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Paper 20
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NOVARTIS GENE THERAPIES, INC. & NOVARTIS PHARMACEUTICALS CORPORATION,
Petitioners,
v.

GENZYME CORPORATION,
Patent Owner.

IPR2023-00608
Patent 9,051,542 B2

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

SNEDDEN, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

A. Background and Summary

Novartis Gene Therapies, Inc. and Novartis Pharmaceuticals Corporation (collectively, "Petitioner") filed a Petition requesting an *inter partes* review of claims 1, 2, 5, and 6 of U.S. Patent No. 9,051,542 B2 ("the '542 patent," Ex. 1001). Paper 2 ("Pet."). Genzyme Corporation ("Patent Owner") filed a Preliminary Response to the Petition. Paper 14 ("Prelim. Resp."). In its Preliminary Response, Patent Owner indicates that claims 1 and 2 are disclaimed, so only claims 5 and 6 remain challenged. *Id.* at 3.

With our authorization, Petitioner filed a Reply to Patent Owner's Preliminary Response (Paper 17) and Patent Owner filed a Sur-reply (Paper 18).

To institute an *inter partes* review, we must determine that the information presented in the Petition shows "a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a) (2018). The Supreme Court has held that a decision to institute under 35 U.S.C. § 314 may not institute on less than all claims challenged in the petition. *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1359–60 (2018). After considering the evidence and arguments presented in the Petition, we determine that Petitioner has not demonstrated a reasonable likelihood of success in proving that either claim 5 or claim 6 of the '542 patent is unpatentable.

B. Real Parties in Interest

Petitioner asserts that Novartis Gene Therapies, Inc. and Novartis Pharmaceuticals Corporation are the real parties in interest. Pet. 67. Patent Owner asserts that "Sanofi, the ultimate parent company of Genzyme

Corporation, Genzyme Corporation, and Aventis, Inc. are the real parties-in-interest." Paper 6, 2.

C. Related Matters

The parties indicate that the '542 patent is asserted against Petitioner in *Genzyme Corporation et al. v. Novartis Gene Therapies, Inc. et al.*, Case No. 1:21-cv-01736 (D. Del.), filed December 10, 2021. Pet. 67–68; Paper 6, 2. Petitioner also filed a petition for *inter partes* review in IPR2023-00609 seeking to challenge claims 5 and 6 of the '542 patent on other grounds. Pet. 68.

D. The '542 patent (Ex. 1001)

The '542 patent is titled "Compositions and Methods to Prevent AAV Vector Aggregation," and issued on June 9, 2015, from U.S. Patent Application No. 12/661,553, filed March 19, 2010. Ex. 1001, codes (21), (22), (45), (54). The '542 patent "relates to compositions and methods of preparing and storing AAV [(adeno-associated virus)] virions that prevent aggregation." *Id.* at 1:17–19. According to the '542 patent, "[t]he solubility of purified AAV2 virus particles is limited, and aggregation of AAV2 particles has been described as a problem." *Id.* at 1:41–46 (citing, e.g., Wright et al., "Recombinant Adeno-Associated Virus: Formulation Challenges and Strategies for a Gene Therapy Vector," *Curr. Opin. Drug Disc. Dev.* 6(2):174–178 (2003) (Ex. 1007, "Wright"); Croyle, et al., "Development of Formulations That Enhance Physical Stability of Viral Vectors for Gene Therapy," *Gene Ther.*, 8:1281–1290 (2001) (Ex. 1013, "Croyle")).

In particular, the '542 patent discloses high ionic strength solutions that are isotonic with the intended target tissue. *Id.* at code (57). The

"combination of high ionic strength and modest osmolarity is achieved using salts of high valency, such as sodium citrate." *Id.*

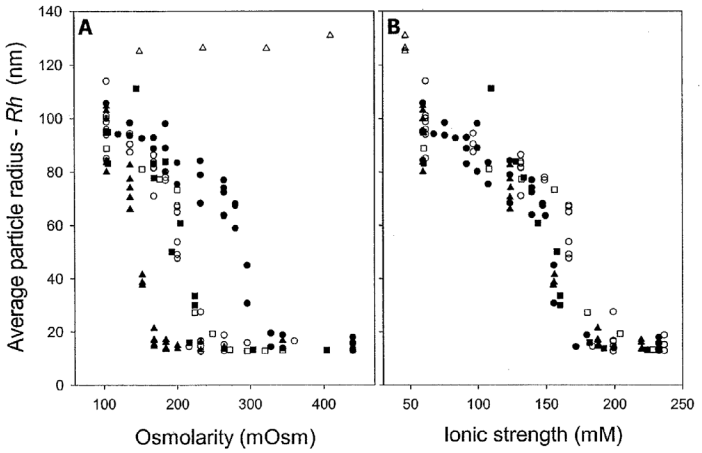
The '542 patent further explains as follows:

> The present invention is based in part on the observation that solution ionic strength is an important parameter in AAV vector aggregation, implicating the involvement of ionic interactions between virus particles in the aggregation process. The observation that elevated ionic strength increases AAV2 [AAV serotype 2] vector solubility regardless of the identity of the charged excipient supports the hypothesis that ionic strength of solution per se, rather than interactions involving a specific ionic species, is the relevant physico-chemical parameter. A threshold ionic strength of at least 200 mM is required to prevent aggregation at vector particle concentrations examined herein.

Id. at 4:53–64. The '542 patent additionally states as follows:

> In embodiments of the present invention the exponential relationship of ionic strength with charge valency is used to develop isotonic formulations with high ionic strengths. Salt species with multiple charge valencies (e.g. salts of sulfate, citrate, and phosphate) that are commonly used as excipients in human parenteral formulations can provide the level of ionic strength needed to prevent AAV2 vector aggregation when used at isotonic concentrations. While isotonic (150 mM) sodium chloride has an ionic strength of 150 mM, a value insufficient to maintain AAV2 solubility at high vector concentrations, isotonic sodium citrate, with an ionic strength of ~500 mM, can support AAV2 vector concentrations of at least 6.4×10^{13} vg/mL without aggregation.

Id. at 5:7–20. Figures 1A and 1B of the '542 patent are reproduced below.



Figures 1A and 1B present the results of a vector aggregation study that tracked aggregation as a function of two parameters, osmolarity (Figure 1A) and ionic strength (Figure 1B) for buffer compositions of sodium chloride (●), sodium citrate (○), sodium phosphate (■), sodium sulfate (□), magnesium sulfate (▲), and glycerol (Δ), and. *Id.* at 6:63–65, 12:33–67 (Example 3), FIGS. 1A, 1B. "Average particle radius is measured by dynamic light scattering (DLS) following vector dilution in varying concentrations of excipients buffered with 10 mM sodium phosphate at pH 7.5." *Id.* at 4:18–28. "Rh values >20 nm are deemed to indicate the occurrence of some level of aggregation." *Id.* at 9:25–27.

The results of Figure 1A, which plots vector aggregation as a function of the osmolarity of selected excipients, are explained as follows:

> For charged species a concentration-dependent inhibition of AAV2 vector aggregation is observed. Salts with multivalent ions achieve a similar degree of inhibition of aggregation at lower concentrations than monovalent sodium chloride. For example, magnesium sulfate prevents aggregation at >200 mOsm whereas sodium chloride requires ≧350 mOsm to achieve a similar effect. Sodium citrate, sodium sulfate, and sodium phosphate are intermediate in their potency to prevent vector aggregation.

Id. at 6:65–7:8.

Figure 1B shows data from the same experiment "plotted as a function of the calculated ionic strength, rather than osmolarity, for each excipient." *Id.* at 7:18–20. Figure 1B's plot of particle radius versus ionic strength shows that "vector aggregation is prevented when ionic strength is ~200 mM or greater regardless of which salt is used." *Id.* at 7:21–22. "These data suggested that the ionic strength (μ) of a solution . . . is the primary factor affecting aggregation." *Id.* at 7:22–25.

The '542 patent discloses the results of a study assessing "the effects of elevated ionic strength and nuclease treatment on AAV2 vector aggregation at a larger scale, using methods to induce and quantify vector aggregation that are relevant to preparative scale vector purification" in Table 2. *Id.* at 8:1–5.

Table 2 of the '542 patent is reproduced, in part, below.

TABLE 2

AAV VECTOR RECOVERY AT PROCESS SCALE

Experiment	Formulation	μ (mM)	Target (vg/mL)	Actual (vg/mL)	Yield % (RSD)
1	CF	160	2.5E13	1.93E13	77 (6.6)
1	TF1	310	2.5E13	2.38E13	95 (7.4)
1	TF2	510	2.5E13	2.33E13	93 (7.4)
2	CF	160	6.7E13	3.98E13	59 (6.0)
2	TF2	510	6.7E13	6.42E13	96 (4.4)

Table 2 shows the results for three solutions of AAV2-AADC vectors filtered through a 0.22 μm filter. *Id.* at 8:1–10, 11:53–12:29. The three solutions are as follows:

> Control Formulation (CF: 140 mM sodium chloride, 10 mM sodium phosphate, 5% sorbitol, pH 7.3); Test Formulation 1 (TF1: 150 mM sodium phosphate, pH 7.5); and Test Formulation 2 (TF2: 100 mM sodium citrate, 10 mM Tris, pH 8.0).

Id. at 11:66–12:3. In Experiment 1, the samples contained 2.5×10^{13} vg/ml vector, and, in Experiment 2, the samples contained 6.7×10^{13} vg/ml vector. *Id.* at 12:4–12. Table 2 shows recoveries exceeded 90% following filtration in formulations TF1 and TF2 having ionic strengths greater than 200 mM, whereas recovery from CF formulations, having ionic strength of 160 mM, was only 77% and 59% for experiments 1 and 2, respectively. *Id.* at 8:19–56.

The '542 patent also discloses the results of a study assessing "stability after storage or freeze-thaw (F/T) cycling is assessed in buffers of the present invention." *Id.* at 9:19–27. Particle radius was measured by dynamic light scattering (DLS) to determine the presence of aggregates. *Id.*

Table 3, reproduced below, summarizes the results of the study.

TABLE 3

STABILITY OF AAV2 VECTORS

	Particle radius - Rh (nm)							
Formu-		4° C.	−20° C.			−80° C.		
lation	Pre	5 d	1 F/T	5 F/T	10 F/T	1 F/T	5 F/T	10 F/T
CF	14.5	27.0	22.4	56.1	94.5	20.6	57.5	141
TF1	13.8	16.3	TH	TH	TH	TH	TH	TH
TF2	13.8	14.4	14.2	14.0	14.1	13.8	21.3	50.9

Pre: DLS radius measured immediately following 0.2 μm filtration.
Vector concentrations (vg/mL): CF: 1.93E13, TF1: 2.38E13, TF2: 2.33E13.
TH: signal intensity is too high to measure because of extensive aggregation.

According to the '542 patent, Table 3 provides data showing as follows:

> AAV2-AADC vector prepared in CF shows some aggregation after 5 days of storage at 4° C., as well as following one or more F/T cycles at −20 or −80° C. For vector prepared in TF1, no aggregation occurs after 5 days at 4° C., but aggregation occurs following a single F/T cycle at −20 or −80° C. as indicated by a DLS signal intensity that is too high to measure. Visual

> inspection of these samples reveals slight cloudiness, which is consistent with aggregation. For vector prepared in TF2, no aggregation is observed at 4° C., or following up to 10 F/T cycles at −20° C. Some aggregation is observed following 5 and 10 F/T cycles at −80° C.

Id. at 9:29–55. According to Patent Owner, the results of the studies disclosed in the '542 patent "confirmed the importance of increased ionic strength in preventing aggregation." Prelim. Resp. 13 (citing Ex. 1001, 10:29–43 (stating "[t]he effect of ionic strength [] on virus particle interactions is determined to elucidate the mechanism of vector aggregation")).

E. The Challenged Claims

Challenged Claims 5 and 6 are reproduced below, along with claim 1 from which they depend.

> 1. A composition for the storage of purified, recombinant adeno-associated virus (AAV) vector particles, comprising:
>
> > purified, recombinant AAV vector particles at a *concentration exceeding 1×10^{13} vg/ml up to 6.4×10^{13} vg/ml*;[1]

[1] The units of measurements used in the art to measure the titer of AAV compositions are explained in the Petition as follows:

> The titer of AAV compositions can be measured in vector genomes (vg)/ml, genome copies (gc)/ml, capsid particles (cp)/ml, or virus particles (vp)/ml. Ex.1025, ¶¶35. The first two are used interchangeably, since both represent the number of functional vectors containing the therapeutic gene. *Id*., ¶¶36-37. By contrast, the latter two measurements include particles that are incomplete, damaged, or lacking genetic material. Ex.1009, [00281]; Ex.1025, ¶36.

Pet. 12.

> a pH buffer, wherein the pH of the composition is between 7.5 and 8.0; and
>
> excipients comprising one or more multivalent ions selected from the group consisting of citrate, sulfate, magnesium, and phosphate; wherein *the ionic strength of the composition is greater than 200 mM*, and wherein the purified AAV vector particles are stored in the composition without significant aggregation.
>
> 5. The composition of claim 1, *wherein the purified, recombinant AAV vector particles have an average particle radius (Rh) of less than about 20 nm as measured by dynamic light scattering*.
>
> 6. The composition of claim 1, *wherein recovery of the purified, recombinant virus particles is at least about 90% following filtration of the composition of said AAV vector particles through a 0.22 μm filter*.

Ex. 1001, 14:15–28, 34–41 (emphasis added to highlight disputed elements).

F. Evidence

Petitioner relies upon information that includes the following.

Ex. 1003, Evans, WO 01/66137 A1, published Sept. 13, 2000 ("Evans").

Ex. 1004, Frei et al., WO 99/41416, published Aug. 19, 1999 ("Frei").

Ex. 1005, Huang J., Gao, et al., "Aggregation of AAV vectors, its Impact on Liver directed Gene Transfer and Development of Vector Formulations to Prevent and Dissolve Aggregation and Enhance Gene Transfer Efficiency," MOL THER. 1:S286 (2000) ("Huang").

Ex. 1006, Mingozzi, et al., "Improved Hepatic Gene Transfer by Using an Adeno-Associated Virus Serotype 5 Vector," J VIROL. Vol. 76, No. 20, pp. 10497–502 (2002) ("Mingozzi").

Ex. 1007, Wright et al., "Recombinant Adeno-Associated Virus: Formulation Challenges and Strategies for a Gene Therapy

Vector," CURR. OPIN. DRUG DISC. DEV. 6(2):174–178 (2003) ("Wright").

Petitioner also relies upon the Declaration of Mansoor M. Amiji, R.Ph., Ph.D. (Ex. 1025) to support its contentions.

Patent Owner relies upon the Declaration of Martyn C. Davies, D.Sc., Ph.D. (Ex. 2004) to support its contentions.

G. Asserted Grounds of Unpatentability

In the Petition, Petitioner challenges claims 1, 2, 5, and 6 on the following grounds:

Ground	Claim(s) Challenged	35 U.S.C. §[2]	Reference(s)/Basis
1	1, 5, 6	103	Evans, Huang, Mingozzi
2	2	103	Evans, Wright, Huang, Mingozzi
3	1, 2, 5, 6	103	Frei, Huang, Mingozzi

Pet. 4. After the Petition was filed, Patent Owner subsequently explained that "[c]laims 1 and 2 were disclaimed to streamline issues for the Board, because only claims 5 and 6 are asserted for infringement in the co-pending litigation." Prelim. Resp. 3 n.3. Accordingly, for the purposes of this Decision, we consider only Petitioner's Grounds 1 and 3 as directed to challenged claims 5 and 6.

H. Claim Construction

We interpret a claim "using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C.

[2] The Leahy-Smith America Invents Act ("AIA") included revisions to 35 U.S.C. §103 that became effective on March 16, 2013. We apply the pre-AIA version of §103 here, because the application identified in the '542 patent was filed before the effective date of the AIA. *See* Ex. 1001, code (22).

282(b)." 37 C.F.R. § 42.100(b) (2019). Under this standard, we construe the claim "in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent." *Id.*

Petitioner asserts that the claim terms require no express construction. Pet. 17. Patent Owner does not challenge Petitioner's position. Prelim. Resp. 14.

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

I. Level of Ordinary Skill in the Art

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

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

> would have possessed at least a BS in biology, chemistry, chemical engineering, biochemistry, pharmaceutical science, or a related discipline, with ≥4 years of industry, laboratory, and/or clinical experience in formulating or developing dispersions for therapeutic biologics, such as proteins or vectors for gene

> delivery. Such person may be familiar with, or consult with someone familiar with, the development and/or administration of viral vectors for gene therapy. Ex. 1025, ¶82.

Pet. 16–17. Patent Owner does not dispute Petitioner's proposal about the POSA's qualifications. Prelim. Resp. 2 n.2.

For this Decision, we adopt and apply Petitioner's proposal for the person of ordinary skill in the art level, which appears to be consistent with the level of skill reflected in the asserted prior art and the '542 patent.

II. ANALYSIS

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

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of

nonobviousness.[3] *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

The obviousness inquiry also typically requires an analysis of "whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) (requiring "articulated reasoning with some rational underpinning to support the legal conclusion of obviousness")). A petitioner cannot prove obviousness with "mere conclusory statements." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1380 (Fed. Cir. 2016). Rather, a petitioner must articulate a sufficient reason why a person of ordinary skill in the art would have combined the prior art references. *In re NuVasive, Inc.*, 842 F.3d 1376, 1382 (Fed. Cir. 2016).

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

A. Summary of Cited Prior Art

1. Evans

Evans discloses viral compositions for use in gene therapy. Ex. 1003, Abstract, 1:15–19. Evans teaches buffer conditions to maintain its compositions for potential human parenteral administration. Ex.1003, 1:15–19. Evans explains that "[a]n ongoing challenge in the field of gene therapy and vaccine research is to generate liquid virus formulations which are stable for longer periods of time within a useful temperature range." *Id*. at 1:16–19, 28–30.

[3] Patent Owner does not present any objective evidence of nonobviousness (i.e., secondary considerations) for the challenged claims.

Evans discloses that its compositions comprise a buffer, a salt, a divalent cation, and a non-ionic detergent. Ex. 1003, 1:19–21. Evans further discloses the identity of and concentration ranges for those components. *See* Ex.1003, 8:22–11:4. Evans also discloses that the compositions support virus concentrations of about 1 x 10^7 to 1 x 10^{13} vp/ml. Ex. 1003, 8:5–11.

Evans claims a virus composition comprising a purified virus with a concentration of about 1 x 10^7 to 1 x 10^{13} vp/ml, a buffer acceptable for human parenteral use at a pH of about 7.5–8.5, sodium chloride at about 25mM–250mM, a divalent cation selected from $MgCl_2$ and $CaCl_2$ at about 0.1mM–5mM, and a non-ionic detergent. Ex. 1003, 36 (claim 5). Evans teaches that its compositions may be used with AAV. Ex. 1003, 3:12–14; 7:16–18.

2. Huang

Huang, an abstract titled "Aggregation of AAV Vectors, its impact on Liver directed Gene Transfer and Development of Vector Formulations to Prevent and Dissolve Aggregation and Enhance Gene Transfer Efficiency," states that "to achieve high level of gene transfer and ensure the safety of vector administration it is desirable to deliver high doses of vector in small volumes." Ex. 1005, S286. According to Huang, "at high concentrations, AAV virions form aggregates of different sizes in a range of different buffer systems and storage conditions." *Id.* Huang states that "when the vector titer reached 5-10 x 10^{13} GCs/ml, gene transfer efficiency was 10-100 folds lower at the same dose as compared to the vector whose titer was 1-5 x 10^{12} GCs/ml. *Id.* Huang states that "a series of formulation studies were performed to prevent and dissolve AAV aggregation," and reported "a 30–

50% reduction in the size of aggregates size at high vector concentrations" for some of the compositions. *Id*.

3. Mingozzi

Mingozzi, titled Improved Hepatic Gene Transfer by Using Adeno-Associated Virus Serotype 5 Vector, states that "AAV vectors do not contain viral coding sequences and have been shown to efficiently transfer genes to nondividing target cells," and that "[a]n excellent safety profile combined with reduced potential for activation of inflammatory or cellular immune responses has made this vector system attractive for clinical application and treatment of genetic disorders." Ex. 1006, 10497. According to Mingozzi, purification of AAV-2 and AAV-5 vectors "by repeated CsCl gradient centrifugation" yielded concentrations of $>10^{13}$ vg/ml. *Id.*

4. Wright

Wright teaches that AAV "is a promising vector for human gene transfer" and has "received considerable attention in the field of gene therapy, because of [its] ability to mediate long-term gene transfer in the absence of significant toxicity." Ex. 1007, 174. Wright teaches that "because AAV and adenovirus are both non-enveloped viruses developed as gene transfer vectors, studies on the latter can provide guidance for AAV vector formulation development." *Id.*

Wright notes that "[t]he mechanism of vector aggregation is not well understood, and purification conditions that may affect aggregation include buffer ionic strength and pH, shear and vector concentration." *Id*. at 175. Wright discloses that

> Our and other research teams have observed that freeze-thaw cycling exacerbates vector aggregation, and can lead to aggregation at vector concentrations significantly lower than

> 10^{14} cp/ml. For example, using dynamic light scattering, we observed that highly purified vector preparations at concentrations of 5×10^{13} cp/ml that are stable in a non-aggregated, monomeric state when stored at 2 to 8°C, can be induced to undergo some aggregation following a single freeze-thaw cycle to -20°C.

Id. Wright notes that "[r]educed yield is one of the deleterious consequences of aggregation during the vector purification process" and notes that "loss of rAAV following a 0.2-μm filtration step correlates with the extent of vector aggregation." *Id.*

Wright teaches that "empty capsids, whose size and surface characteristics are similar to that of genome-containing vector particles, contribute to particle aggregation, and their presence may result in aggregation at lower vector genome (vg) concentrations than would be observed in their absence." *Id.* (citation omitted).

Wright further discloses that "[a]ssuming that full vector particles and empty capsids aggregate by a similar mechanism (an assumption that requires testing), a preparation of AAV vectors containing a 10-fold excess of empty capsids should have a similar risk of aggregation at concentrations of $\geq 10^{13}$ vg/ml (corresponding to $\geq 10^{14}$ cp/ml)." *Id.* at 175–176.

5. Frei

Frei discloses viral formulations comprising polyhydroxy hydrocarbon for use in gene therapy. Ex. 1004, Abstract, 1:15–20. Frei identifies "a critical need to develop formulations that stabilize relatively high concentrations of virus," and discloses a buffered formulation that stabilizes high concentrations of recombinant virus for use in gene therapy and maintains viability after storage. *Id.* at 4:26–36, 7:7–11, 8:27–29, 8:34–36. Frei discloses that its compositions comprise a buffer system that

maintains a pH of about 7.0–8.5 despite storage between -80°C and 27°C. *Id*. at 6:21–24. Frei's compositions include pharmaceutically acceptable divalent metal salt stabilizers, and Frei teaches that magnesium salts are particularly preferred in an amount of about 0.1 mg/ml to 1 mg/ml. *Id*. at 5:31–36. Pharmaceutically acceptable monovalent salt stabilizers are also included, and Frei discloses that sodium chloride in an amount of 0.6 mg/ml to 10.0 mg/ml is preferred. *Id*. at 5:37–6:6. Frei further teaches that "the formulation of the present invention can maintain stability of the virus at concentrations ranging up to 1 x 10^{13} particles/mL." *Id*. at 7:9–11. Frei's example of a virus composition ("Example D-1") comprises purified adenovirus at a concentration of 1.6 x 10^{13} vp/ml, in 20 mM NaPi buffer, 100 mM NaCl, 2 mM $MgCl_2$, 2% sucrose, and 10% glycerol, having pH 8 at 2–10°C. *Id.* at 22:17–31.

B. Ground 1: Obviousness of Claims 5 and 6 over the Combination of Evans, Huang, and Mingozzi

Petitioner asserts that claims 5 and 6 are unpatentable as obvious over Evans, Huang, and Mingozzi. Pet. 23–46. Patent Owner disputes Petitioner's contentions. Prelim. Resp. 14–44.

For the reasons set forth below, we determine that Petitioner has not shown a reasonable likelihood of establishing that at least one of the challenged claims is unpatentable as obvious over Evans, Huang, and Mingozzi.

1. Petitioner's Contentions

With regard to Challenged Claim 5, Petitioner contends that the "average particle radius" limitation is an "inherent characteristic feature of the purified viral composition." Pet. 41–42.

Petitioner next directs our attention to Evans's claim 5, which is directed to a virus composition containing a "divalent cation [] selected from the group consisting of $MgCl_2$ and $CaCl_2$ in an amount from about 0.1 mM to about 5 mM." Ex. 1003, 36 (claim 5); Pet. 42. Petitioner further contends that

> The '542 patent admits that AAV2 particles have a diameter of ~26nm (Ex.1001, 1:29-38). Because Evans's claim 5 composition prevented aggregation, a POSA would have reasonably expected AAV particles stored therein would have an Rh of <~20 nm measured by DLS. Indeed, the '542 patent does not identify anything critical about the recited radius range other than it being exemplary of no aggregation. *Id.*, 9:25-27 ("Rh values >20 nm are deemed to indicate the occurrence of some level of aggregation.").

Pet. 42. Petitioner contends that a person of ordinary skill in the art would have been motivated to minimize any potential aggregation in Evans's claim 5 because it was known that virus aggregation reduces gene transfer efficiency and other potentially deleterious consequences. *Id.* at 42–43 (citing Ex. 1005, S286; Ex. 1007, 176). Petitioner further contends that

> A POSA would have reasonably expected success in minimizing particle size in view of Huang's teaching that its optimized compositions "could lead to a 30-50% reduction in the size of aggregates at high vector concentrations." Ex.1005, S286. Indeed, "no signs of settling or precipitation" were observed for prior art adenovirus compositions stored in a high ionic strength buffer over a 7-day period (Ex.1009, [00369]), and a POSA would have understood that AAV "is significantly more stable than the adenovirus" used in Liu (Ex.1013, 1283); Ex.1025, ¶¶197-198. Thus, only routine optimization would be required to obtain an average AAV Rh of <20nm in Evans's claim 5 composition. Ex.1025, ¶¶ 199-201.

Pet. 43 (citing *Senju Pharm. Co. v. Lupin Ltd.*, 780 F.3d 1337, 1353 (Fed. Cir. 2015) (invalidating a claim directed to "a product of routine optimization that would have been obvious to one of skill in the art.")).

With regard to claim 6, Petitioner contends

> a POSA would have been motivated to minimize any potential aggregation in Evans's claim 5 formulation, since both Wright and Huang linked aggregation to reduced functional activity of AAV vectors. Ex.1007, 176; Ex.1005, S286. Thus, a POSA would have been motivated to maximize virus recovery from a 0.22μm filter through routine optimization of the known stabilization factors in Evans's claim 5 composition. Ex.1025, ¶ 205.

Pet. 45. Petitioner further contends that

> A POSA also would have reasonably expected success in maximizing particle recovery after filtration because POSA knew that Huang taught its optimized compositions "could lead to a 30-50% reduction in the size of aggregates at high vector concentrations" (Ex.1005, S286), Liu observed "no signs of settling or precipitation" for adenovirus particles stored in a high ionic strength buffer over a 7-day period (Ex.1009, [00369]), and Croyle taught that AAV "is significantly more stable than the adenovirus" (Ex.1013, 1283). Thus, only routine optimization would be required to improve AAV recovery following filtration of Evans's claim 5 formulation through a 0.22μm filter. Ex.1025, ¶¶ 206-209.

Pet. 45–46.

2. Patent Owner's Contentions

Patent Owner contends that Petitioner "does not submit any evidence that the particle radius and product recovery elements of claims 5 and 6, respectively, would inherently result from the claimed combination." Prelim. Resp. 16.

Patent Owner contends that Petitioner's reliance on Evans's disclosure of "a virus concentration in the range from about $1x10^7$ vp/mL to about

$1x10^{13}$ vp/mL" to argue that the uppermost endpoint of this range ($1x10^{13}$ vp/mL ± 5%) overlaps with the scope of the claims assumes that 100% of the particles contain vector genomes and that Petitioner "provides no basis for why the POSA would make such an assumption." *Id.* at 17 (citing Pet. 30 ("Assuming that 100% of the particles contain vector genomes, Evans's claim 5 composition therefore comprises viral particles at a concentration exceeding $1x10^{13}$ vg/ml.")). Rather, according to Patent Owner,

> Dr. Amiji's declaration indicates that the POSA would not have assumed that Evans's viral particle compositions were free of empty capsids, and instead would have assumed the opposite—that as many as 90% of capsids in a given composition are empty. [Ex. 2004] ¶¶72-73. Dr. Amiji states that "Wright [Ex. 1007] teaches that ≥ 10^{14} capsid particles (cp)/ml corresponds to ≥ 10^{13} vg/ml)," indicating as much as 10-fold excess in empty capsids. [Ex. 1025] ¶119 (citing Ex. 1007, 176).

Id. (emphasis omitted).

Patent Owner contends that

> [Petitioner] fails to establish that the POSA would have been motivated to develop a composition comprising an rAAV "concentration exceeding $1x10^{13}$ vg/ml," "one or more multivalent ions selected from … citrate, sulfate, magnesium, and phosphate," with an ionic strength "greater than 200mM." [Ex. 2004] ¶¶ 75–79.

Id. at 18. Patent Owner notes that Petitioner relies on "Mingozzi to argue that the POSA would been motivated to administer 'doses of $3.2x10^{13}$ vg for a 60kg human' at a 'concentration exceeding $1x10^{13}$ vg/ml.'" *Id.* (citing Pet. 31). Patent Owner contends, however, that Mingozzi "says nothing about any formulations for AAV vectors let alone anything about ionic strength or multivalent ions." *Id.* at 18–19 (citing Ex. 2004 ¶ 78).

Patent Owner further argues that Petitioner's arguments that the claimed ionic strength range—greater than 200 mM—would have been

achieved by through routine optimization misapplies obviousness case law. Prelim. Resp. 20–21 (citing Pet. 35–36). In particular, Patent Owner contends that "[f]or a range to be obvious, a parameter must first be recognized as a 'result-effective variable,' before the determination of the optimum or workable ranges of that variable might be characterized as routine experimentation. *Id.* at 21 (citing *In re Antonie*, 559 F.2d 618, 620 (CCPA 1977)). Petitioner, however, "fails to identify any disclosure in Evans, Huang, and/or Mingozzi suggesting that ionic strength would impact rAAV aggregation" and failed to establish ionic strength as a "result-effective variable." *Id.* Moreover, Patent Owner contends that Petitioner

> mischaracterizes Wright (Ex. 1007) to support its contention that "ionic strength . . . likely affects vector aggregation." Wright stated that the "mechanism of vector aggregation is not well understood, and purification conditions that may affect aggregation include buffer ionic strength and pH, shear and vector concentration." Ex. 1007, 175. Novartis never explains how Wright's statement that factors causing vector aggregation were "not well understood"—followed by a non-exclusive list of conditions that may impact aggregation—was an indication that "ionic strength . . . likely affects vector aggregation." *Id.*; Davies, ¶¶ 80-81.

Id. at 21–22 (emphasis omitted).[4] According to Patent Owner, "Wright also fails to teach or suggest ionic strength as a results-effective variable for rAAV aggregation." *Id.* at 22 (citing Ex. 2004 ¶¶ 84–85).

[4] We note that while Petitioner does not rely on Wright for its obviousness challenge in Ground 1, Petitioner relies on Wright for its argument that "ionic strength was a known condition that likely affects vector aggregation." Pet. 36 (citing Ex. 1007, 175; Ex. 1025 ¶¶ 175–177).

3. Discussion

Claims 5 and 6 require, respectively, that the composition does not exhibit significant aggregation as determined by particle radius (claim 5) and by percent product recovery following filtration (claim 6). Petitioner's arguments that those elements of claims 5 and 6 are inherent properties to AAV2 particles misses what is required by those claims, because each of those elements of the claims are used as a measure of aggregation achieved by the claimed compositions. Pet. 41–42, 44, 60; Ex. 2004 ¶¶ 126, 130–134; Ex. 1001, 4:61–5:25, 8:19–44, 9:25–27. For example, the '542 patent explains that the effect of ionic strength on aggregation was assessed by measuring vector recovery after filtration through a 0.22 μm filter. Ex. 1001, 8:1–10, 11:53–12:29 (Example 2); Ex. 2004 ¶ 133. Thus, Petitioner's arguments that particle radius (claim 5) and percent product recovery following filtration (claim 6) are inherent properties is insufficient to prove obviousness.

To prove inherency in the context of obviousness "[a] party must . . . meet a high standard . . . the limitation at issue necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art." *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1195–96 (Fed. Cir. 2014). To that point, Petitioner fails to provide sufficient evidence such as prior art or testing evidence to show that the combination of Evans, Huang, and Mingozzi would result in a composition having the recited aggregation outcomes. For example, the '542 patent explains that compositions having ionic strength greater than 200 mM surprisingly resulted in recoveries exceeding 90%, whereas compositions having ionic strengths below 200 mM resulted in recoveries below 80%. Ex. 1001, 8:1–

10, 11:53–12:29 (Example 2); Ex. 2004 ¶ 133. Petitioner fails to submit any evidence that the particle radius and product recovery elements of claims 5 and 6, respectively, would necessarily be present, or the natural result of the combination of teachings explicitly disclosed by Evans, Huang, and Mingozzi.

Petitioner also argues that adjusting the ionic strength of the composition would have been a matter of routine optimization. Pet. 36 (citing Ex. 1003, 11:13–19; Ex. 1025 ¶¶ 61–71, 178–182), 43 (citing Ex. 1025 ¶¶ 199–201), 45 (Ex. 1025 ¶¶ 205–209). We are not persuaded by Petitioner's routine optimization argument as applied to the claimed ionic strength range. We acknowledge that "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456 (CCPA 1955). We also acknowledge, however, an "exception" to this *Aller* rule where "the parameter optimized was not recognized to be a result-effective variable." *In re Antonie*, 559 F.2d 618, 620 (CCPA 1977). Here, Petitioner fails to establish a known relationship between ionic strength and viral particle aggregation. Rather, the evidence of record teaches that "[t]he mechanism of vector aggregation is not well understood, and purification conditions that may affect aggregation include buffer ionic strength and pH, shear and vector concentration." Ex. 1007, 175; Prelim. Resp. 21; Ex. 2004 ¶¶ 84–85. Additionally, as explained in detail by Patent Owner, data presented in Evans does not establish any clear relationship between ionic strength and maintained infectivity after storage. Prelim. Resp 22–27. Accordingly, on this record, we determine that

Petitioner fails to establish ionic strength as a result-effective variable for rAAV aggregation.

For at least the reasons discussed above, we are not persuaded that Petitioner has shown a reasonable likelihood of establishing that either claim 5 or claim 6 is unpatentable as obvious over Evans, Huang, and Mingozzi. Accordingly, Petitioner has not demonstrated a reasonable likelihood of prevailing on Ground 1.

C. Ground 3: Obviousness of Claims 5 and 6 over the Combination of Frei, Huang, and Mingozzi

Petitioner asserts that claims 5 and 6 are unpatentable as obvious over Frei, Huang, and Mingozzi. Pet. 47–61. Patent Owner disputes Petitioner's contentions. Prelim. Resp. 50–60.

As in Ground 1, Petitioner contends that the particle radius and product recovery elements of claims 5 and 6 would inherently result from the claimed combination and additionally that a "selection of an appropriate ionic strength for a therapeutic composition is a matter of routine optimization." Pet. 54–55, 59–61. We are unpersuaded by Petitioner's contentions for the same reasons discussed above in Ground 1 because those contentions are similarly unsupported by the evidence of record. *See, e.g.*, Pet. 55 (relying on Wright for the premise that ionic strength is a parameter that may affect vector aggregation).

Accordingly, we determine that Petitioner has not shown a reasonable likelihood of establishing that at least one of the challenged claims is unpatentable as obvious over Frei, Huang, and Mingozzi.

III. CONCLUSION

After considering the evidence and arguments of record, we determine that Petitioner has not demonstrated a reasonable likelihood of prevailing

with respect to any claim challenged in the Petition.[5] Accordingly, we do not institute an *inter partes* review.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is *denied* as to all challenged claims, and no trial is instituted.

[5] Because we deny the Petition on the merits, we do not reach Patent Owner's argument for discretionary denial under 35 U.S.C. § 314(a) or § 325(d). Prelim. Resp. 44–50, 61–67.

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