ultracentrifugation." Ex.1001, Abstract. The patent acknowledges that AUC is a tool that "may be applied to determine the biophysical properties of many types of particles across a wide range of particle concentrations and sizes" (Ex.1001, 19:25-28) and that it had been around for decades (Ex.1001, 19:22-24 ("AUC analysis has been well characterized over many decades and is highly versatile.")). The '288 patent claims methods that involve characterizing rAAV preparations under boundary sedimentation velocity conditions. Ex.1001, 54:20-58:47. However, the concept of using SV-AUC to analyze preparations of rAAV particles was already well-known before the '288 patent's priority date.

A. The Challenged Claims

The '288 patent claims various methods that involve using SV-AUC to characterize the presence, absence, or relative amounts of recombinant AAV

particle species in a sample. Claims 4-16 are challenged herein.[1] Claim 4 is representative and recites:

> A method to determine the presence of empty capsids or capsid particles comprising variant sized recombinant AAV genomes 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, and
>
> b) plotting the differential sedimentation coefficient distribution value (C(s)) versus the sedimentation coefficient in Svedberg units (S), wherein the presence of one or more peaks other than the peak for full capsid particles comprising intact recombinant AAV genomes indicates that presence of capsid particles comprising variant sized genomes and/or empty capsids.

Ex.1001, 54:56-55:3.

The steps of "subjecting the preparation to analytical ultracentrifugation under boundary sedimentation velocity conditions" and "plotting the differential sedimentation coefficient distribution value (C(s)) versus the sedimentation coefficient in Svedberg units (S)" are common to all challenged claims. The

[1] The remainder of the claims of the '288 patent are challenged in a concurrently filed petition for *Inter Partes* review, IPR2023-01044.

challenged claims differ from each other primarily in the types of analysis or comparisons that they require (e.g., assessing the presence or absence of peaks corresponding to full or empty capsids (e.g., claims 5-9), quantitating them relative to each other (e.g., claims 5, 6, 8, and 15) or the total number of particles (e.g., claims 5-9), etc.), and what the data "indicates" (claims 4, 10-16). These additional steps are not novel.

B. Patent Owner's Admissions in the Specification

The '288 patent's disclosure includes many admissions concerning the elements of the challenged claims known in the art, the motivation to develop the claimed methods, and the expectation of success in doing so. For example, the '288 patent acknowledges that "[t]he 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" (Ex.1001, 1:38-41 (emphasis added)). This mirrors the need long-recognized by others for viral compositions used in gene therapy as well as pharmaceutical compositions generally and provides strong motivation to develop the claimed methods. *See*, *e.g.*, Ex.1004, 16-17, Ex.1005, 149, Ex.1008, 6.

The '288 patent also describes AUC as a well-known method within the ability of a skilled artisan to optimize. For example, the patent notes that "AUC analysis has been well characterized over many decades and is highly versatile" and

that it "may be applied to determine the biophysical properties of many types of particles across a wide range of particle concentrations and sizes." Ex.1001, 19:22-28. The '288 patent also admits that a person skilled in the art would know how to optimize AUC for use with rAAV particles. *See, e.g.*, Ex.1001, 26:4-6 ("It is within the purview of the skilled artisan to optimize the parameters of AUC for different types of viral particles."); *id.*, 28:62-64 ("Suitable ultracentrifugation conditions, analysis algorithms, and other parameters may be determined empirically through methods known in the art."). The '288 patent claims merely recite an application of AUC analysis to an rAAV preparation, which Le Bec had already achieved.

C. Prosecution of the '288 Patent

As originally filed, the claims in the application leading to the '288 patent were directed to the use of SV-AUC to characterize preparations of recombinant viral particles in general. The Examiner issued a non-final rejection of all pending claims, as anticipated or obvious over references teaching SV-AUC methods and principles, including Cole. Ex.1002, 516-529 (citing Ex.1005).

To overcome the Examiner's rejections, Patent Owner amended the claims "to recite that the viral particles are recombinant adeno-associated viral (AAV) particles." Ex.1002, 539. Patent Owner argued that the cited references were silent regarding rAAV particles. *Id.*, 539-540. Patent Owner also argued—without evidentiary support—that "one of skill in the art would not have predicted with a

reasonable expectation of success that methods described for a virus such as adenovirus could be applied to recombinant AAV particles" and that the application was based on "the inventors' surprising finding that AUC could be applied to preparations of recombinant AAV particles to identify variant recombinant viral genomes or empty viral capsid particles impurities with incredible sensitivity, precision, and accuracy." *Id.*, 541.

The Examiner accepted Patent Owner's arguments when allowing the claims, stating that:

> Analytical ultracentrifugation (AUC) was well-described in the art as a means to separate biological molecules, including viruses. While it would be obvious to apply AUC to separation of AAV particles and routine to optimize said parameters, AUC was not noted as having been applied to AAV separation routinely…. Applicants have surprisingly found parameters for AUC that allow for high levels of separation of AAV particles, including accurate separation of AAV subtypes and empty particles.

Ex.1002, 561. The Examiner's allowance was in error because the Examiner (1) was not aware of relevant art asserted herein (e.g., Le Bec), and (2) was led astray by Patent Owner's argument that the ability to apply SV-AUC to rAAV particles was surprising or unexpected. *See* Ex.1020, ¶¶52-56.

V. ASSERTED ART

A. Le Bec

Le Bec is a PCT Publication of International Application Number PCT/EP2014/052978, entitled "Methods for the Production of Double-Stranded AAV Viral Particles." Ex.1003 ("Le Bec"), (21). Le Bec was published on August 21, 2014 and qualifies as prior art under AIA §102(a)(1). *Id.* Le Bec was published in French, and a certified translation has been submitted with this petition. Ex.1003. The Examiner did not consider Le Bec during the prosecution of the '288 patent. Ex.1002. In the EPO, observations have been filed by third parties raising lack of novelty and inventiveness of claims nearly identical to those in the '288 patent. Ex.1012. Le Bec is analogous art because it is from the same field of endeavor as the claimed invention and reasonably pertinent to the problem faced by the inventor. Ex.1020, ¶66.

Le Bec discloses methods to produce double stranded/"self-complementary" AAV particles ("scAAV"), a type of rAAV particles. Le Bec describes the production and purification methods employed to make its scAAV compositions using two different methods, one involving insect derived sf9 cells, and another employing human embryonic kidney (HEK293) cells. Ex.1003, 1:33-3:2.

Le Bec reports characterization data for its AAV preparations, including "[a]nalysis of empty and full AAV viral particles" using "analytical

ultracentrifugation." Ex.1003, 15:17-18. Le Bec explains that "[t]he sedimentation coefficient of the various AAV viral particles (empty, full, aggregate) and other present populations (subparticles, contaminant proteins, aggregate) in the purified products was determined by real-time centrifugation" and that "[c]entrifugation 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." Ex.1003, 15:23-28. Further, Le Bec notes that the densities of empty and full AAV viral particles had been reported in the literature, and that "[k]nowing that the difference in density is sufficiently significant to distinguish them by centrifugation, we have implemented a method today for analytically separating by ultracentrifugation and quantifying the different species present in an AAV viral preparation." *Id.*, 18:1-6.

Figures 2 and 3 of Le Bec depict C(s) v. S plots from the AUC analyses:

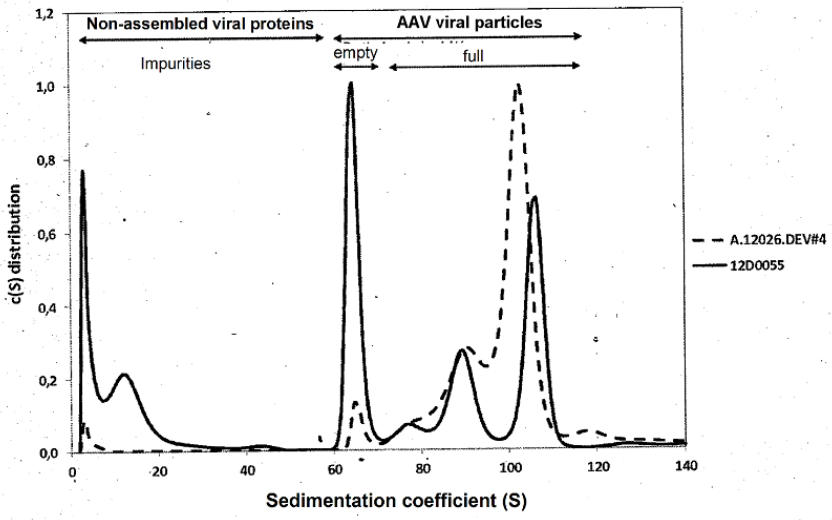


Figure 2

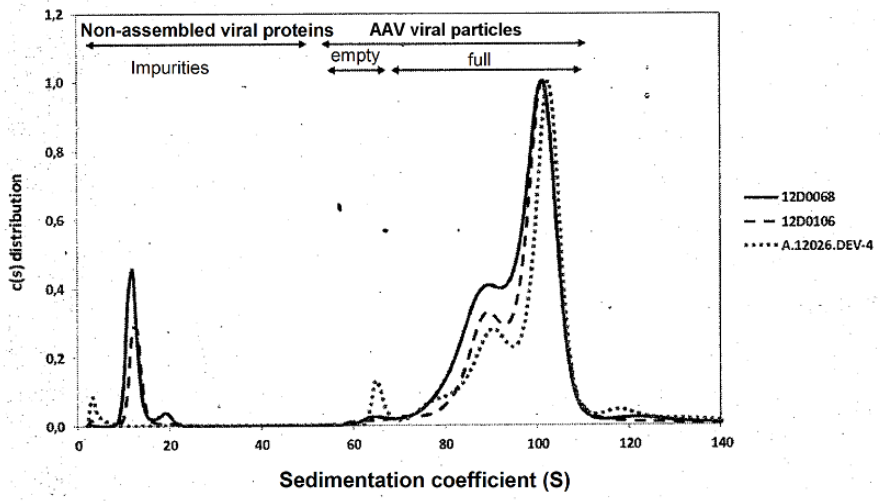


Figure 3

Figure 2 compares the AAV particles produced in sf9 cells with those prepared in HEK293 cells. Ex.1003, Fig. 2. Le Bec explains that the distribution profile reflects the different populations of viral proteins: (1) < 60S represents non-assembled viral proteins or contaminants, (2) the peak at around 65S represents empty AAV particles, (3) a peak at 90S corresponds to particles with the viral

genome in single-stranded form, and (4) a peak at 105S corresponds to particles with the viral genome in double-stranded form. Ex.1003, 18:10-32.

The results in Figure 2 show that the viral preparation made with HEK293 cells has less than 25% full particles (only 10% of which contain the double stranded genome). Ex.1003, 19:1-5. Empty rAAV particles are a substantial portion of the composition, as shown by the large peak at 65S. Ex.1003, Fig. 2. In contrast, viral particles made with sf9 cells contained very few empty particles and were enriched in particles containing the double stranded genome. Ex.1003, 19:7-15.

Thus, AUC's applicability to characterizing heterogeneous compositions of rAAV particles was known and described in a printed publication (Le Bec) before the priority date of the '288 patent. Nothing in Le Bec suggests that the use of AUC to characterize rAAV particle compositions was considered unexpected or required more than routine optimization or experimentation. Ex.1003.

B. Berkowitz[2]

Berkowitz is a scientific article entitled "Adenovirus homogeneity by analytical ultracentrifugation." It was published in 2007 and qualifies as prior art under AIA §102(a)(1). Ex.1004. Berkowitz is cited in the '288 patent specification,

[2] Berkowitz was authored by Petitioner's expert, Dr. Steven Berkowitz.

but it was not relied on by the Examiner during prosecution to support a rejection. Ex.1002, 516-529.

Berkowitz is analogous art from the same field of endeavor as the claimed invention and reasonably pertinent to the problem faced by the inventor. Ex.1020, ¶159. Berkowitz teaches the use of analytical ultracentrifugation to characterize the homogeneity of viral preparations. *Id.*, ¶¶158-163, 180.

Berkowitz explains that for all drug biologic products requiring marketing approval, "drug product quality (with regard to homogeneity and purity) and consistency of manufacturing are of key importance." *Id.* Berkowitz notes that an adenoviral preparation might include empty capsids, incomplete or aberrant particles, sub particles, and/or aggregates. Ex.1004, 16-17.

Berkowitz uses AUC to assess the homogeneity of viral preparations, noting that it had been used in the past. Ex.1004, 17. Berkowitz explains that recent improvements in available hardware and computational improvements in analysis of SV-AUC experiments make it a promising tool for analyzing biological samples. *Id.* Berkowitz teaches that a single SV-AUC experiment can indicate the following:

> (1) amount of intact virus monomer and its heterogeneity, (2) amount of EC [Empty Capsid] material and its heterogeneity, (3) amount of virus aggregation and the distribution of aggregate sizes, (4) detection and quantification of other smaller structural forms of the intact and EC adenovirus particles formed during adenovirus assembly in vivo or

> from damage that may occur after release from infected cells during all phases of virus processing (which would include cell culture production, purification, vialing, or storage), and (5) accurate values for the total concentration of adenovirus material present in a virus sample….

Ex.1004, 17. Berkowitz further teaches that "simple peak area integration, taking into account radial dilution effects . . . allows the percentage of [empty capsid] material present in a virus preparation to be readily calculated." Ex.1004, 21. Berkowitz provides examples of these calculations for empty capsids and aggregates in Table 2. Ex.1004, 29 (Table 2).

VI. LEVEL OF ORDINARY SKILL IN THE ART

A POSA working in the field of the '288 patent on January 19, 2015, 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. Ex.1020, ¶58.

VII. CLAIM CONSTRUCTION

The Board construes claims per *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005). 37 C.F.R. §42.100(b). Claims should only be construed to the extent

necessary to resolve a controversy. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017). For this proceeding, no terms require express construction, because the prior art's disclosures are commensurate with the '288 patent disclosures and Patent Owner's admissions during prosecution. The prior art reads on the claims under any construction consistent with *Phillips*. For purposes of this proceeding, the petition analyzes the claim terms under their "plain and ordinary meaning."[3]

VIII. GROUND 1: CLAIMS 4-8 AND 10-15 ARE ANTICIPATED BY LE BEC

"To anticipate, a prior art reference must place the [invention] in the possession of the public." *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc*., 471 F.3d 1369, 1375 (Fed. Cir. 2006). "A reference can anticipate a claim even if it 'd[oes] not expressly spell out' all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would 'at once envisage' the claimed

[3] Petitioners reserve the right to argue that claim construction is necessary in another forum. For example, Patent Owner's infringement and validity positions in the co-pending litigation may raise controversies that require resolution through claim constructions not implicated here given the similarities between the prior art and the '288 patent.

arrangement or combination." *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015) (quoting *In re Petering*, 49 CCPA 993, 301 F.2d 676, 681 (1962)); *see also Novo Nordisk Pharms., Inc. v. Bio-Tech. Gen. Corp.*, 424 F.3d 1347, 1355 (Fed. Cir. 2005) (anticipation does not require actual performance of suggestions in a disclosure).

A. Claim 4 is Anticipated By Le Bec

Claim 4 recites a method of determining the presence of empty capsid particles in an rAAV particle preparation by subjecting it to boundary sedimentation conditions, plotting the results, and analyzing the relative amounts of different species therein. Claim 4 was expressly taught in Le Bec.

1. "A method to determine the presence of empty capsids or capsid particles comprising variant sized recombinant AAV genomes in a preparation of recombinant AAV particles comprising the steps of"

To the extent the preamble is construed to be limiting,[4] it is taught by Le Bec. Specifically, Le Bec teaches a method for analytically separating, detecting, and

[4] "[A] preamble is not limiting 'where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention'." *Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (quoting *Rowe v. Dror*, 112 F.3d 473, 478 (Fed. Cir. 1997)).

quantifying the presence of empty capsids, full capsids, and aggregates in an rAAV preparation. Ex.1003, 15:17-23 ("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."), 16:25-29, 18:1-6; *see also* Ex.1020, ¶86.

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"

Le Bec teaches subjecting an rAAV preparation to ultracentrifugation under boundary sedimentation velocity conditions. The '288 patent explains the terms "'sedimentation velocity conditions' or 'boundary sedimentation velocity conditions' may refer to any experimental conditions under which a sample solution is subjected to sedimentation velocity analysis." Ex.1001, 17:17-20. Le Bec describes subjecting an rAAV preparation to SV-AUC conditions to determine the sedimentation coefficients of various rAAV particles. Ex.1003, 15:17-23. SV-AUC determines sedimentation coefficients by looking at boundary sedimentation velocity data. Ex.1020, ¶¶73-78; Ex.1005, 146-147. Le Bec's determination of the "sedimentation coefficient[s] of the various AAV viral particles," and plotting those coefficients, confirms that Le Bec was measuring the velocities at which different sedimentation

boundaries were moving and, thereby, performing SV-AUC. Ex.1020, ¶¶77-78; *see also* Ex.1005, 146-147.

Furthermore, the AUC parameters described in Le Bec result in boundary sedimentation conditions for rAAV-sized particles. Ex.1020, ¶¶75-76; Ex.1001, 17:17-20. Le Bec details the parameters of the ultracentrifugation procedure: vectors "are concentrated and formulated in PBS buffer" and "[c]entrifugation of the samples was carried out at a speed of 16,000 rpm using 100µl or 400µl of undiluted pure vectors, sedimentation was followed by the absorbance at the wavelength of 276 nm, the sedimentation coefficient was obtained using the software SEDFIT." Ex.1003, 14:15-16; 15:23-28. Le Bec's rotor speed of 16,000 rpm falls within the range identified in the '288 patent for use with AAV particles (between 10,000 rpm and 20,000 rpm). Ex.1001, 29-30 (Table 1). Similarly, Le Bec's disclosure of measuring absorbance at 276 nm is consistent with the '288 patent's explanation that "[i]n some embodiments, the absorbance is at about 230 nm, 260 nm or 280 nm." *See* Ex.1001, 4:36-37; *see also* Ex.1001, 29-30 (Table 1).

Le Bec further reports acquiring data in "real-time," which means that the sedimentation of rAAV particles was monitored at time intervals. Ex.1020, ¶79. The distribution profiles reported in Le Bec in Figures 2 and 3 and the calculation of sedimentation coefficients of the various populations using the SEDFIT software requires that sedimentation was monitored at time intervals. Ex.1020, ¶79.

A POSA would understand and at once envisage that Le Bec applied boundary sedimentation velocity conditions to rAAV particles. *Kennametal*, 780 F.3d at 1381.

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

Le Bec plots a "differential sedimentation coefficient distribution value (C(s)) versus the sedimentation coefficient in Svedberg units (S)." Ex.1020, ¶¶80-81. Specifically, Le Bec describes Figures 2 and 3 as "a graph showing the analytical ultracentrifugation distribution profile." Ex.1003, 6:4-10. Each graph plots the "c(s) distribution" on one axis and the "sedimentation coefficient (S)" on the other:

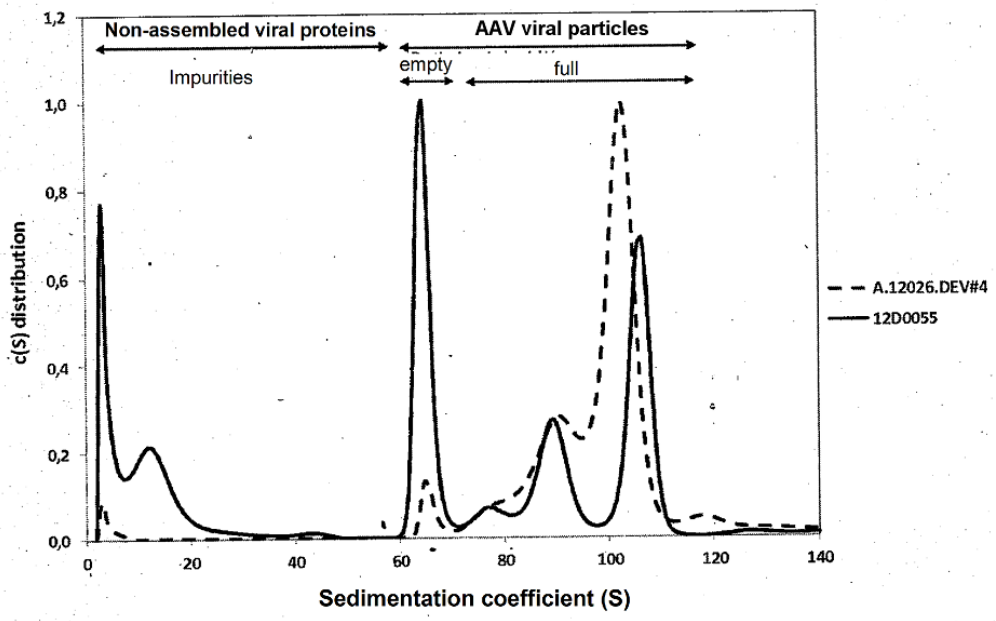


Figure 2

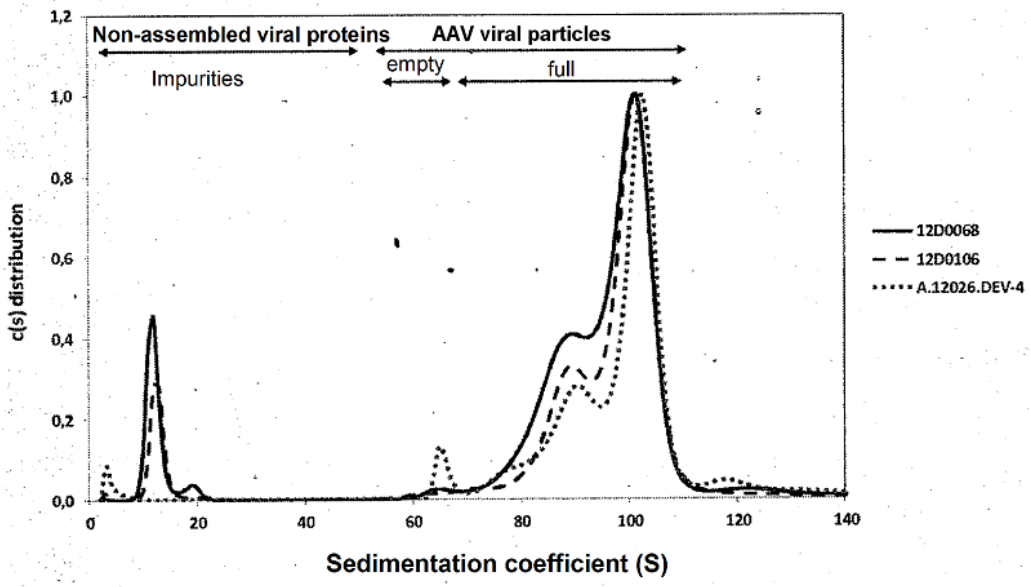


Figure 3

Ex.1003, Figs. 2 and 3; Ex.1020, ¶¶80-81.

4. "wherein the presence of one or more peaks other than the peak for full capsid particles comprising intact recombinant AAV genomes indicates [the] presence of capsid particles comprising variant sized genomes and/or empty capsids"

The final limitation of claim 4 merely describes how to interpret the information generated by the claimed SV-AUC method and should not be afforded any patentable weight. Under the "printed matter" doctrine, "[c]laim limitations directed to the content of information and lacking a requisite functional relationship are not entitled to patentable weight…." *Praxair Distribution, Inc. v. Mallinckrodt Hosp. Prod. IP Ltd.*, 890 F.3d 1024, 1032 (Fed. Cir. 2018); *see also id.*, 1031 ("Claim limitations directed to printed matter are not entitled to patentable weight unless the printed matter is functionally related to the substrate on which the printed matter is

applied."). Similarly, "a limitation that merely claims information by incorporating that information into a mental step will receive patentable weight only if the limitation is functionally related to the substrate." *Id.* at 1033 (collecting printed matter cases arising in the context of anticipation and obviousness).

In considering whether claimed information is functionally related, one must consider "whether the printed matter merely informs people of the claimed information, or whether it instead interacts with the other elements of the claim to create a new functionality in a claimed device or to cause a specific action in a claimed process." *C R Bard Inc. v. AngioDynamics, Inc.*, 979 F.3d 1372, 1381 (Fed. Cir. 2020). In *Praxair*, claims that merely required providing a physician with information and/or required the physician to evaluate the information—a "think about it" step—were not given patentable weight, unlike claims that required the physician to take a specific action based on the information provided. *Praxair*, 890 F.3d at 1033-1035.

Here, the final limitation of claim 4 seeks to claim the content of information (i.e., what is reported by the SV-AUC data) without a functional relationship, and it is entitled to no patentable weight. Specifically, the limitation merely recites that the presence on the distribution profile of one or more peaks other than the peak for full capsids "indicates"—i.e., informs the experimenter of—the presence of capsid

particles comprising variant sized genomes and/or empty capsids in the sample tested. And there is no functional relationship to the remainder of the claim.

To the extent such data analysis steps are entitled any patentable weight, they were disclosed in Le Bec. For example, Le Bec teaches that the sedimentation coefficients of empty, full, and aggregate rAAV particles are sufficiently distinct that those species can be separated by analytical ultracentrifugation. Ex.1003, 18:1-6. Le Bec explains that the 90S and 105S peaks on its C(s) v. S plots correspond to rAAV particles with single- and double-stranded genomes, respectively, while "empty AAV viral particles" correspond to a peak at 65S. *Id.*, 18:19-27. Furthermore, the figures label the peak at a range centered on 65S as "empty" and the peaks between 90S and 110S as "full." *Id.*, Figs. 2 and 3. Le Bec expressly teaches that the presence of the peak at 65S—a peak "other than the peak for full capsid particles comprising intact recombinant AAV genomes"—indicates the "presence of capsid particles comprising variant sized genomes and/or empty capsids."

B. Claim 5 is Anticipated By Le Bec

Claim 5 recites a method of measuring the relative amount of empty capsids in an rAAV particle preparation by subjecting it to boundary sedimentation conditions and analyzing the relative amounts of different species therein. Claim 5 was taught by Le Bec.

1. "A method of measuring the relative amount [of] empty capsids in a preparation of recombinant AAV particles comprising the steps of"

To the extent the preamble is construed to be limiting (fn.5, *supra*), it is taught by Le Bec. Specifically, Le Bec teaches that its method can detect and quantify the presence of empty capsids in rAAV preparations. Ex.1003, 15:17-23, 17:12-15, 18:1-6; Ex.1020, ¶91.

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"

This limitation is anticipated in Le Bec as described above for claim 4. *See* §VIII.A.2.

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

This limitation is anticipated in Le Bec as described above for claim 4. *See* §VIII.A.3.

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

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. A POSA would understand the disclosed percentages to be the relative concentrations of the corresponding rAAV particle species in the sample. Ex.1020, ¶¶82-84; *see also* Ex.1003, 8:10-13 (describing the amount of genome containing rAAV particles as a percentage).

Furthermore, 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. Ex.1020, ¶84; *Novo Nordisk*, 424 F.3d at 1355. Le Bec disclosed that the SEDFIT software was used to determine sedimentation coefficients, and the C(s) v. S distribution profile graphs depicted in Figures 2 and 3 of Le Bec are the type generated by SEDFIT. Ex.1020, ¶¶27-40, 83. In Version 14.4d of SEDFIT, which was publicly available and freely downloadable before the '288 patent's priority date and at the time of Le Bec, users could determine relative concentrations by integrating areas under the curve. Ex.1020, ¶¶27-40. A POSA was aware of this functionality of the SEDFIT software and how to implement it. Ex.1020, ¶27.

5. "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."

The final limitation of claim 5 merely describes a mental comparison one could perform and should not be afforded any patentable weight. *See Praxair*, 890 F.3d at 1031-1035; *see also* §VIII.A.4. Specifically, the limitation recites a mental step of comparing the amount of empty capsid particles to the amount of full capsid particles or the total number of particles, which is analogous to the mental step of requiring a physician to "evaluate" information found to lack patentable weight in *Praxair*.

To the extent such data analysis steps are entitled any patentable weight, they were disclosed in Le Bec. Le Bec explains that in the HEK293 system, "the percentage of empty AAV viral particles, i.e., particles lacking viral DNA, is largely predominant and represents more than 90%" and that their invention was intended "to provide a method for producing double-stranded rAAV particles with an improvement in the ratio of particles containing viral DNA to empty particles and an increased percentage of particles containing a double-stranded genome." Ex.1003, 3:17-29. Accordingly, "quantification of empty and full viral particles were determined." *Id.*, 16:28-29. Le Bec commented that "[h]ighly unexpectedly, we

detected very few empty AAV viral particles with the sf9 system compared to the HEK293 system." *Id.*, 18:27-29. A POSA would understand Le Bec to have reached these conclusions by comparing the peak size at 65S representing the amount of empty capsid particles to the peaks at 90S and 105S, which are labeled "full" in Figures 2 and 3. Ex.1003, 18:11-27; Ex.1020, ¶¶95-96; *Novo Nordisk*, 424 F.3d at 1355; *Kennametal*, 780 at F.3d at 1381.

C. Claim 6 is Anticipated By Le Bec

Claim 6 recites a method of measuring the relative amount of empty capsid or variant genome particles in an rAAV particle preparation by subjecting it to boundary sedimentation conditions and analyzing the relative amounts of different species therein. Claim 6 was taught by Le Bec.

1. "A method of measuring the relative amount of capsid particles comprising variant recombinant AAV genomes or empty AAV capsid particles in a preparation of recombinant AAV particles comprising the steps of"

To the extent the preamble is construed to be limiting (fn.5, *supra*), it is taught by Le Bec. Specifically, Le Bec teaches a method that can analytically separate, detect, and quantify the presence of empty capsids, full capsids, and aggregates. Ex.1003, 16:28-29; *see also id.*, 15:17-23; 18:1-6; Ex.1020, ¶98.

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,"

This limitation is anticipated in Le Bec as described above for claim 4. *See* §VIII.A.2.

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

This limitation is anticipated in Le Bec as described above for claim 4. *See* §VIII.A.3.

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

This limitation is anticipated in Le Bec as described above for claim 5. *See* §VIII.B.4.

5. "d) comparing the amount of recombinant AAV particles having an S value[] that do[es] not correspond to recombinant AAV particles comprising intact AAV genomes to the amount of recombinant AAV particles having an S value that corresponds to recombinant AAV particles comprising intact AAV genomes or to the total amount of recombinant AAV particles in the preparation."

The final limitation of claim 6 merely describes a mental comparison one could perform and should not be afforded any patentable weight. *See Praxair*, 890 F.3d at 1031-1035; *see also* §VIII.A.4. Specifically, the limitation recites comparing the amount of AAV particles with an S value not corresponding to AAV particles

with an intact genome to the amount of AAV particles corresponding to intact AAV particles or the total amount of AAV particles, which is analogous to the mental step of requiring a physician to "evaluate" information found insufficient in *Praxair*.

To the extent this limitation is entitled any patentable weight, it was disclosed in Le Bec. Le Bec explains that their invention was intended "to provide a method for producing double-stranded rAAV particles with an improvement in the ratio of particles containing viral DNA to empty particles and an increased percentage of particles containing a double-stranded genome." Ex.1003, 3:17-29. Accordingly, "quantification of empty and full viral particles [was] determined" and they "detected very few empty AAV viral particles with the sf9 system compared to the HEK293 system." *Id.*, 16:28-29, 18:27-29. A POSA would understand Le Bec to have reached these conclusions by comparing the peak size at 65S representing the amount of empty capsid particles to the peaks at 90S and 105S, which are labeled "full" in Figures 2 and 3. Ex.1003, 18:8-32; Ex.1020, ¶¶95-96, 102; *Novo Nordisk*, 424 F.3d at 1355; *Kennametal*, 780 at F.3d at 1381.

D. Claim 7 is Anticipated by Le Bec

Claim 7 recites a method of measuring the relative amount of capsid particles comprising variant recombinant AAV genomes in a preparation of recombinant AAV particles by subjecting it to boundary sedimentation conditions and analyzing the relative amounts of different species therein. Claim 7 was taught by Le Bec.

1. "A method of measuring the relative amount of capsid particles comprising variant recombinant AAV genomes in a preparation of recombinant AAV particles comprising the steps of"

To the extent the preamble is construed to be limiting (fn.5, *supra*), it is taught by Le Bec. Specifically, the '288 patent defines "variant genomes" to include "aggregates." *See, e.g.*, Ex.1001, Abstract, 4:16-18 ("In some embodiments, the variant genomes are truncated viral genomes, aggregates, recombinants and/or DNA impurities."); 24:67-25:2. Le Bec discloses a method for determining sedimentation coefficients for "various AAV viral particles (empty, full, aggregate) and other present populations (subparticles, contaminant proteins, aggregate) in the purified products [] by real-time centrifugation." Ex.1003, 15:17-23; *see also id.*, 18:1-6. Le Bec would enable a POSA to measure the relative amount of capsid particles comprising variant rAAV genomes and at once envisage such an application of the analytical method described therein. Ex.1020, ¶104; *Novo Nordisk*, 424 F.3d at 1355; *Kennametal*, 780 at F.3d at 1381.

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,"

This limitation is anticipated in Le Bec as described above for claim 4. *See* §VIII.A.2.

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

This limitation is anticipated in Le Bec as described above for claim 4. *See* §VIII.A.3.

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

This limitation is anticipated in Le Bec as described above for claim 5. *See* §VIII.B.4.

5. "d) comparing the amount of recombinant AAV particles having [] S values that do not correspond to recombinant AAV particles comprising intact AAV genomes or empty capsid particles to the total amount of recombinant AAV particles in the preparation."

The final limitation of claim 7 merely describes a mental comparison one could perform and should not be afforded any patentable weight. *See Praxair*, 890 F.3d at 1031-1035; *see also* §VIII.A.4. Specifically, the limitation recites comparing the amount of AAV particles with an S value not corresponding to full AAV particles or empty AAV particles to the total amount of AAV particles, which is analogous to the mental step of requiring a physician to "evaluate" information found insufficient in *Praxair*.

To the extent such comparison/analysis is entitled any patentable weight, it was nevertheless disclosed in Le Bec. While Le Bec does not label a specific S value

as corresponding to aggregates and/or rAAV particles having variant genomes, the publication indicates that the sedimentation coefficient of the various rAAV particles "(empty, full, aggregate)" was determined using the SEDFIT software. Ex.1003, 15:17-28. Indeed, Le Bec identified at least two populations of rAAV particles (singled-stranded and double-stranded), that sedimented at different rates (sedimentation coefficients of 90S and 105S), because they have different amounts of DNA incorporated. Ex.1020, ¶109; *see also* Ex.1017. Le Bec would enable a POSA to measure the relative amount of capsid particles comprising variant rAAV genomes, and at once envisage such an application of the analytical method described therein. Ex.1020, ¶¶95-96, 108-109; *Novo Nordisk*, 424 F.3d at 1355; *Kennametal*, 780 at F.3d at 1381.

E. Claim 8 is Anticipated By Le Bec

Claim 8 recites a method of measuring the relative amount of intact genome AAV particles in an rAAV particle preparation by subjecting it to boundary sedimentation conditions and analyzing the relative amounts of different species therein. Claim 8 was taught by Le Bec.

1. "A method of measuring the relative amount of recombinant AAV particles comprising intact AAV genomes in a preparation of recombinant AAV particles comprising the steps of"

To the extent the preamble is construed to be limiting (fn.5, *supra*), it was taught by Le Bec. Specifically, Le Bec teaches a method that can detect and quantify the presence of rAAV particles with intact genomes. Ex.1003, 16:28-29; *see also id.*, 15:17-23; 18:1-6; Ex.1020, ¶111. Le Bec also expressly reported the relative amount of "full" AAV particles for various preparations. Ex.1003, 19:1-15.

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,"

This limitation is anticipated in Le Bec as described above for claim 4. *See* §VIII.A.2.

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

This limitation is anticipated in Le Bec as described above for claim 4. *See* §VIII.A.3.

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

This limitation is anticipated in Le Bec as described above for claim 5. *See* §VIII.B.4.

5. "d) comparing the amount of recombinant AAV particles having an S value[] corresponding to recombinant AAV particles comprising intact AAV genomes to the amount of recombinant AAV particles having an S value corresponding to empty capsid particles, to capsid particles comprising variant recombinant AAV genomes, and/or to the total amount of recombinant AAV particles in the preparation"

The final limitation of claim 8 merely describes a mental comparison one could perform and should not be afforded any patentable weight. *See Praxair*, 890 F.3d at 1031-1035; *see also* §VIII.A.4. Specifically, the limitation recites comparing the relative concentration of AAV particles having full capsids to one of several other species of particles in the preparation, which is analogous to the mental step of requiring a physician to "evaluate" information found insufficient in *Praxair*.

To the extent such comparison/analysis is entitled any patentable weight, it was disclosed in Le Bec. Le Bec provides "a method for producing double-stranded rAAV particles with an improvement in the ratio of particles containing viral DNA to empty particles and an increased percentage of particles containing a double-stranded genome." Ex.1003, 3:17-29. Accordingly, "quantification of empty and full viral particles [was] determined" and they "detected very few empty AAV viral particles with the sf9 system compared to the HEK293 system." *Id.*, 16:28-29, 18:27-29. A POSA would understand Le Bec to teach that 90S and 105S are "S value[s] corresponding to recombinant AAV particles comprising intact AAV genomes" and

would further understand Le Bec to have used the peak sizes at 90S and 105S to quantify the relative amount of full particles. Ex.1020, ¶¶95-96, 115; Ex.1003, 19:1-5 (< 25% full particles); 19:11-15 (> 80% full particles). Finally, a POSA would understand the disclosed percentages to be the relative concentration of a given rAAV particle species present in the preparation. Ex.1020, ¶¶95-96, 115; s*ee also id.*, ¶¶27-40; Ex.1003, 8:10-13; *Novo Nordisk*, 424 F.3d at 1355.

F. Claim 10 is Anticipated By Le Bec

Claim 10 depends from claim 4, and further requires that "the presence of a peak that corresponds to the S value of empty capsid particles indicates the presence of empty capsid particles; or the presence of one or more peaks other than the peak for full capsid particles comprising intact rAAV genomes or empty capsid particles indicates that presence of capsid particles comprising variant sized genomes." This limitation merely describes how to interpret the information generated by the clamed SV-AUC method and should not be afforded any patentable weight. *See Praxair*, 890 F.3d at 1031-1035; *see also* §VIII.A.4. For example, the limitation merely recites that the presence on the distribution profile of a peak that corresponds the S value of empty capsids "indicates"—i.e. informs the experimenter of—the presence of empty capsid particles.

To the extent this is entitled any patentable weight, it was disclosed in Le Bec. *Novo Nordisk*, 424 F.3d at 1355; Ex.1020, ¶¶117-118. Specifically, Le Bec teaches

that "empty AAV viral particles" correspond to a peak at an S value of "65S" and Figures 2 and 3 depict distribution profiles and label the peak centered on 65S as "empty." Ex.1003, 18:22. Le Bec also compared the percentages of particles containing a single-stranded genome (corresponding to a sedimentation coefficient of 90S) to the percentage of particles containing a double-stranded genome (with a sedimentation coefficient of 105S). Ex.1003, 19:11-15; Ex.1020, ¶109. Le Bec confirmed that the graphs convey the relativity quantity of empty capsids. *Id.*, 18:27-29. A POSA would understand from Le Bec that the presence of a peak on a C(s) v. S plot indicates the presence of a species corresponding to that sedimentation coefficient in the tested composition. Ex.1020, ¶118.

G. Claim 11 is Anticipated By Le Bec

Claim 11 depends from claim 10, and further requires that when the presence of capsid particles comprising variant sized genomes is indicated, "the capsid particles comprising variant sized genomes comprises truncated genomes, aggregates, recombinants and/or DNA impurities compared to the intact recombinant AAV genome." This limitation merely defines the particles with variant sized genomes and recites the information available from the claimed SV-AUC method and should be afforded no patentable weight. *See Praxair*, 890 F.3d at 1031-1035; *see also* §VIII.A.4.

To the extent this step is entitled any patentable weight, it was disclosed in Le Bec. The '288 patent includes "aggregates" among the types of recombinant viral particles with variant genomes. *See, e.g.*, Ex.1001, Abstract; 4:16-18; 24:67-25:2. Le Bec discloses a method for determining sedimentation coefficients for "various AAV viral particles (empty, full, aggregate) and other present populations (subparticles, contaminant proteins, aggregate) in the purified products [] by real-time centrifugation." Ex.1003, 15:17-23; *see also id.*, 18:1-6. Further, Le Bec identified at least two populations of rAAV particles (singled-stranded and double-stranded), that sedimented at different rates (sedimentation coefficients of 90S and 105S), because they have different amounts of DNA incorporated. Ex.1020, ¶109; *see also* Ex.1017. A POSA would understand Le Bec to teach the use of SV-AUC to distinguish the presence of rAAV aggregates from empty capsids or full particles because of the peak differences on its C(s) v. S plots owing to their different sedimentation coefficients. Ex.1020, ¶¶121-122; *Novo Nordisk*, 424 F.3d at 1355; *Kennametal*, 780 at F.3d at 1381.

H. Claim 12 is Anticipated By Le Bec

Claim 12 recites a method of determining the heterogeneity of an rAAV particle preparation by subjecting it to boundary sedimentation conditions and analyzing the relative amounts of different species therein. Claim 12 was taught by Le Bec.

1. "A method of determining the heterogeneity of recombinant AAV particles in a preparation of recombinant AAV particles comprising the steps of"

To the extent the preamble is construed to be limiting (fn.5, *supra*), it is taught by Le Bec. Specifically, Le Bec explains that "we have implemented a method today for analytically separating by ultracentrifugation and quantifying the different species present in an AAV viral preparation." Ex.1003, 18:3-6; *see also id.*, 16:26-29. Le Bec taught that SV-AUC can be used to assess the heterogeneity—*i.e.*, presence of different species—in an AAV particle preparation. Ex.1003, 18:1-6; Ex.1020, ¶¶124-125.

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,"

This limitation is anticipated in Le Bec as described above for claim 4. *See* §VIII.A.2.

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

This limitation is anticipated in Le Bec as described above for claim 4. *See* §VIII.A.3.

4. "wherein the presence of peaks in addition to the peak representing capsids comprising an intact AAV genome indicates heterogeneity of recombinant particles in the preparation."

The final limitation of claim 12 merely describes how to interpret the information generated by the claimed SV-AUC method and should not be afforded any patentable weight. *See Praxair*, 890 F.3d at 1031-1035; *see also* §VIII.A.4. Specifically, the limitation recites that the presence of certain peaks "indicates"—i.e., informs the experimenter—of the heterogeneity of recombinant particles in the preparation. And there is no functional relationship to the remainder of the claim because the experimenter is not required to do anything with the information or take any specific action based on the knowledge.

To the extent this limitation is entitled any patentable weight, it was disclosed in Le Bec. Le Bec teaches that the peaks at 90S and 105S on its C(s) v. S plots correspond to rAAV particles with single- and double-stranded genomes, respectively, and "empty AAV viral particles" correspond to a peak at "65S." Ex.1003, 18:8-32. Further, Figures 2 and 3 depict distribution profiles with multiple peaks; the '288 patent explains that the presence of multiple peaks indicates the presence of different particle species in the preparation, *i.e.*, that it is heterogenous. Ex.1003, Figs. 2 and 3; Ex.1001, 49:2-8, 51:5-11; Ex.1020, ¶128. *Kennametal*, 780 at F.3d at 1381.

I. Claims 13 and 14 are Anticipated By Le Bec

Claim 13 depends from claim 12, and further requires that "the presence of additional peaks indicates the presence of empty capsid particles and/or recombinant AAV particles comprising variant genomes." Claim 14 depends from claim 13, and further requires that "the variant genomes are truncated AAV genomes, aggregates, recombinants and/or DNA impurities compared to the intact recombinant AAV genome." These limitations merely describe how to interpret the information generated by the claimed SV-AUC method and should be afforded no patentable weight. *See Praxair*, 890 F.3d at 1031-1035; *see also* §VIII.A.4.

To the extent these limitations are entitled any patentable weight, they were disclosed in Le Bec. Le Bec discloses a method for determining sedimentation coefficients for "various AAV viral particles (empty, full, aggregate) and other present populations (subparticles, contaminant proteins, aggregate) in the purified products [] by real-time centrifugation." Ex.1003, 15:17-23. Le Bec discloses that "empty AAV viral particles" correspond to a peak at an S value of "65S." Ex.1003, 18:22. And Figures 2 and 3 refer to "empty" particles at a range centered on 65S. *Id.*, Figs. 2 and 3. Le Bec discloses that at least the presence of the peak at 65S is "an additional peak" that "indicates the presence of empty capsid particles." Ex.1020, ¶130. And while Le Bec did not expressly identify a peak corresponding to variant genomes, the single-stranded and double-stranded rAAV particles have different

amounts of viral DNA and a POSA would immediately envisage the applicability to variant genomes from the Le Bec disclosure and would be able to practice it without undue experimentation. Ex.1020, ¶¶109, 130, 132; *Kennametal*, 780 at F.3d at 1381; *Novo Nordisk*, 424 F.3d at 1355.

J. Claim 15 is Anticipated by Le Bec

Claim 15 depends from claim 12, and further requires "integrating the area under each peak in the C(s) distribution to determine the relative concentration of each species of recombinant AAV particles." This limitation is anticipated in Le Bec as described above for claim 5. *See* §VIII.B.4; Ex.1020, ¶134.

IX. GROUND 2: CLAIMS 4-8 AND 10-15 ARE OBVIOUS IN VIEW OF LE BEC ALONE

Claims 4-8 and 10-15 should be found anticipated in view of Le Bec, but to the extent not anticipated, claims 4-8 and 10-15 are obvious over Le Bec alone in view of the general knowledge of a POSA. A single prior art reference can invalidate a patent claim for obviousness if it would have been obvious to modify that reference to arrive at the patented invention. *Koninklijke Philips N.V. v. Google LLC*, 948 F.3d 1330, 1338 (Fed. Cir. 2020).

A. Applying SV-AUC to rAAV Particles was Obvious

Le Bec discloses "methods for producing double-stranded AAV viral particles . . . for therapeutic applications such as gene therapy." Ex.1003, 1:5-9. 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 contributing to the immunogenicity of the vector." *Id.*, 3:16-22. Others similarly acknowledged the problem with having excess empty capsids in a gene therapy product comprising AAV particles. Ex.1008, 1. Thus, POSAs were motivated to assess virus preparations for such undesirable contaminants. *See Spectrum Pharms., Inc. v. Sandoz Inc.*, 802 F.3d 1326, 1334 (Fed. Cir. 2015) ("A physician would not likely want to administer a contaminant or a less pure material to a patient if one could use a pure material. Thus, there is always in such cases a motivation to aim for obtaining a pure, resolved material."). Indeed, the '288 patent acknowledged as much. *See* §IV.B.

The art taught that SV-AUC was a powerful tool for assessing the homogeneity of viral vectors used in gene therapy applications. Ex.1004, 17; Ex.1008, 6; Ex.1019, 5 ("Critical information about aggregation, empty capsids, virus subparticles, and other lower molecular weight species was gained from AUC experiments…. The aggregates, empty capsids, and low molecular weight degradation products can also be quantified."). The '288 patent itself notes that "AUC analysis has been well characterized over many decades and is highly versatile" and that it "may be applied to determine the biophysical properties of many types of particles across a wide range of particle concentrations and sizes."

Ex.1001, 19:22-28. The many uses of SV-AUC were well known and explained in the prior art, including for assessing the homogeneity of viral preparations. Ex.1004. In view of (1) the importance of drug product quality (with regard to homogeneity and purity) to achieve licensure (Ex.1004, 16; Ex.1008, 1, 6), and (2) the recognized benefits of using boundary sedimentation velocity analysis for analyzing such aspects of biological samples (Ex.1003, 17:30-18:27; Ex.1005 145, 149, 161-168), a POSA would have been motivated to choose SV-AUC when seeking to characterize a preparation of rAAV particles to assess homogeneity. Ex.1020, ¶¶180, 184-188; Ex.1019, 4-5; *Spectrum*, 802 F.3d at 1334.

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. Ex.1003, 15:19-23; Ex.1020, ¶¶181, 185-188. Patent Owner has not described or claimed any changes to the well-known SV-AUC method itself. *See Southwire Co. v. Cerro Wire LLC*, 870 F.3d 1306, 1311 (Fed. Cir. 2017) (affirming obviousness finding where the patented steps did not differ in any material way from the process disclosed in the prior art). *In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990) ("It is a general rule that merely discovering and claiming a new benefit of an old process cannot

render the process again patentable."). Instead, Patent Owner incorrectly claims to be the first to apply SV-AUC to rAAV particles, ignoring Le Bec's teachings.

B. Using Integration to Determine Relative Concentrations was Obvious

To 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.

As explained above, a POSA would have been motivated to use SV-AUC to assess homogeneity of rAAV preparations and accurately quantify the rAAV species in a consistent and reliable way for clinical lots of drug product. *See* Ex.1008, 1. Integrating 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. Ex.1020, ¶182. Indeed, Le Bec itself 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. Ex.1003, 3:16-22; 15:27-28; 17:29:18:6.

Moreover, the SEDFIT software used for analyzing SV-AUC data included the ability to calculate concentration information based on integration of peaks selected by the user. Ex.1020, ¶27-40. 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. Ex.1003, 15:18-28; Ex.1020, ¶¶182, 185-188. Using a process disclosed in the prior art for achieving the same purpose is obvious. *See KSR*, 550 U.S. at 401; *Southwire,* 870 F.3d at 1311; *In re Woodruff*, 919 F.2d at 1578.

X. GROUND 3: CLAIMS 4-16 ARE OBVIOUS OVER LE BEC IN VIEW OF BERKOWITZ

Claims 4-16 are also obvious over Le Bec in view of Berkowitz. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 401 (2007) ("When a work is available in one field, design incentives and other market forces can prompt variations of it, either in the same field or in another. If a person of ordinary skill in the art can implement a predictable variation, and would see the benefit of doing so, § 103 likely bars its patentability.").

A. Claims 4-8 and 10-15 Are Obvious Over Le Bec When Combined with Berkowitz

As set forth above, every limitation of claims 4-8 and 10-15 was taught by Le Bec, but to the extent that any claim limitation is found to be missing from Le Bec, these claims nevertheless would have been obvious to a POSA in view of Le Bec in combination with Berkowitz. Berkowitz, which teaches the use of AUC to characterize the homogeneity of virus preparations (Ex.1004), is analogous art to the

claimed invention because it is from the same field of endeavor and reasonably pertinent to the problem faced by the inventor. Ex.1020, ¶159.

1. Applying SV-AUC to rAAV Particles was Obvious

Le Bec discloses "methods for producing double-stranded AAV viral particles using the insect/baculovirus cell system to produce sufficient amounts of product for therapeutic applications such as gene therapy." Ex.1003, 1:5-9. 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 contributing to the immunogenicity of the vector." *Id.*, 3:16-22. Others similarly acknowledged the problem with having excess empty capsids in a gene therapy product comprising AAV particles. Ex.1008, 1. *See Spectrum Pharms., Inc. v. Sandoz Inc.*, 802 F.3d 1326, 1334 (Fed. Cir. 2015) ("A physician would not likely want to administer a contaminant or a less pure material to a patient if one could use a pure material. Thus, there is always in such cases a motivation to aim for obtaining a pure, resolved material.")

To the extent Le Bec's teachings alone do not motivate a POSA to apply SV-AUC to rAAV particles with a reasonable expectation of success, the combination of Le Bec and Berkowitz does. Berkowitz instructs as to the "overall capability of boundary sedimentation velocity analysis," refers to it as "conventional," and describes it as "a uniquely useful characterization tool that can assess adenovirus

product quality and manufacturing consistency." Ex.1004, 16-18. Subjecting 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 to identify and quantify empty capsids, intact monomers, aggregates, and incompletely formed species. Ex.1004, 17; Ex.1020, ¶¶216-219. *KSR*, 550 U.S. at 401. A POSA would have been motivated to apply Berkowitz's teachings to Le Bec's preparations for reasons (1)-(2) articulated above. And the POSA would have had a reasonable expectation of success because the SV-AUC method was well known and within the skill of an ordinary skilled artisan to optimize, the art recognized no difficulties in applying SV-AUC to rAAV and, in fact, a POSA would have expected SV-AUC to be easier to apply to rAAV than the larger adenovirus particles examined in Berkowitz. Ex.1001, 19:22-28; Ex.1020, ¶200; *KSR*, 550 U.S. at 401.

2. Using Integration to Determine Relative Concentrations was Obvious

To 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 in view of Le Bec in combination with Berkowitz.

As explained above, a POSA would have been motivated to use SV-AUC to assess homogeneity of rAAV preparations and to accurately quantify the rAAV species in a consistent and reliable way for clinical lots of drug product. *See* Ex.1008, 1. Integrating the area under the peaks generated in an SV-AUC experiment is a standard technique used to determine the relative concentrations of the various components in the analyzed sample. Ex.1020, ¶182. Indeed, Le Bec itself provides motivation to integrate peak areas of C(s) v. S plots to ascertain the relative concentration of rAAV particles: 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. Ex.1003, 3:16-22; 15:27-28; 17:29:18:6; *see also* Ex.1004, 16; Ex.1008, 1, 6.

Moreover, the SEDFIT software used for analyzing SV-AUC data included the ability to calculate concentration information based on integration of peaks selected by the user. Ex.1020, ¶¶27-40. 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. Ex.1003, 15:18-28; Ex.1020, ¶182. The '288 patent also describes use of the SEDFIT algorithm and cites use of same in the prior art. Ex.1001, 4:55-58, 17:56-63, 20:58-21:11. Using a process disclosed in the prior art for achieving

the same purpose is obvious. *See KSR*, 550 U.S. at 401; *Southwire,* 870 F.3d at 1311; *In re Woodruff*, 919 F.2d at 1578.

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." Ex.1004, 20. 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. Ex.1020, ¶¶199-202, 217-219; Ex.1008, 1; *KSR*, 550 U.S. at 401. And 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. Ex.1020, ¶202; *Unwired Planet, LLC v. Google Inc.*, 841 F.3d 995, 1003 (Fed. Cir. 2016) ("For the technique's use to be obvious, the skilled artisan need only be able to recognize, based on her background knowledge, its potential to improve the device and be able to apply the technique.").

3. Comparing Amounts of the Components was Obvious

Claims 5, 6, 7, and 8 each have a limitation regarding comparing the relative amounts of various species of particles in the viral preparations. To the extent that these limitations are given patentable weight (which they should not), and Patent

Owner argues they are not present in Le Bec, they were obvious in view of Le Bec when combined with Berkowitz.

As set forth above, a POSA would have been motivated to use SV-AUC to assess homogeneity of rAAV preparations. Ex.1020, ¶¶180-182, 185. A POSA would have been motivated to compare the amounts of empty particles to the amounts of full particles, given the risks associated with having empty particles and other contaminants in a pharmaceutical preparation. *Id.*; Ex.1008, 1; *Spectrum*, 802 F.3d at 1334. And a POSA would have had a reasonable expectation of success in implementing the comparisons as they require simple mathematical computations routinely performed by those skilled in the art. Ex.1020, ¶185; *KSR*, 550 U.S. at 401.

Berkowitz explained that a variety of different types of information about the composition of viral preparations could be derived "from a single sedimentation velocity experiment using the computer software program SEDFIT. Ex.1004, 17. Specifically, Berkowitz teaches that you can determine "(1) amount of intact virus monomer and its heterogeneity," as contemplated by claim 8. Berkowitz teaches that you can determine "(2) amount of [empty capsid] material and its heterogeneity," as contemplated by claims 5 and 6. And Berkowitz teaches that you can determine "(3) amount of virus aggregation and the distribution of aggregate sizes, [and] (4) detection and quantification of other smaller structural forms of the intact and [empty capsid] adenovirus particles," as contemplated by claim 7. 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. Ex.1020, ¶¶199-202, 217-219. Using a process disclosed in the prior art for achieving the same purpose is obvious. *See KSR*, 550 U.S. at 401; *Southwire,* 870 F.3d at 1311; *In re Woodruff*, 919 F.2d at 1578.

4. What the SV-AUC Data "Indicates" was Obvious

Claims 4 and 10-15 each have a limitation regarding what the SV-AUC data generated by the claimed methods "indicates." As explained above, these limitations merely claim the content of the information provided by the SV-AUC procedure and are not entitled to patentable weight. *See Praxair*, 890 F.3d at 1031-1035; *see also* §VIII.A.4.

To the extent that these limitations are given patentable weight (which they should not), and Patent Owner argues they are not present in Le Bec, they were obvious from Le Bec's teaching when combined with Berkowitz. Specifically, Le Bec teaches that the peak appearing at 65S corresponds to empty rAAV particles and that the peaks at 90S and 105S correspond to different types of full particles. Ex.1003, 18:19-32. A POSA would understand that the presence of other peaks in a sample would indicate the presence of other subpopulations, including populations having variant genomes, because that is the type of information an SV-AUC experiment is

designed to determine. Ex.1020, ¶¶185-188; Ex.1004, 17; *Kennametal*, 780 at F.3d at 1381.

Berkowitz expressly discusses the types of information that can be obtained from an SV-AUC experiment. Ex.1004, 17. 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. Ex.1020, ¶¶199-202, 217-219; *see also* Ex.1008, 1; *Spectrum*, 802 F.3d at 1334. And a POSA would have had a reasonable expectation of success in collecting the information described in Berkowitz, especially in view of Le Bec's teaching that the sedimentation coefficients of rAAV particles were sufficiently different to distinguish them by analytical ultracentrifugation. Ex.1003, 18:1-6; Ex.1020, ¶202; *KSR*, 550 U.S. at 401. Using the same AUC method that was well known to elicit the type of information it was known to elicit is obvious. *See KSR*, 550 U.S. at 401; *Southwire,* 870 F.3d at 1311; *In re Woodruff*, 919 F.2d at 1578.

B. Claim 9 is Obvious Over Le Bec Alone or in View of Berkowitz

Claim 9 recites a method of monitoring the removal of empty capsids or capsids with variant genomes during purification of an rAAV preparation by sampling the preparation, analyzing the samples using the method of claim 5, and recognizing that a decrease in empty capsids or capsids with variant genomes reflects

removal of those species from the preparation. As discussed above, Le Bec anticipates claim 5 and/or renders it obvious. A POSA would have found it obvious to use the method of claim 5 to monitor a preparation of rAAV particles to assess the overall preparation status during purification as recited in claim 9.

1. "A method of monitoring the removal of empty capsids and/or capsid particles comprising variant recombinant AAV genomes during the purification of a preparation of recombinant AAV particles, the method comprising"

To the extent the preamble is construed to be limiting (fn.5, *supra*), it would have been obvious in view of Le Bec alone or with Berkowitz. Le Bec discloses "a method [] for analytically separating by ultracentrifugation and quantifying the different species present in an AAV viral preparation." Ex.1003, 18:1-6. The methods for producing rAAV particles described in Le Bec included purification steps (Ex.1003, 10:5-11:9), and Le Bec's SV-AUC analysis was performed on purified products (*id.*, 15:19-23). While Le Bec compares contaminant levels between different production methods and teaches that SV-AUC is an effective method for identifying contaminants in a heterogenous mixture of rAAV particles, it does not discuss comparing contaminant levels at different steps in the purification process. Nevertheless, Le Bec teaches that empty capsids are undesirable. Ex.1003, 3:16-22; Ex.1020, ¶¶222-223; *see also* Ex.1008, 6.

Berkowitz provides an example in which the same virus preparation was purified by two different purification methods and the results were evaluated by looking to analytical ultracentrifugation data. Specifically, Figures 1 and 2 in Berkowitz and the accompanying text compare adenovirus preparations subjected to two different methods of purification: Ion-Exchange Chromatography ("IEC") and CsCl density gradient sedimentation equilibrium. Ex.1004, 18. The figures show empty capsid peak(s) for one purification method and an absence of empty capsid peaks for the other purification method, and the authors comment that: "[s]imilar analyses conducted on adenovirus samples purified by preparative CsCl density gradient sedimentation equilibrium instead of IEC, as expected, did not show any signs of [empty capsid] material (see Fig. 2C) since this material is removed during adenovirus purification." Ex.1004, 21. Berkowitz teaches that a decrease in the relative amount of empty capsids as determined by an AUC method indicates removal of empty capsids, and is an example of using an analytical ultracentrifugation technique to monitor a purification process.[5]

It would have been obvious for a POSA to apply the techniques of Le Bec and Berkowitz throughout the purification process to determine the point at which the

[5] Berkowitz discussed use of band sedimentation ultracentrifugation, but that method uses similar principles as SV-AUC. Ex.1004, 17.

preparation is sufficiently pure for its intended purpose. *Spectrum*, 802 F.3d at 1334. A POSA would have been motivated to monitor the purity of rAAV preparations, because "[t]o achieve drug licensure, drug product quality (with regard to homogeneity and purity) and consistency of manufacturing are of key importance." Ex.1004, 16; Ex.1008, 6; Ex.1020, ¶223; *Spectrum*, 802 F.3d at 1334. And a POSA would have had a reasonable expectation of success in doing so, as one of the benefits of SV-AUC is that samples can be measured in their native state (Ex.1020, ¶¶224-225; Ex.1004, 17), and it would merely require running the SV-AUC analysis at multiple steps of the purification process. *KSR*, 550 U.S. at 401.

2. "removing a sample of the recombinant AAV particles from the preparation following one or more steps in the purification process and analyzing the sample for the relative amount of empty capsids and/or capsid particles comprising"

Le Bec teaches removing a 100µl or 400µl sample from purified rAAV preparations for SV-AUC analysis. Ex.1003, 15:24-25.

3. "variant recombinant AAV genomes according to the method of claim 5,"

Claim 5 is anticipated and/or obvious, as described above. *See* §§VIII.B and IX.A.

4. "wherein a decrease in the relative amount of empty capsids and/or capsids comprising variant genomes to full capsids indicates removal of empty capsids from the preparation of recombinant AAV particles."

The final step of claim 9 merely describes how to interpret the information generated by the claimed SV-AUC method and should not be afforded any patentable weight. *See Praxair*, 890 F.3d at 1031-1035; *see also* §VIII.A.4. Specifically, the limitation recites that a decrease in the relative amount of empty or variant genome-containing capsids "indicates"—i.e., informs the experimenter—as to removal of empty capsids from the preparation. And there is no functional relationship to the remainder of the claim.

Additionally, the limitation should not be accorded any patentable weight, because it merely recites the relationship between the tested composition and associated result of the method. *See, e.g.*, *Minton v. Nat'l Ass'n of Sec. Dealers, Inc.*, 336 F.3d 1373, 1381 (Fed. Cir. 2003) ("A whereby [or wherein] clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited."); *see also In re Kubin*, 561 F.3d 1351, 1357 (Fed. Cir. 2009) (stating "[e]ven if no prior art of record explicitly discusses the [limitation], [applicant's] application itself instructs that [the limitation] is not an additional requirement imposed by the claims on the [claimed invention], but rather a property

necessarily present in [the claimed invention]"); *Texas Instruments Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1169 (Fed. Cir. 1993).

To the extent such an "indication" limitation is entitled any patentable weight, it would have been obvious. Le Bec explicitly discloses that empty capsids are an undesirable contaminant in rAAV preparations intended for therapeutic use. Ex.1003, 3:20-21. This is consistent with Berkowitz's more general teaching that drug product quality—including purity—is of key importance. Ex.1004, 16. A POSA would have been motivated to use the characterization method in Le Bec to monitor the removal of empty capsids. Ex.1020, ¶¶221-225; *Spectrum*, 802 F.3d at 1334; *KSR*, 550 U.S. at 401.

And a POSA would have had a reasonable expectation of success in using a decrease in the relative amount of empty rAAV particles as an indication that empty rAAV particles had been removed as a result of purification steps. Ex.1020, ¶225; *KSR*, 5505 U.S. at 421 ("A person of ordinary skill is also a person of ordinary creativity, not an automaton."). Le Bec teaches that that the rate of sedimentation of empty particles and full particles are sufficiently different that they can be identified and quantified (Ex.1003, 18:1-6) and Berkowitz teaches the use of sedimentation data to assess the effectiveness of purification methods (Ex.1004, Figs. 1 and 2). *Southwire,* 870 F.3d at 1311; *In re Woodruff*, 919 F.2d at 1578.

C. Claim 16 is Obvious Over Le Bec in View of Berkowitz

Claim 16 recites a method of monitoring homogeneity during purification of an rAAV preparation by sampling the preparation, analyzing the samples using the method of claim 15, and recognizing that an increase in capsids containing intact genomes reflects an increase in homogeneity. Le Bec anticipates claim 15 and/or renders it obvious. A POSA would have found it obvious to use the method of claim 15 to monitor a preparation of rAAV particles to assess the overall preparation status during purification. *Spectrum*, 802 F.3d at 1334; *KSR*, 550 U.S. at 401.

1. "A method of monitoring the homogeneity of recombinant AAV particles during the purification of a preparation of recombinant AAV particles"

Claim 16's preamble is not limiting (fn.5, *supra*), but to the extent the preamble is construed to be limiting, it would have been obvious in view of Le Bec and Berkowitz. Monitoring the removal of empty rAAV particles (in claim 9) and monitoring the homogeneity of the entire rAAV composition (in claim 16) are two sides of the same coin because as empty rAAV particles are removed, homogeneity increases. *See* §X.B.1.

Le Bec teaches that empty rAAV particles are undesirable (Ex.1003, 2:15-17) and that empty and full rAAV particles can be distinguished via SV-AUC (Ex.1033, 18:1-6). Further, Berkowitz teaches the importance of purity (i.e. homogeneity) in pharmaceutical preparations (Ex.1004, 16), and that sedimentation distribution data

can be used to compare/evaluate different purification processes (*Id.*, 20-21). In pursuing a licensed drug product, a POSA would have been motivated to monitor the homogeneity of rAAV particles during the purification process using SV-AUC and would have had a reasonable expectation of success doing so based on successful application of the technique taught by Le Bec and Berkowitz. Ex.1020, ¶¶221-225; Ex.1004, 16; Ex.1008, 8; *Spectrum*, 802 F.3d at 1334; *KSR*, 550 U.S. at 401.

2. "removing a sample of the recombinant AAV particles from the preparation following one or more steps in the purification process and"

Le Bec teaches removing a 100µl or 400µl sample from purified rAAV preparations for AV-AUC analysis. Ex.1003, 15:24-25.

3. "determining the heterogeneity of recombinant AAV particles according to the method of claim 15,"

Claim 15 is anticipated and/or obvious, as described above. *See* §§VIII.J and IX.

4. "wherein an increase in the relative amount of recombinant AAV particles comprising intact viral genomes indicates an increase in the homogeneity of full AAV particles in the preparation of recombinant AAV particles."

The final limitation of claim 16 merely describes how to interpret the information generated by the claimed SV-AUC method and should not be afforded any patentable weight. *See Praxair*, 890 F.3d at 1031-1035; *see also* §VIII.A.4. Specifically, the limitation recites that an increase in intact particles "indicates"—

i.e., informs the experimenter—of an increase in homogeneity. And there is no functional relationship. Additionally, the limitation should not be accorded patentable weight, because it merely recites the relationship between the tested composition and associated result of the method. *See* §X.B.4.

To the extent the "indication" limitation is entitled any patentable weight, it would have been obvious for the same reasons outlined above with respect to the preamble. *See* §X.C.1. In pursuing a licensed drug product and given the preference for increased homogeneity of full rAAV particles in such products, a POSA would have been motivated to monitor the homogeneity of rAAV particles during the purification process using SV-AUC and would have had a reasonable expectation of success doing so based on successful application of the technique taught by Le Bec and Berkowitz. Ex.1020, ¶221-225; Ex.1004, 16; Ex.1008, 6; *Spectrum*, 802 F.3d at 1334; *KSR*, 550 U.S. at 401.

XI. SECONDARY CONSIDERATIONS

Petitioner is unaware of any objective evidence of nonobviousness that would outweigh the compelling conclusion of obviousness set forth above and reserves the right to address any such evidence submitted in this proceeding.

XII. DISCRETIONARY DENIAL IS NOT WARRANTED

Institution should not be denied under 35 U.S.C. §325(d) because the arguments and evidence presented here were not previously and/or properly

considered by the Office. *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 (PTAB Feb. 13, 2020); *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (PTAB Dec. 15, 2017) (precedential).

A. The Prior Art and Arguments Presented to the Office Were Not the Same or Substantially the Same

During prosecution the Examiner did not consider or cite Le Bec, a critical reference teaching the use of SV-AUC with rAAV particles that anticipates many of the challenged claims. Indeed, the Examiner appeared to lack any knowledge of Le Bec, commenting in the notice of allowance that "AUC was not noted as having been applied to AAV separation routinely," (Ex.1002, 561), despite the teachings of Le Bec to the contrary. And while Berkowitz was cited by Patent Owner in the background, it was not relied on or discussed by the Examiner in any of the office actions. Ex.1002.

Moreover, the art asserted in Grounds 1-3 and Petitioners' associated arguments are not cumulative with those substantively considered during prosecution, because the crux of Patent Owner's prosecution argument was that although SV-AUC was well known, it would not have been obvious to apply it to rAAV particles. Ex.1002, 541. Specifically, Patent Owner argued that the art relied on by the Examiner was "completely silent regarding recombinant AAV particles"

and that "one of skill in the art would not have predicted with a reasonable expectation of success that methods described for a virus such as adenovirus could be applied to recombinant AAV particles." *Id.* Patent Owner also 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 rAAV particles, much less with the sensitivity, precision, and accuracy discussed below." *Id.* The Examiner credited these arguments when allowing these claims. *Id.*, 561-562. Because Le Bec shows these arguments are incorrect, Grounds 1-3 present a substantially different argument than considered by the Examiner.

Furthermore, because the Examiner did not apply the primary reference Le Bec as prior art—and indeed was apparently unaware of Le Bec—there was no consideration given to the combinations of references asserted in Grounds 1-3 or Petitioners' rationales for motivation to combine and reasonable expectation of success based on the asserted art. *St. Jude Medical, LLC v. Snyders Heart Valve LLC*, Case No. IPR2018-00105, Paper 15 at 12 (PTAB May 3, 2018) (instituting where "evidence of record does not demonstrate that the Examiner considered the references in the combinations relied upon by Petitioner or addressed arguments similar to those Petitioner now presents"). Thus, *Becton Dickenson* Factors (a), (b), and (d) support institution.

B. The Office Erred in a Manner Material to the Patentability of the Challenged Claims

The Board need not reach Part Two of the *Advanced Bionics* framework. But if it does, the *Becton Dickenson* Factors also favor institution.

As explained above, the Examiner did not substantively evaluate Petitioners' primary asserted art or the combinations presented. Thus, factor (c) favors institution. *Microsoft Corporation v. SurfCast, Inc.*, IPR2022-00590, Paper 9 at 15 (PTAB Oct. 7, 2022) (finding factor (c) favors institution because the cited art "was not extensively evaluated during examination and was not the basis for a rejection"); *Amazon.com, Inc. v. M2M Sols. LLC*, IPR2019-01205, Paper 14 at 16 (PTAB Jan. 27, 2020) ("a reference that 'was neither applied against the claims nor discussed by the Examiner' does not weigh in favor of exercising the Board's discretion under § 325(d) to deny a petition").

Factor (e) also supports institution in view the Examiner's mistakes. The Examiner was led astray by Patent Owner's unsupported attorney argument that a person or ordinary skilled would not have expected that AUC—a well-known method recognized for its ability to analyze a wide range of molecules (from peptides and oligosaccharides to viruses and organelles)—could be employed to characterize rAAV particles. Indeed, Le Bec not only teaches exactly the method Patent Owner argues would have been unexpected, the inventors in Le Bec did not even comment

on the novelty of using SV-AUC with AAV particles. The Examiner erred in allowing the claims based on Patent Owner's factually incorrect and unsupported arguments.

In addition to presenting art and arguments that were not considered by the Examiner, Petitioners also provide Dr. Steven Berkowitz's declaration, which further explains a POSA's understanding of the art as of January 19, 2015. Dr. Berkowitz confirms that application of SV-AUC to rAAV particles was not surprising or unexpected. Ex.1020, ¶¶52-56. Thus, *Becton Dickenson* Factor (f) likewise favors institution. *Celltrion, Inc. v. Genentech, Inc.*, No. IPR2017-01140, Paper 31 at 13-14 (PTAB Jan. 25, 2018) (instituting when, "taking the expert declaration…into account, Petitioner's testimonial evidence presents the prior art in a new light.").

Institution should not be denied under 35 U.S.C. §325(d).

XIII. MANDATORY NOTICES UNDER 37 C.F.R. §42.8

Pursuant to 37 C.F.R. §42.8, Petitioner states as follows:

A. Real Parties-in-Interest (37 C.F.R. §42.8(b)(1))

Novartis Gene Therapies, Inc. and Novartis Pharmaceuticals Corporation are the real parties-in-interest.

B. Related Matters (37 C.F.R. §42.8(b)(2))

The '288 patent has been asserted against Petitioners in an action for infringement: *Genzyme Corporation and Aventis Inc. v. Novartis Gene Therapies, Inc., and Novartis Pharmaceuticals Corporation*, Case No. 1:23-cv-00554-UNA (D. Del.).

C. Lead and Backup Counsel and Service Information (37 C.F.R. §§42.8(b)(3) and (b)(4))

Lead Counsel	Backup Counsel
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XIV. CERTIFICATION UNDER 37 C.F.R §42.24(D)

Pursuant to 37 C.F.R. §42.24(a)(1)(i), the foregoing PETITION FOR *INTER PARTES* REVIEW contains 13,869 words, excluding parts of this Petition exempted under §42.24(a), as measured by the word-processing system used to prepare this paper.

Respectfully submitted,

Date: June 30, 2023

By: /John D. Livingstone/
John D. Livingstone, Reg. No. 59,613
Counsel for Petitioner

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), the undersigned certifies that on June 30, 2023, a copy of the foregoing **Petition for *Inter Partes* Review** and **the associated powers of attorney** were served by FedEx Priority Overnight on the correspondence address of record indicated in the Patent Office's Patent Center website for U.S. Patent No. 10,429,288:

Lisa P. Rasmussen
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A courtesy copy of the foregoing was also served by FedEx Priority Overnight upon the following counsel of record for the Patent Owner in litigation pending before the United States District Court for the District of Delaware Case No. 1:23-cv-00554:

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Date: June 30, 2023

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