

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAREPTA THERAPEUTICS, INC.
Petitioner

v.

GENZYME CORPORATION,
Patent Owner.

Case: IPR2025-01195
Patent No. 7,704,721

PATENT OWNER'S PRELIMINARY RESPONSE

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Exhibit No.	Description
2001	Declaration of Katherine A. Helm
2002	Complaint, <i>Genzyme Corporation v. Sarepta Therapeutics, Inc., and Sarepta Therapeutics Three, LLC</i> , D.I. 1 (1:24-cv-00882-UNA)
2003	Second Amended Complaint, <i>Genzyme Corporation v. Sarepta Therapeutics, Inc., and Sarepta Therapeutics Three, LLC</i> , D.I. 81, (1:24-cv-00882-UNA)
2004	Second Amended Complaint, Ex. K, <i>Genzyme Corporation v. Sarepta Therapeutics, Inc., and Sarepta Therapeutics Three, LLC</i> , D.I. 81-2 (1:24-cv-00882-UNA)
2005	Second Amended Complaint, Ex. M, <i>Genzyme Corporation v. Sarepta Therapeutics, Inc., and Sarepta Therapeutics Three, LLC</i> , D.I. 81-3 (1:24-cv-00882-UNA)
2006	<i>Collabo Innovations, Inc. v. Sony Corp.</i> , 15-cv-1094-RGA, D.I. 43 (D. Del. Jan. 5, 2017)
2007	<i>Ansell Healthcare Prods. LLC v. Reckitt Benckiser LLC</i> , 15-cv-915-RGA, D.I. 105 (D. Del. Dec. 1, 2016)
2008	<i>RainDance Techs., Inc. v. 10X Genomics, Inc.</i> , 15-cv-152-RGA, D.I. 27, 37 (D. Del. Feb. 29, 2016)
2009	Notice of Service of Plaintiff's Initial Claim Chart, <i>Genzyme Corporation v. Sarepta Therapeutics, Inc., and Sarepta Therapeutics Three, LLC</i> , D.I. 59 (1:24-cv-00882-UNA)
2010	Notice of Service of Stipulation to Extend Time, <i>Genzyme Corporation v. Sarepta Therapeutics, Inc., and Sarepta Therapeutics Three, LLC</i> , D.I. 68 (1:24-cv-00882-UNA)
2011	So Ordered re 77 Joint Stipulation to Amend Scheduling Order, <i>Genzyme Corporation v. Sarepta Therapeutics, Inc., and Sarepta Therapeutics Three, LLC</i> , D.I. 78 (1:24-cv-00882-UNA)
2012	Notices of Service for Interrogatories and Requests for Production, <i>Genzyme Corporation v. Sarepta Therapeutics, Inc., and Sarepta Therapeutics Three, LLC</i> , D.I. 28 (1:24-cv-00882-UNA)

Exhibit No.	Description
2013	A.R. Kucernak et al., <i>Avoid Using Phosphate Buffered Saline (PBS) as an Electrolyte for Accurate OER Studies</i> , 9 ACS Energy Lett. 3939–3946 (2024)
2014	Oral Order on April 5, 2016 Denying Motion to Stay, <i>RainDance Technologies, Inc. et al v. 10X Genomics, Inc.</i> (1-15-cv-00152)
2015	A.E. Smith, “ <i>Gene Therapy: Where Are We</i> ,” 354 The Lancet SI1 (July 1999)
2016	<i>Remington: The Science and Practice of Pharmacy</i> , Nineteenth Ed., Vol. I, Chapters 17, 18, 23, and 36 (1995).
2017	<i>Remington: The Science and Practice of Pharmacy</i> , Nineteenth Ed., Vol. II, Chapter 87(1995).
2018	Carpenter, J. F. & Manning, M.C. (Eds.), <i>Rational Design of Stable Protein Formulations: Theory and Practice</i> , Vol. 13 (2002).
2019	Gatlin, L., Chapter 17, “Formulation and Administration Techniques to Minimize Injection Pain and Tissue Damage Associated with Parental Products,” in <i>Injectable Drug Development: Techniques to Reduce Pain and Irritation</i> , (eds. P. Gupta and G. Brazeau), pp. 401-421 (1999).
2020	International Patent Pub. No. WO 99/41416 to Frei, et al.
2021	Croyle, et al., “Development of Formulations That Enhance Physical Stability of Viral Vectors for Gene Therapy,” <i>Gene Ther.</i> , 8:1281-1290 (2001).
2022	Adadevoh, K. et al., “A Short-Term Field Use and Shipping Stability Study of a Wild Type Ad5 Adenoviral Reference Material,” <i>BioProcessing</i> 1(2) 62-69 (2002).
2023	Declaration of Martyn Davies
2024	Curriculum Vitae of Martyn Davies
2025	Ayache, J. et al., <i>Sample Preparation Handbook for Transmission Electron Microscopy</i> . (2010).
2026	Arista-Romero, M. et al., “Towards a Quantitative Single Particle Characterization by Super Resolution Microscopy: From Virus Structures to Antivirals Design.” (2021).

Exhibit No.	Description
2027	Chu, J. et al., “A bright cyan-excitable orange fluorescent protein facilitates dual-emission microscopy and enhances bioluminescence imaging in vivo.” <i>Nat Biotechnol.</i> 2016 July ; 34(7): 760–767 (2016).
2028	Aaron, K. et al., “Selection of Viral capsids and promoters affects the efficacy of rescue of Tmprss3-deficient cochlea.” <i>Molecular Therapy: Methods & Clinical Development</i> (2023).
2029	Jia, F. et al., “A nonviral minicircle vector for deriving human iPS cells” <i>Nature Methods</i> (2010).
2030	[Reserved]
2031	J.O. Konz et al. “Development of a Purification Process for Adenovirus: Controlling Virus Aggregation to Improve the Clearance of Host Cell DNA,” 21 <i>Biotechnol. Prog.</i> 466 (2005)
2032	Booy, F. P., et al. “Electron microscopy of influenza virus: a comparison of negatively stained and ice-embedded particles.” <i>Journal of Molecular Biology</i> 184.4 (1985): 667-676.

Patent owner Genzyme Corp. (“Genzyme” or “Patent Owner”) respectfully submits this preliminary response to the *Inter Partes* Review (“IPR”) petition filed by petitioner, Sarepta Therapeutics, Inc. (“Sarepta”), alleging that claims 1, 4, 6, 7, and 11 (the “challenged claims”) of U.S. Patent No. 7,704,721 (EX1001, the “’721 patent”) are obvious (the “Petition”).

I. INTRODUCTION

Sarepta’s Petition fails to establish any reasonable likelihood that at least one of the challenged claims is unpatentable. A continuation of the ’721 patent, U.S. Patent No. 9,051,542 (the “’542 patent”), was previously subjected to two IPR challenges, and both denied institution on the merits (*infra* §III). The claims of the ’721 patent require the same elements as in the ’542 patent that the Board found nonobvious. Sarepta’s Petition fails to provide any new art or arguments that would compel the Board to deviate from its thorough and well-reasoned institution denials in the prior IPRs. In fact, doing so would upend settled expectations surrounding a patent that issued more than 15 years ago and has already expired.¹

¹ Genzyme reserves its right to oppose the IPR of the ’721 patent based on a holding that the Board lacks the authority to review the patentability of expired patent claims. See Petition for Writ of Certiorari, *Gesture Tech. Partners, LLC v. Apple Inc.*, No. 24-1280 (June 16, 2025).

The '721 patent claims an inventive breakthrough in preventing aggregation of recombinant adeno-associated virus ("rAAV") for preparations used in gene therapy, developed over twenty years ago by inventors at Avigen Inc. The '721 patent was later acquired by Genzyme. Administering rAAV vectors to patients "may require small volumes of highly concentrated vector." EX1001, 2:7-10. The development of storable concentrated rAAV preparations was hindered by rAAV particle aggregation, which caused loss of infectivity, biodistribution issues, and adverse immune responses. *Id.*, 2:12-25. Without solving the problem of rAAV aggregation, gene therapy formulations would be therapeutically ineffective. EX2015, 4 ("[H]igh doses of viral vector ... are usually required to achieve measurable gene transfer"); EX1047, 1; EX1043, 1.

While this problem and its severity were well-documented in the prior art, the '721 patent's inventors were the first to solve it. They surprisingly identified a method to prevent aggregation in rAAV preparations by increasing the ionic strength of those preparations to at least 200 mM. EX1001, 6:67-7:21. The method allowed the inventors to make rAAV preparations that were isotonic and suitable for human parenteral administration by including multivalent ions to increase ionic strength above the 200 mM threshold. *Id.*, 6:67-7:7.

When seeking approval of its own gene therapy product, Elevidys®, Sarepta cited the inventors' discovery—that high ionic strength minimized rAAV

aggregation—as being critical to the development of Elevidys[®]. *Infra* §II.C. Now, years later, Sarepta belies its contemporaneous statements by arguing the ’721 patent’s claims are obvious. Sarepta cobbles together piecemeal art for each claim element, including the claimed rAAV concentration and ionic strength limitations. Establishing obviousness, however, requires the evaluation of the claimed combination as a whole to guard against “hindsight reasoning, using the invention as a roadmap to find its prior art components.” *Ruiz v. A.B. Chance Co.*, 357 F.3d 1270, 1275 (Fed. Cir. 2004); *see also KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). Yet, improper hindsight and speculation by Sarepta’s expert, Dr. Mark A. Kay (EX1005, the “Kay Declaration”), is all that props up its Petition. The cited references fail to connect preventing rAAV aggregation with increased ionic strength. The Petition, therefore, fails to establish that a person of ordinary skill in the art (“POSA”) would have been motivated to prevent rAAV aggregation by increasing ionic strength.

Sarepta also disregards teachings that contradict its arguments. It is a “longstanding principle that the prior art must be considered for all its teachings, not selectively” for only those teachings that allegedly support obviousness. *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019). Konz (EX1008), which Sarepta relies on in all grounds for the ionic strength element (Petition, 38-39, 57-58), never discloses a “formulation buffer” with an ionic

strength above 200 mM. Konz's formulation buffers have ionic strengths well below 200 mM. EX1008, 25:22-27. Thus, Konz would direct a POSA to lower, not raise, the ionic strength of rAAV preparations. Sarepta also cites Evans (EX1020), which Konz "incorporates [] by reference." Petition 38-39, 57-58. But Evans is the same reference relied on in the two prior failed IPRs challenging the '542 patent. *Infra* §§III.A-III.B. Evans never connects high ionic strength with improving stability. The Board, in its prior institution denials, expressly found Evans unpersuasive for proving that it was obvious to adjust ionic strength to prevent aggregation. EX1017, 23-24.

Sarepta's Petition and the Kay Declaration also fail to support its additional "Hail Mary" arguments. Neither Auricchio nor Potter addresses preventing aggregation in a high-concentration rAAV preparation by adjusting ionic strength. Petition, 34-35, 53-54. Sarepta ignores other prior art indicating that high salt concentration rAAV preparations, like the ones Sarepta relies on for disclosures relating to ionic strength in Auricchio, Potter, and Konz/Evans, were associated with tissue damage and pain when injected. Neither does Sarepta address prior art demonstrating that high salt concentration led to rAAV instability. Finally, Sarepta's citation of far afield, 1970s publications relating to polio virus aggregation in drinking water and wastewater is irrelevant to purifying rAAV preparations for therapeutic purposes. *Id.*, 9, 18 (citing EX1030, EX1031,

EX1032). Such literature would not motivate a POSA to prevent rAAV aggregation in rAAV preparations by increasing ionic strength. For all these reasons, Sarepta fails to establish a reasonable likelihood of succeeding in this Petition. As with the prior '542 patent IPR petitions, the Board should deny institution of this petition challenging the '721 patent.

II. THE '721 PATENT

The '721 patent issued on April 27, 2010. The '721 patent was filed in 2005 and claims priority to two provisional applications filed in 2004. As described in the specification, the inventors were able to overcome the challenge of concentration-induced rAAV aggregation. Their inventive method of preventing aggregation ensured that the resulting rAAV preparations are suitable for human parenteral administration. EX1001, 5:7-18. The claimed method addresses considerations of tonicity, pH, and the pharmaceutical acceptability of excipients. The balancing of these considerations elevated the complexity of solving the rAAV aggregation problem.

A. Disclosed Invention

After many unsuccessful attempts at preventing rAAV aggregation, the inventors discovered that high ionic strength was the key to preventing vector aggregation. As a result, the inventors prepared rAAV compositions suitable for human administration. *Id.*, Abstract. The '721 patent discloses “high ionic strength

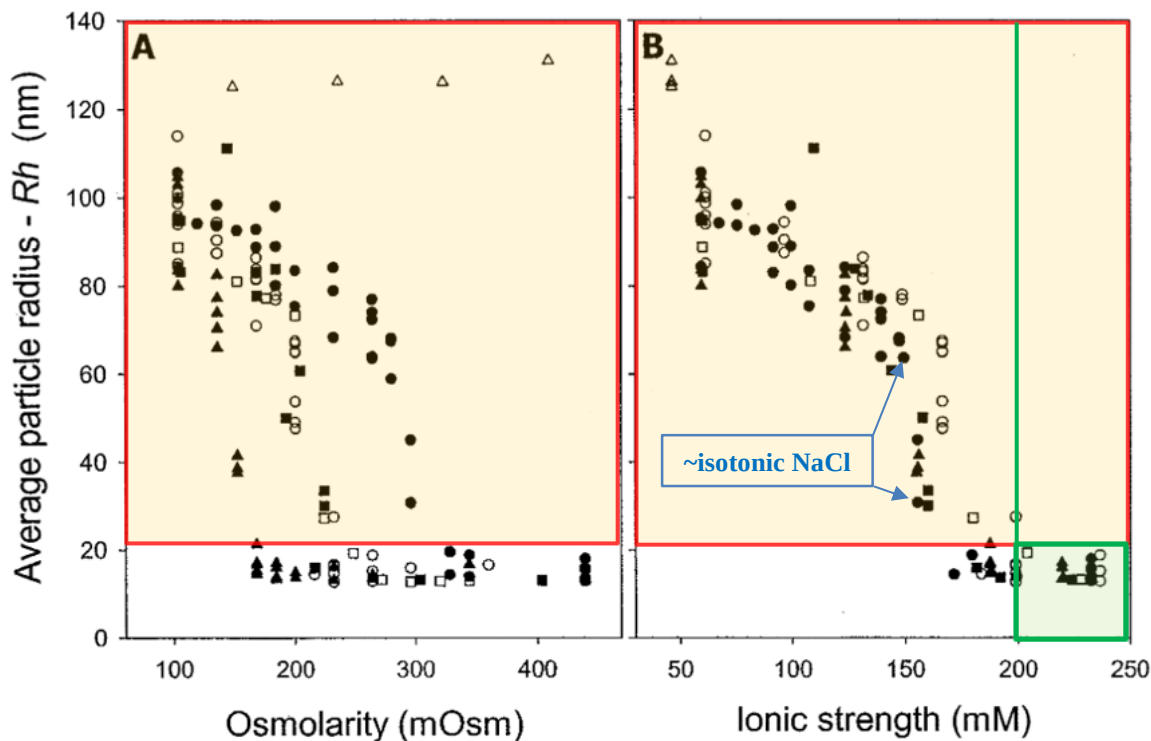
solutions...that are nonetheless isotonic with the intended target tissue...achieved using salts of high valency.” *Id.* The inventors studied vector aggregation in solutions of sodium chloride, sodium citrate, sodium phosphate, sodium sulfate, magnesium sulfate, and glycerol, and tracked aggregation as a function of two parameters, osmolarity (Figure 1A) and ionic strength (Figure 1B). *Id.*, 6:62-64, 12:33-13:3 (Example 3), FIGS. 1A, 1B.

Osmolarity is a measure of the number of particles of solute per liter. For a salt that fully dissociates, like NaCl, there are two solute particles, one Na^+ and one Cl^- , for every equivalent of NaCl. EX2023 (“Davies”), ¶¶31-34 (citing EX2016, 56-58). Therefore, the osmolarity of NaCl, expressed in osmols, is double its molarity. *Id.*, ¶34 (citing EX2016, 58). For magnesium chloride (MgCl_2), which contains three particles of solute, one Mg^{2+} and two Cl^- ions, the osmolarity is triple the molarity of MgCl_2 . *Id.*, ¶35. A concept related to osmolarity is tonicity. A therapeutic preparation is isotonic with human serum if it has the same osmolarity as human serum, hypertonic if its osmolarity is greater than human serum, or hypotonic if its concentration is less than human serum. *Id.*, ¶¶36-37. When administered, hypotonic and hypertonic preparations can cause pain and even tissue damage, so formulators seek to make preparations that are isotonic with human serum. *Id.*, ¶¶38-40.

“Ionic strength . . . is a measure of the intensity of the electrical field in a solution,” and it increases exponentially as a function of an ion’s charge. *Id.*, ¶41 (citing EX2016, 5). A 100 mM NaCl solution has an osmolarity of 200 mOsm and an ionic strength of 100 mM, whereas a 100 mM MgCl₂ solution has an osmolarity of 300 mOsm and an ionic strength of 300 mM. *Id.*, ¶¶42-43. This illustrates that the ionic strength of multivalent ion-containing salts (*e.g.*, MgCl₂) is higher per osmol than salts of monovalent ions (*e.g.*, NaCl). *Id.*, ¶¶43-45.

Figures 1A and 1B present data showing aggregation of AAV vector particles as a function of osmolarity and ionic strength, respectively. EX1001, 4:11-13; Davies, ¶62. In Figures 1A and 1B, “[a]verage 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.*, 4:15-18; Davies, ¶¶49-51. Given that the average radius of these viral particles is approximately 13 nm and “Rh values >20 nm are deemed to indicate the occurrence of some level of aggregation,” this indicates the level of aggregation. *Id.*, 9:25-27; Davies, ¶¶63-64.

In annotated Figures 1A and 1B below, the excipients are denoted as follows: sodium chloride (NaCl) (●), sodium citrate (Na₃(C₆H₅O₇)) (○), sodium phosphate (Na₃(PO₄)) (▪), sodium sulfate (Na₂(SO₄)) (□), magnesium sulfate (Mg(SO₄)) (▲), and glycerol (C₃H₈O₃) (Δ):



Id., FIGS. 1A, 1B (annotation added). In both Figures, preparations falling within the orange shaded portion of the plots exhibited significant aggregation ($R_h > 20$ nm), whereas preparations in the unshaded or green shaded portions of the plot did not ($R_h < 20$ nm).

The results of Figure 1A, which plots particle radius as a function of osmolarity, showed no consistent relationship between aggregation and osmolarity across the tested excipients. At the extremes, “magnesium sulfate [(▲)] prevent[ed] aggregation at >200 mOsm whereas sodium chloride [(●)] require[d] ≥ 350 mOsm to achieve a similar effect,” while glycerol (Δ) never prevented aggregation even at >400 mOsm. *Id.*, FIG. 1A, 6:67-7:7 (Stating that “[s]odium

citrate, sodium sulfate, and sodium phosphate are intermediate in their potency to prevent vector aggregation”); Davies, ¶65.

Figure 1B shows data from the same experiment “plotted as a function of the calculated ionic strength, rather than osmolarity, for each excipient.” *Id.*, 7:17-19. In contrast to Figure 1A’s particle radius versus osmolarity plot, Figure 1B’s plot of particle radius versus ionic strength shows a clear trend; “vector aggregation is prevented when **ionic strength is ~200 mM or greater** regardless of which salt is used” as shown by the green line at 200 mM ionic strength in annotated Figure 1B, above. *Id.*, 7:19-21.² These data led to the breakthrough “that the ionic strength (μ) of a solution ... is the **primary factor affecting aggregation.**” *Id.*, 7:21-24. The green box in annotated Figure 1B illustrates the scope of claim 6 requiring both “an ionic strength of at least 200 mM” and an “average particle radius (R_h) of the virions in the preparation of virions is less than about 20 nm as measured by dynamic light scattering.” *Id.*, 14:19-20, 14:34-36; Davies, ¶66.

The identification of ionic strength as a key to preventing aggregation unlocked a new path. This innovative method of preventing rAAV aggregation allowed for isotonic preparations that could be used for human parenteral administration by employing multivalent ions to adjust ionic strength. As the

² Emphasis is added unless otherwise noted.

inventors explained, “[o]f practical concern, commonly used buffered saline solutions have insufficient ionic strength to prevent AAV2 vector aggregation at concentrations exceeding 10^{13} particles/mL.” *Id.*, 4:62-64. “Isotonic (150 mM) [NaCl] has an ionic strength of 150 mM, a value insufficient to maintain AAV2 solubility at high vector concentrations,” as shown in annotated Figure 1B. *Id.*, 5:12-14. Thus, making a concentrated rAAV preparation in NaCl would require the formulation to be hypertonic. *Id.*, 5:1-4; Davies, ¶67.

Because of the exponential relationship between ionic strength and charge valency, “multivalent ions” (*i.e.*, ions having a charge of two or more) “achieve a similar degree of inhibition of aggregation at lower concentrations than monovalent [NaCl],” for which Na^+ and Cl^- only contribute one charge each. *Id.*, 6:67-7:2. Davies, ¶68; *see also id.* ¶¶42-45. The inventors recognized and capitalized on the “exponential relationship of ionic strength with charge [v]alency ... to develop isotonic formulations with high ionic strengths.” EX1001, 5:5-7. Preparations containing multivalent ions, including pharmaceutically acceptable excipients containing citrate, sulfate, magnesium, and/or phosphate can be formulated with an ionic strength of at least 200 mM, while remaining isotonic, because multivalent ions have high ionic strength even at low concentrations.

The inventors analyzed data from particle size detection (*id.*, 9:5-50 (Table 3)) and percent product recovery following filtration (*id.*, 7:65-8:40 (Table 2))

experiments to confirm that high ionic strength preparations did not exhibit significant rAAV aggregation. The inventors prepared three solutions for AAV2-AADC vectors: “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.*, 11:65-12:2. 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.*, 12:3-11; Davies, ¶69.

In Example 2, the exemplary formulations were filtered through a 0.22 μ m filter. *Id.*, 8:1-9, 11:51-12:30. Table 2 summarizes the results of Experiments 1 and 2. *Id.*, 8:19-44.

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)

As Table 2 shows, recoveries exceeded 90% following filtration in formulations TF1 and TF2 having ionic strengths of at least 200 mM, whereas recovery from CF formulations, having ionic strength of less than 200 mM, was only 77% and 59% for experiments 1 and 2, respectively. Davies, ¶¶70-71.

The inventors also conducted storage and freeze-thaw (“F/T”) cycle studies on the CF, TF1, and TF2 formulations, with the results presented in Table 3, in which particle radius was measured by DLS to determine the presence of aggregates. *Id.*, 9:5-65; Davies, ¶72.

TABLE 3

STABILITY OF AAV2 VECTORS								
Formu- lation	Particle radius - Rh (nm)							
	4° C.		-20° C.			-80° C.		
	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.

“As shown in Table 3 ... CF shows some aggregation after 5 days For vector prepared in TF1, no aggregation occurs after 5 days [of storage] at 4° C For vector prepared in TF2, no aggregation is observed at 4° C., or following up to 10 F/T cycles at -20° C” *Id.*, 9:44-55. These studies further confirmed the importance of increased ionic strength in preventing aggregation. *Id.*, 10:28-42; Davies, ¶73.

B. Challenged Claims

Challenged claim 1, from which claims 2-4, 6, 7, and 11 depend, recites, *inter alia*:

- “A method of preventing aggregation of recombinant adeno-associated virus (rAAV) virions in a purified preparation of rAAV virions, comprising”
- “adding one or more salts of multivalent ions selected from the group consisting of citrate, phosphate, sulfate and magnesium to said purified virions to produce a preparation of virions with an ionic strength of at least 200 mM;” and
- “the concentration of purified rAAV virions in said preparation exceeds 1×10^{13} vg/ml up to 6.4×10^{13} vg/ml.”

C. Sarepta Acknowledged the Importance of the Claimed Method of Preventing rAAV Aggregation through High Ionic Strength

In regulatory documentation relating to the development of its proprietary gene therapy product, Elevidys®, Sarepta acknowledged the importance of the inventors’ discovery that high ionic strength is critical to preventing rAAV aggregation. The Biological License Application (“BLA”) for Elevidys® cites a publication co-authored by the inventors of the ’721 patent, John Fraser Wright, and Guang Qu, describing the importance of high ionic strength for preventing rAAV aggregation. EX2005 (citing EX1047, “Wright (2005)”). Sarepta’s BLA states that the “extent of AAV aggregation is a critical concern for safety and efficacy in a drug product. It has been reported in the literature that ionic strength is critical for the minimization of AAV aggregation (Wright 2005).” *Id.*

Wright (2005) describes the inventors' discovery that "an ionic strength of ≥ 200 mM was required to prevent aggregation" for high-concentration rAAV particle preparations. EX1047, 6. The Wright (2005) disclosure substantially overlaps with the '721 patent's disclosure. *Compare* EX1001, Figs. 1-3, Tables 1-3 *with* EX1047, Figs. 1-2, Tables 1-3. Thus, by Sarepta's own account, the claimed method of preventing rAAV aggregation by making high ionic strength rAAV preparations is critical to the safety and efficacy of Elevidys[®].

D. Claim Construction

For this Preliminary Response only, Genzyme does not challenge the Petition's alleged constructions. Petition, 30-31.

III. THE PRIOR FAILED IPR CHALLENGES OF SUBSTANTIALLY SIMILAR CLAIMS

Two prior IPR petitions challenging the '542 patent were denied institution on the merits in detailed decisions. *Novartis Gene Therapies, Inc. v. Genzyme Corp.*, IPR2023-00608, Paper 20 (PTAB Aug. 30, 2023) (EX1017); *Novartis Gene Therapies, Inc. v. Genzyme Corp.*, IPR2023-00609, Paper 22 (PTAB Aug. 30, 2023) (EX1018). The claimed compositions in the '542 patent share the same elements as the '721 patent's "preparation of virions," including elements relating to the addition of multivalent salts, ionic strength, rAAV concentration, and pH required by all challenged claims.

A. The Board Found that the Prior Petitions Failed to Establish a Motivation to Prepare High-Concentration rAAV Compositions at High Ionic Strength

Both prior institution denials found that the petitions and cited art failed to establish that a POSA would have been motivated to make rAAV compositions with an ionic strength of at least 200 mM as required by all the presently challenged claims. EX1017, 23-24; EX1018, 27 n.10. The Board found that although the prior art disclosed ranges of ionic strengths that, in some cases, overlapped with the claims, it was not known that ionic strength was a “result-effective variable” for rAAV aggregation. *Id.* In both institution denials, the Board further found that petitioner, Novartis, could not show a likelihood of obviousness where it “fail[ed] to demonstrate the ionic strength was a recognized result effective variable” and “fail[ed] to establish a known relationship between ionic strength and viral particle aggregation.” EX1017, 23-24; EX1018, 26-27 n.10.

In IPR2025-00608, the Board found that Novartis’ citation of Evans (EX1020) specifically failed to establish a POSA’s motivation to make high ionic strength rAAV compositions. EX1017, 23-24. Notably, Sarepta relies heavily on Evans, as incorporated by Konz, for the motivation arguments in its Petition. §§ IV.B.3(b)(ii), VIII.A. Novartis’ ionic strength argument relied on disclosure from Evans’ claim 5 composition contain[ing] “‘sodium chloride from about 25 mM to about 250 mM’ and either MgCl₂ or CaCl₂ ‘in an amount from about 0.1 mM to

about 5 mM.” EX1014, 35 (citing EX1020, claim 5). Novartis argued that “[a]ccepting the high end of both ranges, Evans’s claim 5 composition comprising 250mM of NaCl and 5mM of MgCl₂ has an ionic strength of 265mM,” which exceeds the claimed ionic strength of 200 mM. *Id.* Novartis argued that a “POSA would have been motivated to select the high end of the concentration ranges for NaCl and MgCl₂ in Evans’ claim 5 composition” because “selection of an appropriate ionic strength for a therapeutic composition is a matter of routine optimization.” *Id.*, 36.

The Board, however, rejected Novartis’s arguments. The Board explained that “data presented in Evans does not establish any clear relationship between ionic strength and maintained infectivity after storage” such that a POSA would have reason to adjust ionic strength. EX1017, 23 (citing EX1016, 22-27). The Board also found that Novartis had failed “to establish a known relationship between ionic strength and viral particle aggregation. Rather, the evidence of record teaches 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.’” *Id.* (citing EX1045, 2; EX1016, 21; EX1060, ¶¶84-85). Because the art and argument did not demonstrate recognition of any connection between ionic strength and aggregation, it did not provide a reason for a POSA to arrive at the claimed ionic strength. The Board

concluded that the prior petitions did not establish a reasonable likelihood that the challenged claims were unpatentable.

B. Sarepta’s Petition Relies Heavily on the Same Art and Arguments Found Unpersuasive by the Board

Sarepta’s Petition falls squarely within the category of AIA challenges singled out in the Acting Director’s September 16, 2025 memorandum.³ The Petition challenges claims of the ’721 patent that are “substantially similar” to claims addressed in IPR2023-00608. All challenged claims depend from claim 1 and share elements, including the recited rAAV concentration range and an ionic strength of at least 200 mM.

Sarepta’s Petition does not warrant a different outcome than IPR2023-00608 because the Petition relies on the same citation to Evans’ NaCl concentration range to satisfy the ionic strength limitation that the Board found unpersuasive in its institution denial. Genzyme addressed this issue in its discretionary denial briefing in the context of 35 U.S.C. § 325(d). *See* Paper 8. Genzyme raises this issue here because Sarepta’s reliance on the same art and argument is also relevant to the recent memorandum’s guidance requiring a “more detailed explanation” if the

³ C. Morgan Stewart, PTAB Consideration of Prior Findings of Fact and Conclusions of Law (Sept. 16, 2025).

Board departs from its prior institution denials. There is no reason for the Board to make such a departure here.

Sarepta purports to rely on Konz (EX1008) for the ionic strength element, not Evans (EX1020). The Petition's sections on the ionic strength limitation, however, cite Konz only to the extent it "incorporates Evans by reference." Petition, 38-39, 58 (citing EX1020). This means Sarepta relies on Konz in name only.

Despite claiming its arguments are "materially different" (*id.*, 17 (citing EX1017, 17-21)), the Petition's ionic strength arguments substantively rely on the same disclosure in Evans as the petition in IPR2023-00608. The petition in IPR2023-00608 states "Evans's claim 5 composition comprising **250 mM of NaCl and 5mM of MgCl₂ has an ionic strength of 265 mM.**" EX1014, 35 (citing EX1020, claim 5); *see also id.*, 36-37 (citing EX1020, 9:16-20, 11:13-19); EX1017, 14, 18-20 (discussing Evans' sodium chloride concentration range disclosures cited in the petition (EX1014) and preliminary response (EX1016)). Sarepta's Petition states "Evans ... discloses formulation buffers ... [which include a multivalent ion, a non-ionic surfactant, and **NaCl at a concentration up to 250 mM**] A POSA would have understood that the **ionic strength of this buffer would be at least 250 mM.**" Petition, 38-39 (citing EX1020, 11:31-12:4, 14:15-28, 11:13-30, 36:21-22 (claim 4), 41:14-15 (claim 37)). Both IPR2023-00608 and this

Petition rely upon the same Evans disclosure of a buffer having ≥ 250 mM NaCl as being the major contributor to ionic strength.

After again relying on Evans for the ionic strength disclosure, and further repeating the failures of IPR2023-00608, neither Sarepta's Petition nor the Kay Declaration explain *why*, out of all the buffers in Evans ranging from low (25 mM) to high (>250 mM) ionic strength, a POSA would have chosen the >250 mM buffer. EX1005, ¶¶316-317, 390-391. Similarly, the Petition states that "Konz also discloses choosing formulation buffers to maximize product stability" by "refer[ring] to a PCT publication (Evans), which it incorporates by reference." Petition, 35 (citing EX1008, 22:15-16; EX1005, ¶292); *see also id.*, 54 (citing EX1008, 22:15-16; EX1005, ¶374). But neither the Petition nor Kay Declaration explain where Konz discloses any specific high ionic strength buffer system from Evans for use in its viral particle aggregation analysis. *Id.* Where Konz discloses "formulation buffers," they contain between 10 mM and 75 mM of NaCl. EX1008, 25:20-27. The 10 mM and 75 mM NaCl concentrations in Konz's "formulation buffers" are far below the NaCl concentration of 250 mM cited by the Petition. Sarepta ignores that Konz undercuts the Petition's alleged motivation to prevent aggregation by making rAAV preparations with a high ionic strength buffer. A POSA following Konz would have made a formulation buffer containing 10 to 75

mM NaCl, which would have an ionic strength well below the claimed 200 mM threshold. *Infra* §IV.A.1.c.i.

The Petition suffers from the same fatal flaw as IPR2023-00608: it fails to explain why a POSA would choose a high ionic strength buffer over the lower ionic strength formulation buffers favored by both Evans and Konz. Sarepta alleges that “background, state of the art references” from the 1970s “demonstrate that a POSA at the relevant date would have been well aware that ionic strength was a ‘results-effective variable’ for viral particle aggregation.” Petition, 18 (citing EX1030; EX1031; EX1032). In fact, a POSA would not have considered these references because they relate to the disinfection of wastewater using toxic chemicals, including chlorine and bromine, to destroy viral infectivity. *Infra* §IV.A.1.f. Sarepta fails to establish why a POSA “in the field of gene therapy, including development of viral vector formulations” (EX1005, ¶163) that sought to maximize the infectivity of viral particle-based gene therapies would consider literature about disinfecting sewage. Sarepta fails to supply any reason for the Board to decide this Petition differently than the prior IPRs. Denial of institution is warranted.

IV. THE PETITION FAILS TO ESTABLISH A REASONABLE LIKELIHOOD THAT CLAIMS 1-4, 6, 7, AND 11 ARE OBVIOUS

Sarepta fails to meet its burden to establish a reasonable likelihood that a method of preventing aggregation of rAAV virions in a purified preparation “with

an ionic strength of at least 200 mM, wherein the concentration of purified rAAV virions in said preparation exceeds 1×10^{13} vg/ml up to 6.4×10^{13} vg/ml” was obvious. Sarepta’s arguments for Grounds 1 and 2 have at least four major failings, any one of which results in the Petition’s failure to prove the challenged claims obvious.

The Petition alleges that a POSA would have been motivated to use high salt concentrations disclosed in Auricchio, Potter, and Konz/Evans to achieve high ionic strength rAAV preparations. Petition, 35, 38-39, 57-58. However, it fails to establish that a POSA would have had any motivation to increase ionic strength ***to prevent aggregation***. The cited art does not establish any connection between rAAV aggregation and ionic strength.

State of the art references from before 2004 undermine Sarepta’s motivation argument. Sarepta alleges that a POSA would have been motivated to prevent aggregation by making a high salt concentration rAAV preparation to reach the claimed ionic strength. A POSA understood, however, that high salt concentration solutions are “hypertonic.” Hypertonic solutions were known to cause tissue damage and pain upon injection. This would have led a POSA to avoid making a high salt concentration rAAV preparation.

Prior art publications also showed that high salt concentrations destabilized viral particles. This would have further deterred a POSA from high salt concentration rAAV preparations.

Finally, the Petition fails to establish that a POSA would have reasonably expected that the claimed high-concentration rAAV preparation having an ionic strength of at least 200 mM would prevent aggregation.

A. Ground 1: The Petition’s Combination of Auricchio and Konz Fails to Render Claims 1-4, 6, 7, and 11 Obvious

Sarepta assembles several disclosures from Auricchio and Konz, alleging that the combined references satisfy each element of the claimed “method of preventing aggregation of recombinant adeno-associated virus (rAAV) virions in a purified preparation of rAAV virions,” including: (i) “an ionic strength of at least 200 mM” and (ii) “wherein the concentration of purified rAAV virions in said preparation exceeds 1×10^{13} vg/ml up to 6.4×10^{13} vg/ml.” But “a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” *KSR*, 550 U.S. at 418.

“Failure to consider the claimed invention as a whole,” as Sarepta does here, “is an error of law.” *Jones v. Hardy*, 727 F.2d 1524, 1529 (Fed. Cir. 1984); *see also Rockwell Int’l Corp. v. United States*, 147 F.3d 1358, 1364 (Fed. Cir. 1998); *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1548 (Fed. Cir. 1983).

1. The Petition Fails to Establish a Motivation to Arrive at an Ionic Strength of at Least 200 mM

Sarepta never explains “how or why the references would be combined to produce the claimed invention.” *TriVascular, Inc. v. Samuels*, 812 F.3d 1056, 1066 (Fed. Cir. 2016). Neither Auricchio nor Konz discloses any connection between rAAV aggregation and ionic strength. Davies, ¶¶76-80. In fact, Sarepta does not point to any prior art connecting ionic strength with rAAV aggregation at high rAAV concentrations. This failure is unsurprising. In 2003, shortly before the effective filing date, the “mechanism of vector aggregation [was] ***not well understood.***” EX1045, 2. The cited prior art does not contradict this lack of understanding. Thus, Auricchio and Konz alone, or in combination, do not provide a POSA with any reason to prevent rAAV aggregation by making a preparation with an ionic strength of at least 200 mM. In fact, the cited art points away from the claimed ionic strength.

a. The Petition Fails to Establish that Auricchio and Konz Connect Ionic Strength and rAAV Aggregation

There are several reasons why Auricchio and Konz would not lead a POSA to the claimed method. Sarepta fails to identify where Auricchio or Konz, alone or in combination, connect ionic strength with rAAV aggregation in high-concentration rAAV preparations. In fact, Sarepta also fails to identify any correlation in the prior art between ionic strength and any advantageous property

associated with an rAAV preparation, such as rAAV infectivity or stability.

Davies, ¶¶83-84.

The Petition states that “Auricchio is directed to preventing aggregation of purified rAAV.” Petition, 35. Sarepta’s contention is erroneous. Auricchio relates to the development of a technique to purify AAV2 without the need for CsCl or HPLC. EX1007, 1-2; Davies, ¶¶85-86. As the Petition acknowledges, “Auricchio teaches that purified rAAV2 is not stable in CsCl.” Petition, 22 (citing EX1007, 2-3, 6, Fig. 1; EX1005, ¶171). Auricchio, however, does not attribute the instability caused by CsCl to AAV2 aggregation. Instead, Auricchio attributes this low infectious titer to the presence of “CsCl₂ itself,” which might have motivated a POSA to use AAV purification methods that avoid CsCl. EX1007, 2-3. It would not, however, motivate a POSA to connect increased ionic strength with prevention of rAAV aggregation. Thus, a POSA would not have considered Auricchio relevant to preventing rAAV aggregation. Davies, ¶86.

Konz similarly provides no connection between ionic strength and preventing aggregation in high-concentration viral vector particle preparations. Davies, ¶87. The Petition states that Konz also discloses methods to inhibit particle aggregation and promote stability during storage, including by reference to Evans. Petition, 35-36. Sarepta ignores that Konz’s “sterile filtration” and “DLS” studies were conducted on preparations having viral particle concentrations at magnitudes

below the claimed 1×10^{13} vg/ml threshold. Petition, 27 (citing EX1008, 30:13-30 (The purified adenovirus product “will be diluted to *ca.* 1.1×10^{12} vp/mL”)); see *also* EX1008, 42:4-19 (“The product peak was diluted and adjusted to an adenovirus concentration of approximately 1.05×10^{12} vp/mL”), 48:4-5 (disclosing adenovirus concentrations ranging from 1.83×10^{10} vp/ml to 3.55×10^{12} vp/ml).

Konz’s particle concentration would be understood to include empty and partially filled capsids, in addition to particles with complete viral genomes. A POSA would have understood that a concentration in vp/ml could have as much as a ***10-fold excess in empty capsids***, which would mean that Konz’s most concentrated preparations of $\sim 10^{12}$ vp/ml could have a viral ***genome*** concentration of only $\sim 10^{11}$ vg/ml, which is 100-fold lower than the claimed rAAV concentration of 1×10^{13} vg/ml. Davies, ¶88.

A POSA would have also understood that rAAV particle aggregation was especially a problem at high rAAV concentrations (e.g., $>10^{13}$ vg/ml). Thus, a POSA would not have considered Konz relevant to overcoming the challenge of rAAV aggregation at high concentrations. *Id.*, ¶¶88-89. Moreover, even at lower concentrations, Konz does not address how ionic strength impacts viral particle aggregation.

Finally, because Konz's "formulation buffers" have ionic strengths far below 200 mM, Konz does not give a POSA any reason to increase ionic strength to prevent rAAV aggregation. *Id.*, ¶90.

b. Auricchio Would Not Have Motivated a POSA to Prevent Aggregation by Making a High Ionic Strength rAAV Preparation

A POSA would understand that (1) Auricchio's high concentration of NaCl in its elution solvent is unrelated to preventing aggregation, but rather was used only for eluting AAV2 from a column, and (2) Auricchio teaches lowering the NaCl concentration to physiological levels for any therapeutic composition. To the extent that Sarepta argues that Auricchio teaches the use of high concentrations of NaCl, Auricchio does not connect this use to preventing aggregation, which the claims require. A POSA would not read Auricchio as teaching that adding 0.4 M NaCl to an rAAV preparation does anything to prevent aggregation.

Sarepta cherry picks, out of context, the elution solvent disclosed in Auricchio's single-step column purification ("SSCP") protocol, which the Petition alleges to have an ionic strength of 550 mM. Petition, 38 (citing EX1007, 2; EX1005, ¶306). Sarepta cannot prove that the claimed ionic strength was obvious, however, "merely by demonstrating that [it] was, independently, known in the prior art." *KSR*, 550 U.S. at 418. Auricchio discusses its elution solvent, which contains 400 mM NaCl, only in the context of eluting rAAV2 from the heparin

column. The SSCP protocol in Auricchio states that most NaCl is removed once the product has eluted. EX1007, 2; Davies, ¶¶91-92. Specifically, Auricchio describes “adjust[ing] the NaCl concentration [of its preparation] to physiological levels.” *Id.* In separate sections, the Petition and Kay Declaration acknowledge that Auricchio adjusts the NaCl concentration to “physiological levels by refilling the filter device with PBS pH 7.4.” Petition, 24 n.2; EX1005, ¶179. The physiological level of NaCl, which is 154 mM, has a lower ionic strength than claimed in the ’721 patent. Davies, ¶93.

Auricchio thus does not connect the ionic strength of the elution solvent to preventing aggregation or even to improving stability of its rAAV preparation. If Auricchio had made such an observation, its authors would not have reduced the NaCl concentration, and thereby the ionic strength of the AAV2 preparation, right after the elution step. Davies, ¶92. This signals to a POSA that NaCl and ionic strength were not relevant to Auricchio’s SSCP protocol or to the aggregation of AAV2 particles in Auricchio’s formulations. Davies, ¶97. Auricchio’s elution solvent, therefore, would not have motivated a POSA to make an rAAV preparation with an ionic strength of at least 200 mM to prevent aggregation. There is nothing in Auricchio that teaches or suggests that ionic strength is relevant to the aggregation of AAV2 particles in Auricchio’s formulations.

Based on Auricchio's NaCl concentration reduction step, a POSA also would not have understood Auricchio to advocate for an AAV2 preparation with 400 mM of added NaCl to prevent aggregation. The Kay Declaration has no support for this contention. Indeed, a POSA would have considered such high NaCl concentrations unsuited to therapeutic use. *See infra* §IV.A.1.d.i. Physiological NaCl concentration is about 154 mM. Davies, ¶93. According to the Kay declaration, the Auricchio PBS²⁺ buffer system contains 138 mM NaCl. EX1005, ¶¶314-315. Auricchio adds another 400 mM NaCl to this amount, for a total NaCl concentration of 538 mM. *Id.* A POSA would have understood that Auricchio removes all but 154 mM of NaCl from its AAV2 preparation following its elution from the column. Davies, ¶¶94-96.

According to Dr. Kay's calculations, 138 mM of the ionic strength in Auricchio's PBS²⁺ buffer is from 138 mM of NaCl. EX1005, ¶314. This means only 16 mM of added NaCl can remain in Auricchio's AAV2 preparation once it is adjusted to the physiological NaCl concentration of 154 mM. Davies, ¶¶95-96. This purported 16 mM of NaCl would contribute 16 mM of ionic strength to the AAV2 preparation. For the sake of argument, accepting the assumptions in the Kay Declaration that the ionic strength calculations are at pH 7.5 and pH 8.0, which are higher than Auricchio's pH 7.4 buffer (Ex. 1007, 2), the PBS²⁺ buffer contributes ionic strength values of 166 and 169 mM to the preparation. The remaining 16 mM

of NaCl would add 16 mM of ionic strength, for totals of about 182 mM and 185 mM. Davies, ¶96. Both values are below the 200 mM threshold of the claims.

Based on Auricchio's SSCP protocol, a POSA would have been motivated to **reduce** the NaCl concentration from the elution solvent to a physiological concentration. This is consistent with a POSA's typical approach to formulations, which emphasized isotonicity and lower NaCl concentrations. *See infra* §IV.A.1.d.i. Thus, Auricchio would have motivated a POSA to make an AAV2 preparation having an ionic strength considerably below 200 mM. Davies, ¶98.

c. Konz/Evans Would Not Motivate a POSA to Prevent Aggregation of rAAV by Increasing Ionic Strength to at Least 200 mM

For the ionic strength element, the Petition relies on Konz's incorporation of Evans by reference. Petition, 38-39. To reach the claimed ionic strength of at least 200 mM, Sarepta argues that a POSA would have prepared an rAAV preparation by adding the maximum amount of sodium chloride (NaCl), 250 mM, disclosed in Evans. Petition, 38-39 (citing EX1005, ¶316). The Board, however, has already found that Evans would not have motivated a POSA to make rAAV preparations with an ionic strength of at least 200 mM to prevent aggregation. *Supra* §III.A. By relying on Konz's incorporation of Evans, Sarepta's argument is even weaker. Konz did not select Evans' highest NaCl concentration buffer to make its rAAV preparation. Instead, Konz's formulation buffers contain from only 10 mM to 75

mM NaCl. Konz confirms that a POSA would also select a much lower salt concentration buffer from Evans than Sarepta alleges. Davies, ¶¶99.

i. Sarepta Disregards that Konz’s Formulation Buffers All Have Ionic Strengths Far Below 200 mM

Sarepta disregards that Konz discloses several formulation buffers, all of which contain a fraction of NaCl compared to the maximum 250 mM NaCl concentration in Evans. Davies, ¶¶100-101. Right after Konz references Evans (WO 0166137), Konz discloses a list of what it refers to as “formulation buffer[s].”

The particular diafiltration buffer chosen should be an appropriate formulation buffer (see WO 0166137) or a subset of the desired components. Examples include, but are not limited to (1) 5 mM Tris, 1 mM MgCl₂, **75 mM NaCl**, 5% sucrose, 0.005% PS-80, pH 8.0, (2) 10 mM Tris, 10 mM Histidine, 1 mM MgCl₂, **75 mM NaCl**, 5% sucrose, 0.005% PS-80, pH 7.4, (3) 5 mM Tris, 10 mM NaCl, 1 mM MgCl₂, 5% sucrose, 0.005% PS-80, pH 7.4, and (4) 10 mM Tris, 10 mM Histidine, 1 mM MgCl₂, **75 mM NaCl**, 5% sucrose, 0.02% PS-80, 0.1 mM EDTA, 0.5%(v/v) ethanol, pH 7.4.

EX1008, 25:20-27. Each of Konz’s formulation buffers contain only 75 mM NaCl. The ionic strength contribution of the 75 mM NaCl in Konz’s formulation buffers would be only 75 mM. Davies, ¶¶102-103.

Konz discloses several other formulation buffers, none of which have a NaCl concentration exceeding 75 mM. *Id.*, ¶104.

The AEX product will be diluted to $ca. 1.1 \times 10^{12}$ vp/mL (approximately 16 liters) and is then diafiltered using flux control against 5 volumes of formulation buffer (5 mM Tris, 1 mM MgCl₂, **75 mM NaCl**, 5% sucrose, 0.005% PS-80, pH 8.0).

EX1008, 30:16-19.

The batch was diafiltered into formulation buffer (5 mM Tris, **75 mM NaCl**, 1 mM MgCl₂, 5% sucrose, 0.005% PS-80, pH 8.0).

Id., 42:14-15.

The batch was diafiltered into buffer (5 mM Tris, **10 mM NaCl**, 1 mM MgCl₂, 5% sucrose, 0.005% PS-80, pH 7.4).

Id., 52:31-32.

Konz, therefore, specifically exemplifies formulation buffers having NaCl concentrations ranging from 10 mM to 75 mM, which contribute only 10 mM to 75 mM ionic strength to Konz's enumerated formulations. The other formulation buffer components do not increase this ionic strength significantly. Davies, ¶105.

ii. Sarepta Disregards the Totality of Evans' Buffer Disclosure

Because Konz directs a POSA to buffers having ionic strengths far below the claimed 200 mM, Sarepta's ionic strength argument relies on Konz's incorporation by reference of Evans. Petition, 38-39. The Petition cites Evans' disclosure of buffers that would yield a range of NaCl concentrations from 25 mM to 250 mM, but it relies specifically on the endpoint concentration of 250 mM

NaCl for the ionic strength element. Petition, 38-39 (citing EX1020; EX1005, ¶¶316-317). But the “disclosure of a range ... does not constitute a specific disclosure of the endpoints of that range.” *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 1000 (Fed. Cir. 2006). For a range to render a value obvious, a parameter must first be recognized as a “result-effective variable.” *In re Antonie*, 559 F.2d 618, 620 (CCPA 1977). Sarepta fails to establish that Evans’ disclosure would render ionic strength a result-effective variable.

First, Evans itself does not contain any disclosure regarding particle aggregation. Davies, ¶106. Although the Petition alleges that Konz uses Evans’ buffer systems in particle aggregation studies, the formulation buffers evaluated by Konz all have ionic strengths far below 200 mM. There are no examples in Konz or Evans of rAAV preparations containing Evans’ outer endpoint concentration of 250 mM NaCl. Indeed, although Konz incorporates Evans by reference, it exemplifies only formulation buffers with a maximum of 75 mM NaCl. Davies, ¶107. This is strong evidence that a POSA would not have focused on Evans’ endpoint concentration as relevant or advantageous to preventing aggregation in high-concentration rAAV preparations.

Second, the Petition omits that Evans conducted stability testing only on formulations having viral particle concentrations ranging from 10^7 to 10^{11} vp/ml, which are orders of magnitude below the claimed 1×10^{13} vg/ml concentration.

Davies, ¶106. EX1020, 24:22 and 25:13-14 (Example 2), 25:31-32 and 26:4 (Example 3), 29:6 (Example 7), 30:14 (Example 9). As explained above for Konz, an rAAV concentration expressed in vg/ml can be as much as 100-fold lower than its concentration expressed in vp/ml. *Supra* §IV.A.1.a. A POSA would have understood that rAAV particle aggregation was a more significant issue at high rAAV concentrations (e.g., $>10^{13}$ vg/ml). Given their substantially lower vector genome concentrations, neither Konz nor Evans would have been considered by a POSA as relevant to addressing the challenge of preventing aggregation of rAAV virions at concentrations greater than 10^{13} vg/ml. *Infra* §IV.A.1.a

Evans' stability study examples contradict Sarepta's argument that a POSA would have been motivated to select the upper end of the concentration ranges for NaCl in Evans' buffer system. All examples in Evans utilized NaCl concentrations of 75 mM or 150 mM NaCl, and none would have directed a POSA toward NaCl concentrations above 200 mM. Evans contained other ionic species, such as $MgCl_2$ and Tris, but these were present at such low concentrations that they did not contribute significantly to the total ionic strength of these preparations. Davies, ¶107.

In addition, Evans' stability studies indicated an inverse relationship between NaCl concentration and formulation stability. Specifically, formulations with higher concentrations of NaCl exhibited **less** stability and infectivity. Evans'

exemplary formulations A105 and A104 differ only by their NaCl concentrations (150 mM NaCl in A104, 75 mM NaCl in A105) and the presence of 5% sucrose in A105 versus no sucrose in A104. The Table below compares these two formulations. Davies, ¶108.

Example	Description
A104	5mM Tris, 150 mM NaCl , 1 mM MgCl ₂ , 0.005% PS-80, pH 8.0
A105	5 mM Tris, 75 mM NaCl , 5% sucrose (w/v), 1 mM MgCl ₂ , 0.005% PS-80, pH 8.0

EX1020, 22:1-2. Despite these minor differences, the formulations exhibited vast differences in stability (*id.*, FIG. 2) and infectivity (*id.*, FIG. 3) after freeze-thaw cycles. *Id.*, 24:18-25:24 (Example 2). As demonstrated in Evans' Figure 2, the higher 150 mM NaCl concentration in A104 resulted in significant material loss after just a single freeze-thaw cycle. In contrast, A105—with its lower NaCl concentration of 75 mM—exhibited substantially better stability, retaining considerably more material under identical conditions. Davies, ¶109.

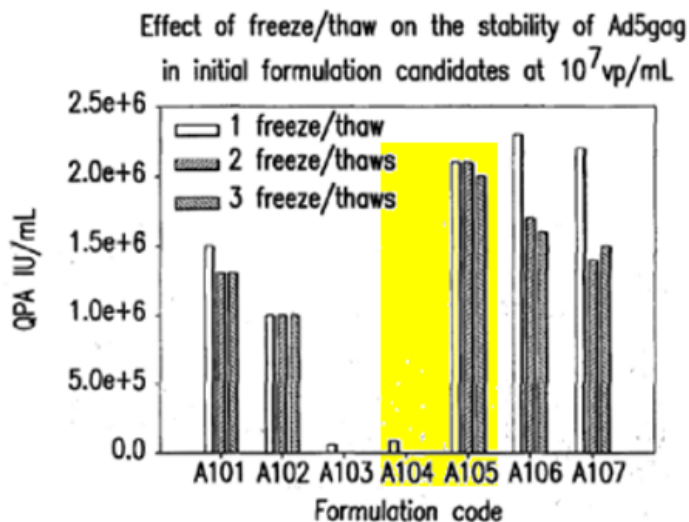


FIG.2

This pattern extended to infectivity measurements (*id.*, FIG. 3), further confirming that lower NaCl concentrations provided superior formulation performance. Figure 3 demonstrates that A105 also maintained much better infectivity than A104 after one freeze/thaw cycle. Thus, Evans' Example 2 indicates that a **lower NaCl concentration** was better for ensuring viral particle stability. Davies, ¶110.

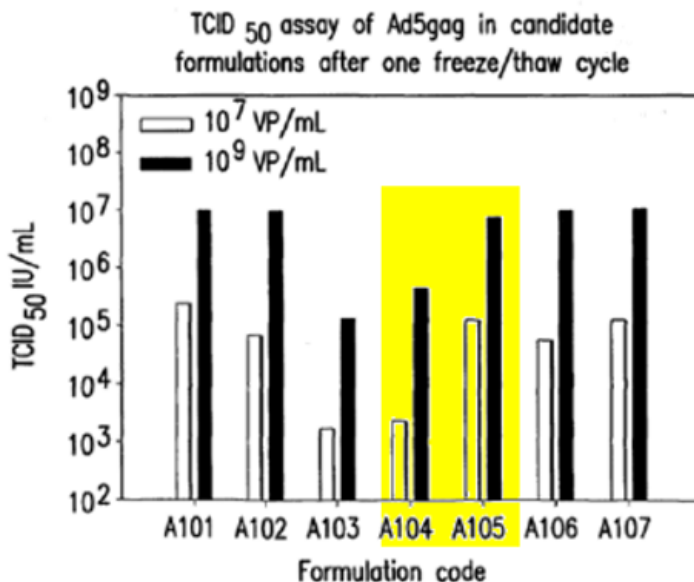


FIG.3

In the short-term stability study of Example 3, Evans compares the stability of Ad5gag in A102, A105, A106, and A107, at 10⁷ and 10⁹ vp/mL. *Id.*, 25:27-26:17. Shown below, A102 has the highest NaCl concentration (150 mM) of the tested formulations, whereas A105 has a lower NaCl concentration (75 mM), and A106 and A107 do not contain NaCl. Davies, ¶111.

Example	Description
A102	6mM phosphate, 150 mM NaCl , 10% glycerol (v/v), pH 7.2
A105	5 mM Tris, 75 mM NaCl , 5% sucrose (w/v), 1 mM MgCl ₂ , 0.005% PS-80, pH 8.0
A106	5 mM Tris, 14% sucrose (w/v), 1 mM MgCl ₂ , 0.005% PS-80, pH 8.0
A107	5 mM Tris, 8% sorbitol (w/v), 1 mM MgCl ₂ , 0.005% PS-80, pH 8.0

Figure 6 of Evans shows that of these formulations, A102, with the **highest NaCl concentration**, **lost significantly more infectivity** in 72 hours than A105, A106,

and A107, as shown below with A102's results highlighted. *Id.*, 26:3-17; Davies, ¶112.

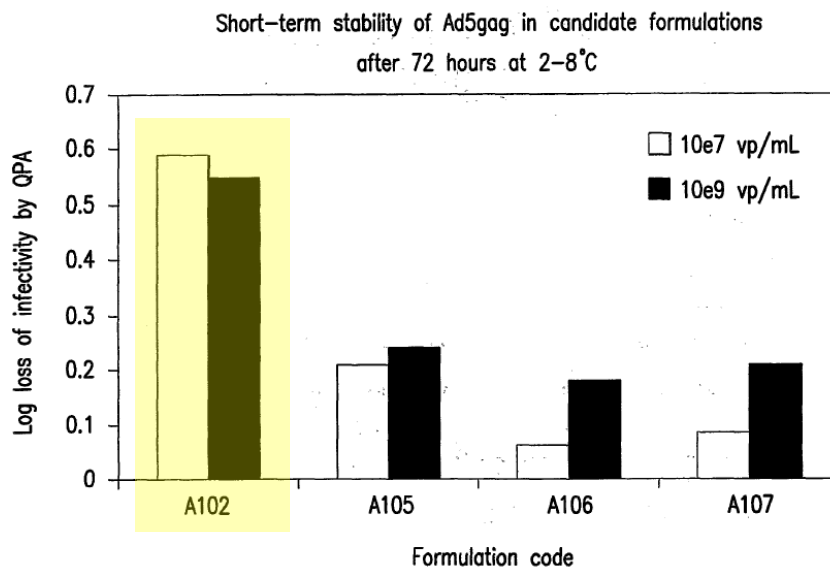


FIG.6

Evans' Example 10, which measured accelerated and real-time stability, also showed that formulations with higher NaCl concentrations, A102-A104 (each containing 150 mM NaCl), were less stable than A105, which contained a lower concentration of NaCl (75 mM NaCl). *Id.*, 30:17-25; Davies, ¶113.

In summary, Evans' studies consistently demonstrate that higher NaCl concentrations in rAAV formulations correlate with decreased stability and infectivity. Davies, ¶116. Across multiple experiments—including freeze-thaw cycles, short-term stability tests, and both accelerated and real-time stability assessments—formulations with lower NaCl concentrations (particularly 75 mM) consistently outperformed those with higher NaCl levels (150 mM). These findings

directly contradict Sarepta's assertion that a POSA would be motivated to select higher NaCl concentrations from Evans' disclosed range. Davies, ¶117.

In an obviousness analysis, "[e]vidence that supports, rather than negates, patentability must be fairly considered," as a POSA has "knowledge of the entire body of technological literature, including that which might lead away from the claimed invention." *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). The Petition's arguments have disregarded Evans' disclosure that supports patentability and refutes Sarepta's theory that a POSA would have been motivated to use Evans' high salt concentration buffer.

iii. Konz and Evans Both Direct a POSA to Ionic Strengths Lower than 200 mM

Sarepta's analysis violates a cardinal rule of obviousness law by selectively citing portions of the prior art while ignoring contradictory teachings within the same references. "It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *In re Wesslau*, 353 F.2d 238, 241 (CCPA 1965); *see also Henny Penny*, 938 F.3d at 1332; *W.L. Gore*, 721 F.2d at 1551.

Sarepta points to Auricchio's elution solvent containing 400 mM of added NaCl to argue that the claimed ionic strength element was obvious. Sarepta,

however, ignores Auricchio's own disclosure of significantly reducing the NaCl concentration down to physiological levels once the elution step is complete. This lowered the ionic strength of Auricchio's AAV2 preparation below 200 mM as well.

Similarly, Sarepta highlights Evans' 250 mM NaCl concentration endpoint, while disregarding that every single stability example in Evans and all of Konz's formulation buffers have ionic strengths well below the claimed 200 mM threshold. Notably, while Sarepta focused on Evans' 250 mM NaCl concentration, its actual reference, Konz, utilized NaCl concentrations ranging from only 10 mM to 75 mM. This narrow range alone demonstrates that a POSA would not have sought to prevent aggregation by adding high concentrations of NaCl.

Moreover, Evans' experimental data contradicts Sarepta's obviousness argument. Evans' stability studies showed that viral particle stability improved with lower ionic strength preparations containing 75 mM NaCl compared to higher ionic strength preparations containing 150 mM NaCl. This data directed a POSA away from high ionic strength buffers.

Indeed, the Board previously evaluated substantially the same evidence in the prior IPR challenges of the '542 patent and found it unpersuasive. *Supra* §III.B. Specifically, the Board explained that "data presented in Evans does not establish any clear relationship between ionic strength and maintained infectivity after

storage” such that a POSA would have reason to adjust ionic strength. EX1017, 23 (citing EX1016, 22-27). Sarepta’s evidence and arguments provide no reasons to disturb this finding.

d. The Prior Art Directed a POSA Away from Therapeutic rAAV Preparations with High NaCl Concentrations

The Petition and Kay Declaration fail to address the many reasons why a POSA would have been motivated *not* to use a high-concentration of NaCl to achieve a high ionic strength. Prior art evidence that was not considered by the Petition indicated that high salt concentrations, like the 400 mM of added NaCl in Auricchio and the 250 mM NaCl in Evans, were undesirable for therapeutic rAAV preparations. In fact, such high NaCl concentrations were observed to worsen rAAV stability. Davies, ¶118.

i. A POSA Would Have Avoided Preparations with High NaCl Concentrations that Are Hypertonic and Cause Tissue Damage and Pain When Injected

“Recognizing the difficulty of casting one’s mind back to the state of technology at the time the invention was made, courts have long recognized the usefulness of evidence of the contemporaneous attitude toward the asserted invention.” *Interconnect Plan. Corp. v. Feil*, 774 F.2d 1132, 1143 (Fed. Cir. 1985).

As of the effective filing date, a major concern that would have driven the development of therapeutic rAAV preparations was isotonicity. Davies, ¶119. The prior art “emphasize[d] the two formulation parameters, pH and tonicity, that are

usually associated with tissue damage and injection pain” and “provide[d] a parenteral product development outline” that include[d] guidance on ways in which pH and tonicity “may be modified to minimize tissue damage and pain caused by a parenteral product.” EX2019, 3-4; see also EX2017, 4 (“Solutions to be administered subcutaneously require strict attention to tonicity adjustment.”).

The POSA would have understood that to minimize tissue damage and pain, the osmolarity (total concentration of dissolved solutes in a solution) of therapeutic rAAV preparations should be close to serum osmolarity. Davies, ¶120. Serum osmolarity is about 300 mOsm. EX2016, 57. “Physiological solutions with an osmotic pressure lower than that of body fluids, or of 0.9% [~150 mM] sodium chloride solution, are referred to commonly, as being hypotonic. Physiological solutions having a greater osmotic pressure are termed hypertonic.” *Id.*, 55; see also EX1001, 5:13-14. A 300 mOsm NaCl solution is isosmotic with 300 mOsm serum, and thus isotonic. Davies, ¶120. Thus, a POSA would have understood that “optimal formulations for pre-clinical and clinical studies ***should be close to isotonic*** (280-400 mOsm), especially for *in vivo* administration of vector to sites where dilution of hypertonic solutions may be slow.” EX1001, 5:1-4. “For an isotonic product, often it is ***advantageous to keep the concentration of salt as low as possible.***” EX2018, 197.

Sarepta's obviousness argument relies on a POSA selecting Auricchio's elution solvent containing 138 mM NaCl from a PBS²⁺ buffer system with an added 400 mM NaCl, for a total of 538 mM NaCl. Petition, 38-39; EX1005, ¶¶306-315; Davies, ¶121. This buffer would have an osmolarity of over 1076 mOsm attributable to NaCl, or over 350% of serum osmolarity. Davies, ¶121. Sarepta's obviousness argument also relies on a POSA selecting the Evans buffer containing 250 mM NaCl and 5 mM MgCl₂. This buffer would have an osmolarity of 515 mOsm (500 mOsm from NaCl and 15 mOsm from MgCl₂), which is also much higher than 300 mOsm serum, and is therefore hypertonic. Davies, ¶121. A POSA, who would be concerned about the adverse effects of hypertonicity, including pain and tissue damage, would not have been motivated to use a buffer formulation with an osmolarity of 1076 mM or 515 mOsm. Davies, ¶¶122-123. Indeed, for its AAV2 preparation, Auricchio "adjust[ed] the NaCl concentration to physiological levels," presumably mindful of this concern. EX1007, 2. Evans taught that its virus formulations should be made "useful for parenteral, and especially intramuscular, injection." EX1020, 10:18-21. Thus, by focusing on suitability for clinical and therapeutic use, the state of the art emphasized that injectable formulations should be isotonic, particularly for "intramuscular delivery," which is Evans' "especially preferred method" of delivery. *Id.*, 20:17-18; Davies, ¶123.

Sarepta fails to prove obviousness by not explaining why a POSA focused on making preparations suitable for clinical use nonetheless would have been motivated to use high NaCl concentration hypertonic buffers discouraged for such use. *See Trivascular*, 812 F.3d at 1068 (finding no motivation to modify the prior art where doing so “would destroy the basic objective” of the prior art); *see also Chemours Co. FC, LLC v. Daikin Indus., Ltd.*, 4 F.4th 1370, 1376 (Fed. Cir. 2021), *cert. denied*, 142 S. Ct. 1418 (2022) (holding “the board did not adequately grapple with why a skilled artisan would find it obvious” to modify the prior art in a manner that would undermine a critical property of that art.). Neither Sarepta nor Dr. Kay explains why a POSA would have violated the principle of maintaining isotonicity when a POSA would have considered such an issue central to formulation development. Davies, ¶124.

Despite the evidence showing that isotonicity was an important consideration in preparing formulations, Sarepta argues for preparing formulations with NaCl concentrations that greatly exceed this isotonic threshold. Petition, 38-39. This contradiction exposes that Sarepta’s case for obviousness “is only straightforward in hindsight.” *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1355 (Fed. Cir. 2013).

ii. High Salt Concentrations Were Observed to Promote Precipitation of rAAV Particles

High salt concentration solutions were also observed to cause instability of rAAV particles. Davies, ¶125. For example, Xie (EX1028) explained that “[h]igh concentrations of AAV-2 in the ~3.3 M CsCl from ultracentrifugal purification remained mostly in solution at 4°C, although there was some precipitation and adhesion to glass- and plastic-ware with time....” EX1028, 7. Thus, even for *molar* salt solutions of CsCl having osmolarity of ~ 6600 mOsm that would be unsuitable as parenteral formulations, AAV particle precipitation was observed. Moreover, Xie further stated that a solution of “0.25 M NaCl [250 mM] resulted in **significant loss**” of AAV. *Id.* Thus, Xie teaches that a salt concentration of 250 mM NaCl, the NaCl concentration that Sarepta advocates (Petition, 38-39), was observed as inadequate to prevent significant rAAV aggregation in Xie’s solution. Xie’s observation, published near the time of the effective filing date, contradicts the Petition’s motivation argument. Davies, ¶125.

Xie, however, was not the only reference to suggest that high salt concentrations could lead to undesirable results for rAAV preparations. For example, WO 99/41416, published Aug. 19, 1999, to Frei et al. (EX2020), which was relied-upon prior art in IPR2023-00608, states that a POSA “must take into account the additional **threat to stability posed by the high salt concentrations.**” EX2020, 19:9-14; *see also id.*, 18:19-24; 21:25-26; 21:42-22:6; Davies, ¶126.

Sarepta also disregards this reference. In an obviousness analysis, “[e]vidence that supports, rather than negates, patentability must be fairly considered,” as a POSA has “knowledge of the entire body of technological literature, including that which might lead away from the claimed invention.” *Dow*, 837 F.2d at 473. Fairly considering the evidence disregarded in its Petition, Sarepta has failed to establish a motivation to practice the claimed method with an ionic strength of at least 200 mM.

e. The Petition Improperly Incorporates Arguments on a POSA’s Alleged Background Knowledge by Reference

The Petition alleges that Sarepta “relies on background, state of the art references (that were also not before the Patent Office during prosecution or the PTAB during the prior IPR proceedings) to demonstrate that a POSA at the relevant date would have been well aware that ionic strength was a ‘results-effective variable’ for viral particle aggregation.” Petition, 18 (citing EX1030; EX1031; EX1032); *see also id.*, 9 (citing EX1005, ¶¶37-64). Despite these lofty statements, however, the only explanation the Petition provides is that the “Floyd studies showed that dilution of viral particle preparations, which reduces ionic strength, can result in aggregation.” *Id.*, 9 (citing EX1030, Abstract, 2; EX1005, ¶¶37-64). The Petition, however, never ties these brief mentions of background art to its motivation argument. To the extent Sarepta’s submissions address this background art, the Petition improperly incorporates all arguments from the Kay

Declaration, as explained in Genzyme’s discretionary denial submissions. See Paper 8.

“Arguments must not be incorporated by reference from one document into another document.” 37 C.F.R. § 42.6(a)(3); *see also* PTAB Consolidated Trial Practice Guide, 35-36 (Nov. 2019) (“CTPG”). “The burden of production cannot be met simply by throwing mountains of evidence at the Board without explanation or identification of the relevant portions of that evidence.” *Parus Holdings, Inc. v. Google LLC*, 70 F.4th 1365, 1371 (Fed. Cir. 2023). In the interests of avoiding abuse and supporting fairness and efficiency, the Board is not required “to play archeologist with the record” *3M Co. v. Evergreen Adhesives, Inc.*, 860 F. App’x 724, 725 (Fed. Cir. 2021) (internal quotations omitted); *see also* CTPG at 35-36; *Parus*, 70 F.4th at 1372 (holding that “the prohibition against incorporation of arguments . . . eliminate[s] abuses that arise from incorporation and combination.”) (internal quotations omitted); *Nearmap US, Inc. v. Pictometry Int’l Corp.*, IPR2024-00729, Paper 9 at 21-22 (PTAB Oct. 10, 2024).

The Petition imports by reference four publications and 29 paragraphs of the Kay Declaration with minimal explanation. Petition, 9 (citing EX1030; EX1031; EX1032; EX1041, 6; EX1005, ¶¶36-64). Sarepta’s incorporation of arguments by reference for the ionic strength element circumvents the word count requirement and allows for multiple grounds for every claim. *Id.*, 8. Sarepta burdened Genzyme

with sifting through Sarepta's lengthy submissions, including the 155-page Kay Declaration and responding to those arguments in its own word-limited Preliminary Response. To maintain a fair process, the Board should not consider this testimony improperly incorporated by reference. CTPG at 35-36.

f. A POSA Would Not Have Considered Sarepta's Cited Background Art Relevant to Preventing Aggregation in rAAV Preparations

The "background, state of the art references" or "Floyd studies" (Exs. 1030-1032) relate to 1970s era research on disinfecting virus-containing "water passing through sewage or water treatment plants," which were irrelevant to the issues faced by a POSA in 2004. EX1030, 1. A POSA looking to prevent rAAV aggregations in therapeutic preparations would not have considered such references relevant to a POSA's understanding of rAAV aggregation. Davies, ¶128.

The purpose of the Floyd study was to study the disinfection of poliovirus and reoviruses for water treatment, which is relevant to disinfecting sewage streams with agents such as chlorine or bromine. EX1030, 1. Aggregation allowed viruses to survive and remain infective, whereas disrupting viral aggregates allowed disinfecting agents to access and inactivate the viruses. *Id.*, 1. Thus, "the disinfection of water supplies under conditions in which the virus is in the dispersed state may lead to a more nearly complete inactivation." *Id.*, 8.

In contrast, a POSA formulating an rAAV preparation, who would be seeking to maximize infectivity, would not consider the Floyd studies, which focused on eliminating infectivity. The demands of developing a therapy to be injected into a human are completely different than treating sewage and water supplies. Davies, ¶¶129-130.

A POSA also would not have considered the poliovirus and reovirus subjects of the Floyd study to exhibit behavior as representative of rAAV particles. For example, “[i]n the pH region of 7 to 10.5, both poliovirus and reovirus showed ***no tendency to aggregate.***” EX1032, 6 (emphasis added); Davies, ¶131. In contrast, researchers observed aggregation of rAAV particles at pH 8.0. EX1001, 1:62-2:5; EX1045, 3; EX2022, 3-4.

Additionally, the Floyd references studied viral aggregation on “[p]article concentrations of stocks [that] ranged from 10^{10} to 2×10^{12} particles/ml.” EX1030, 1; EX1005, ¶39. A POSA understood that rAAV aggregation is concentration dependent. EX2021, 6 (“High concentrations of protein may induce aggregate formation.”); EX1045, 2 (“rAAV undergoes concentration-dependent aggregation.”). The Kay Declaration acknowledges that aggregation led to significant losses in infectivity in high-concentration rAAV preparations above 10^{13} vg/ml, such that high-concentration preparations could be less infective than lower concentration preparations. EX1005, ¶69 (citing EX1043) (“[W]hen the

concentration reached $5\text{-}10 \times 10^{13}$ vg/ml, gene transfer efficiency was **10-100-fold lower** compared to the same vector administered at the same dose but having a concentration of $1\text{-}5 \times 10^{12}$ vg/ml.”). Therefore, the Floyd studies, which dealt with much lower viral concentrations, would not have been relevant to a POSA. Davies, ¶¶131-132.

2. Sarepta’s Ground 1 Fails to Establish a Reasonable Expectation that an Ionic Strength of at Least 200 mM Would Prevent rAAV Aggregation

As a “touchstone of obviousness,” a reasonable expectation of success requires not only an “expectation that prior art elements are capable of being physically combined, but also that the combination would have **worked for its intended purpose.**” *Depuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009). Sarepta fails to establish that the prior art would have led a POSA to a reasonable expectation that the claimed method of increasing ionic strength to at least 200 mM would have prevented aggregation in a high concentration rAAV preparation. The inventors were the first to overcome rAAV aggregation at “concentration[s] exceeding 1×10^{13} vg/ml” by formulating preparations with an ionic strength of at least 200 mM that did not exhibit significant aggregation. *Supra* §II.A (citing EX1001, Figs. 1A, 1B). This was neither predictable nor expected given the state of the art at the time of invention. Davies, ¶133.

a. Sarepta Fails to Consider the Unpredictability of Liquid Biological Preparations

Carpenter states that “[i]t can be assumed that *most proteins will not exhibit sufficient stability in aqueous solution to allow a liquid formulation to be developed.*” EX2018, 198. Carpenter further explains that “[e]very protein and product has unique characteristics, some of which may cause difficulty in designing stable formulations.” *Id.*, 130. Considering references that Sarepta cites, including Huang (EX1043), Croyle (EX2021), and Wright (2003) (EX1045), a POSA would have been skeptical that high-concentration rAAV aqueous preparations would have been feasible. *Supra* §IV.A.1.d, IV.A.1.f; Davies, ¶¶134-139. Evans demonstrated that even for a single viral vector, minor changes in excipients can produce dramatic changes in stability. *Supra* §IV.A.1.c.ii (citing Evans 24:18-25:24 (Example 2), FIGS. 2, 3) (comparing stabilities of formulations A104 and A105).

The Board should find here, as it has before (*supra* §III), that a reasonable expectation of success argument that fails to account for and rebut this well-recognized unpredictability cannot prove obviousness. *Amneal Pharms. LLC v. Cubist Pharms. LLC*, IPR2020-00193, Paper 7 at 22-32 (PTAB May 29, 2020); *Sandoz Inc. v. AbbVie Biotechnology Ltd.*, IPR2017-01823, Paper 16 at 14 (PTAB Feb. 9, 2018); *Coherus Biosciences Inc. v. AbbVie Biotechnology Ltd.*, IPR2016-

01018, Paper 14 at 4 (PTAB Feb. 2, 2017); *Momenta Pharms., Inc. v. Bristol-Myers Squibb Co.*, IPR2015-01537, Paper 37 at 12-13 (PTAB Dec. 22, 2016).

b. The Combination of Auricchio and Konz/Evans Fails to Establish a Reasonable Expectation of Success

The Petition and Kay Declaration fail to identify where Auricchio would have provided a POSA with a reasonable expectation that high ionic strength prevents rAAV aggregation. Davies, ¶140. Auricchio does not address viral particle aggregation in any way. *Supra* §§IV.A.1.a, IV.A.1.b; Davies, ¶140. Auricchio disclosed AAV2 particle purification methods that maximized virus recovery “without the major cellular contaminants present when a physical separation method such as CsCl₂ density centrifugation is used.” EX1007, 5-6. A POSA would not have considered Auricchio’s AAV2 purification study as relevant to the issue of aggregation. *Supra* §IV.A.1.a; Davies, ¶140. Moreover, a POSA would have understood Auricchio to direct a POSA to preparations having *less than* 200 mM ionic strength. *Supra* §IV.A.1.b; Davies, ¶140.

Sarepta ignores that Konz’s “sterile filtration and DLS” studies were conducted on adenovirus preparations having concentrations that were magnitudes below the claimed 1×10^{13} vg/ml threshold. Petition, 27 (citing EX1008, 30:13-30 (The purified adenovirus product “will be diluted to *ca.* 1.1×10^{12} vp/mL”)); see *also* EX1008, 42:4-19 (“The product peak was diluted and adjusted to an adenovirus concentration of approximately 1.05×10^{12} vp/mL”), 48:4-5 (disclosing

adenovirus concentrations ranging from 1.83×10^{10} vp/ml to 3.55×10^{12} vp/ml);

Davies, ¶141.

Similarly, Evans, which is cited by Konz and relied on by Sarepta for the ionic strength element (Petition, 38-39), conducted stability testing only on formulations having viral particle concentrations ranging from 10^7 vp/mL to 10^{11} vp/ml, which is several orders of magnitude below both the 10^{13} vp/ml upper limit of Evans' concentration range and the 1×10^{13} vg/ml threshold of the claims. *Supra* §IV.A.1.c.ii (citing EX1020, 24:22 and 25:13-14 (Example 2), 25:31-32 and 26:4 (Example 3), 29:6 (Example 7)); Davies, ¶144. A POSA would not have considered the disclosures in Auricchio or Konz/Evans to be predictive of aggregation in higher concentration rAAV preparations, which were known to present more significant aggregation issues than lower concentration rAAV preparations. *Supra* §§IV.A.1.a - IV.A.1.c.

Additionally, none of the exemplary formulations in Konz or Evans had a NaCl concentration greater than 150 mM NaCl. Davies, ¶145. Konz does not address rAAV aggregation and discloses several formulation buffers, none of which have an NaCl concentration exceeding 75 mM. Davies, ¶142. In Evans, the most stable formulations contained 75 mM or less NaCl, with ionic strengths below 200 mM. *Supra* §IV.A.1.c.ii. Evans nonetheless demonstrated that even small changes to excipients can dramatically change the stability of viral vector

preparations, with the highest NaCl concentration buffer resulting in the poorest stability results. *Id.* (citing Evans 24:18-25:24 (Example 2), FIGS. 2, 3); Davies, ¶144-145.

Thus, Sarepta fails to point to any disclosure in Auricchio, Konz, or Evans that would have supplied a POSA with a reasonable expectation that an ionic strength of at least 200 mM would prevent aggregation in rAAV preparations having rAAV concentrations $>10^{13}$ vg/ml. Sarepta has failed to meet its burden. Davies, ¶146.

B. Ground 2: The Petition’s Combination of Potter and Konz Fails to Render Claims 1-4, 6, 7, and 11 Obvious

The Petition fails to establish how substituting Potter for Auricchio merits a different result than Ground 1. Sarepta repeats its strategy of assembling disparate disclosures from Potter and Konz/Evans for the rAAV concentration and ionic strength without explaining why it would have been obvious for a POSA to prevent aggregation by a method comprising the claimed combination of elements. *KSR*, 550 U.S. at 418. Once again, a “[f]ailure to consider the claimed invention as a whole,” as Sarepta does here, “is an error of law.” *Jones*, 727 F.2d at 1529; *see also Rockwell*, 147 F.3d at 1364; *W.L. Gore.*, 721 F.2d at 1548.

1. The Petition Fails to Establish a Motivation to Arrive at an Ionic Strength of at Least 200 mM

As explained in Ground 1 (*supra* §IV.A.1), the “mechanism of vector aggregation [was] ***not well understood***” for rAAV preparations. EX1045, 2. Like Auricchio, Potter never addresses rAAV aggregation, much less any factors that influence rAAV aggregation. Sarepta never explains “how or why the references would be combined to produce the claimed invention.” *TriVascular*, 812 F.3d at 1066. Potter and Konz alone, or in combination, do not provide a POSA with any reason to prevent rAAV aggregation by producing a preparation with an ionic strength of at least 200 mM for multiple reasons. Davies, ¶¶147-150.

a. The Petition Fails to Establish that Potter and Konz Connect Ionic Strength and rAAV Aggregation

The Petition states that Potter “discloses an electron microscopy analysis of the purified rAAV preparation The analysis shows no evidence of aggregation in the purified rAAV preparation.” Petition, 54 (citing EX1009, 16-17, Fig. 5; EX1005, ¶371). But Potter never addresses rAAV aggregation in its purified rAAV particles or connects the alleged lack of aggregation with ionic strength. Davies, ¶151. Sarepta alleges that Potter’s stock preparations are stored in a buffer containing a 0.5 M NaCl, which would have an ionic strength of 500 mM. Petition, 57 (citing EX1009, 7, EX1005, ¶388). But the purified preparation that Sarepta cites for ionic strength are in a separate embodiment from the stocks that Sarepta

cites for the high rAAV concentration. *Id.*, 58 (citing EX1009, 9, Table II); Davies, ¶152. And the preparation that Sarepta cites for preventing aggregation element is yet another separate preparation that has undergone further chemical manipulation. *Id.*, 54 (citing EX1009, 16-17, Fig. 5); *infra* §IV.B.1.c.iv; Davies, ¶153. Sarepta fails to provide any reason for why a POSA would combine these separate rAAV embodiments into a single embodiment satisfying the rAAV concentration, ionic strength, and aggregation claim elements. Thus, neither the Petition nor Kay Declaration explain why a POSA would have had any reason to suspect, much less conclude, that ionic strength was responsible for Potter's results.

As explained for Ground 1, Sarepta fails to identify where Konz connects ionic strength with any advantageous property (such as lack of aggregation or rAAV infectivity). *Supra* §§IV.A.1.a. Sarepta, likewise, fails to identify where Potter connects ionic strength with rAAV aggregation (or any advantageous property), because Potter does not do so. The POSA would not have been motivated to follow Potter's disclosure for preventing significant aggregation of rAAV particles. Davies, ¶154.

Potter's electron microscopy analysis focused on analyzing a small highly magnified sample of a purified preparation. Potter also manipulates the chemical and physical environment of the rAAV particles for its analysis before conducting any electron micrographic study. *Id.*, ¶¶54-61.

b. Konz/Evans Would Not Motivate a POSA to Prevent rAAV Aggregations with an Ionic Strength of at Least 200 mM

For the ionic strength element, the Petition relies on Konz's incorporation of Evans by reference. Petition, 58 (citing EX1005, ¶¶390-391). Sarepta makes the same arguments for Ground 2 as in Ground 1, and thus the Petition fails to establish motivation for the same reasons as described for Ground 1. *Supra* §IV.A.1.c. Sarepta ignores that Konz discloses several formulation buffers, all of which contain a fraction of NaCl (10-75 mM) compared to the maximum 250 mM NaCl concentration in Evans. *Supra* §IV.A.1.c.i. Sarepta's arguments disregard the totality of Evans teachings that would have directed a POSA to lower salt concentration, and therefore, making rAAV preparation with ionic strength well below 200 mM. *Supra* §IV.A.1.c.ii. In sum, Konz and Evans, considered in their totality, directed a POSA to producing purified rAAV preparations with ionic strengths much lower than 200 mM. *Supra* §IV.A.1.c.iii; Davies, ¶¶155-157.

c. Potter Would Not Motivate a POSA to Prevent rAAV Aggregation with an Ionic Strength of at Least 200 mM

Sarepta's argument fails to establish that a POSA would have considered Potter to disclose the claimed rAAV preparations with an ionic strength of at least 200 mM. The Petition cites to Potter's "National Reference Standard rAAV." Petition, 58; EX1005, ¶397 (citing EX1009, Table II). Potter, however, does not provide specifics as to ionic strength or even to the components of the National

Reference Standard rAAV solution. Without this information, a POSA would be unable to determine ionic strength. Davies, ¶158.

For ionic strength information, the Petition and Kay Declaration cite to a different preparation in Potter, an rAAV preparation resulting from the elution of a heparin affinity chromatography purification step that contains 0.5 M (500 mM) NaCl. Petition, 57; EX1005, ¶¶388-389; EX1009, 7; Davies, ¶¶151-152. The Petition and Kay Declaration, however, never explain why a POSA would have understood the National Reference Standard rAAV stock solution to have the same buffer system as the chromatographically purified preparation. A POSA would have considered the preparations summarized in Table I to be different than the stocks in Table II.

i. Potter's Large-Scale rAAV Preparation

Potter discloses a protocol for purifying rAAV comprising three chromatographic steps. Davies, ¶159. For its ionic strength proof, Sarepta cites the solution used to elute the viral particles, "PBS containing 0.5 M NaCl." Petition, 56-57 (citing EX1009, 7; EX1005, ¶384). Potter summarizes the results of this purification in Table I, shown below.

[24]

rAAV LARGE-SCALE PRODUCTION

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TABLE I
SUMMARY OF rAAV-UF5 PURIFICATION

Run	Crude lysate		Streamline heparin affinity chromatography		HIC phenyl sepharose chromatography		Heparin affinity chromatography	
	Total inf. particles	% yield	Total inf. particles	% yield	Total inf. particles	% yield	Total inf. particles	% yield
1	4.8×10^{12}	100	2.7×10^{12}	56	2.3×10^{12}	48	1.3×10^{12}	27
2	9.6×10^{12}	100	1.8×10^{13}	186	1×10^{13}	104	4.2×10^{12}	43
3	3.6×10^{12}	100	1.2×10^{12}	33	1.3×10^{12}	36	1.2×10^{12}	33

EX1009, 7.

The rAAV product yields are provided in “total inf[ectious] particles,” but Potter does not disclose the rAAV concentration in the eluted rAAV solution. Potter states that the final step results in several “[o]ne ml fractions_g collected” of the eluted rAAV solution, but does not state how many total fractions of the purified product are collected. *Id.*, 4-7. It is not possible to determine the concentration of rAAV particles in each 1 ml fraction without knowing the total volume of the collected solutions. For example, if ten one milliliter fractions were pooled to result in the highest yielding run of 4.2×10^{12} infectious particles, each fraction would have a concentration of only 4.3×10^{11} infectious particles/ml, roughly **100X less** than the claimed concentration of 1×10^{13} vg/ml up to 6.4×10^{13} vg/ml. Davies, ¶¶160-161. Even if only one ml fraction were collected, a concentration of 1.2 - 4.2×10^{12} infectious particles per ml is about **10X less** than the claimed concentration. A POSA would have understood, however, that multiple

one milliliter fractions were likely pooled. Davies, ¶162. Therefore, the concentrations for each run would have likely been even lower than 10^{13} vg/ml, respectively, for runs 1-3. *Id.*

ii. Potter's National Reference Standard rAAV Stock

A POSA would have understood that the concentrations in Potter's National Reference Standard stock solutions are considerably higher than the pooled fractions from Table 1. Davies, ¶162. Potter is silent on how it arrives at its National Reference Standard rAAV stock solution or what components are present in that solution. A POSA would not assume that the National Reference Standard rAAV stock solution had the same buffer system as the large scale production batch pooled fractions. Davies, ¶¶164-167. Sarepta never explains how a POSA would infer from Potter that the eluted rAAV preparation was the same as the National Reference Standard rAAV. Sarepta "has the responsibility to make plain its challenges to the disputed claims." *Nearmap*, IPR2024-00729, Paper 9 at 20-21 (citing 37 C.F.R. § 42.104(b)(4)); *see also id.* (citing 37 C.F.R. § 42.22(a)(2)) ("It is not the Board's responsibility to weave together Petitioner's evidence into a cohesive case."); *Parus*, 70 F.4th at 1371-72. Sarepta does not satisfy its responsibility.

Sarepta also fails to supply any reason for why it would have been obvious to use Potter's large scale purification buffer system with its National Reference

Standard rAAV stock solutions. “It is not sufficient to demonstrate that each of the components in a challenged claim is known in the prior art; Petitioner must also explain why a POSITA would have combined the elements disclosed in the separate embodiments described” in a single reference. *Intel Corp. v. Tela Innovations, Inc.*, IPR2019-01521, Paper 65 at 25 (PTAB Mar. 9, 2021) (citing *KSR*, 550 U.S. at 418); *see also In re Stepan*, 868 F.3d 1342, 1345–46 n.1 (Fed. Cir. 2017) (If obviousness is based on “combining multiple embodiments from a single reference ... there must be a motivation to make the combination and a reasonable expectation that such a combination would be successful, otherwise a skilled artisan would not arrive at the claimed combination.”).

iii. Sarepta Misrepresents Prior Genzyme Submissions Regarding the Potter Reference

Genzyme’s Preliminary Response in IPR2023-00608 correctly explained that Potter’s rAAV preparation on page 419 (EX1009, 7), which had a buffer containing PBS²⁺ and 0.5 M NaCl and “reported yields of $1.2\text{--}4.2 \times 10^{12}$ total infectious particles,” had rAAV concentrations “well below the claimed rAAV concentration.” EX1016, 48. As described above (*supra* §IV.A.1.c.i.), Dr. Davies previously explained that the experiments that Potter discloses on page 419 “relate to pooled fractions from column chromatography experiments, so the 10^{12} total infectious particles are likely in several milliliters of solution. EX1060, ¶123. Thus,

the viral genome concentrations in Potter's cited experiments are likely significantly below 10^{13} vg/ml." *Id.*

Sarepta, however, accuses Genzyme and Dr. Davies of materially "mischaracteriz[ing] the concentration of the disclosed formulations in Potter," Petition, 15, based on the rAAV concentration of Potter's National Reference Standard rAAV stock solutions on page 421. EX1009, 9. Neither Genzyme nor Dr. Davies, however, addressed Potter's National Reference Standard rAAV stock solutions, Petition, 15 (citing EX1009, 9-10), because Potter provides no information about their ionic strength, pH, or what other ingredients are present. *Supra* §IV.B.1.c.ii. Likewise, the petition in IPR2023-00608, which cited Potter's 0.5 M NaCl buffer, did not cite the National Reference Standard rAAV stock solutions on page 421. EX1014, 13, 15 (citing EX1009, 5-7); Davies, ¶163.

This is not surprising. There is nothing in the record to support Sarepta's contention that the elution solvent for the chromatographic purification on page 419 is also present in the National Reference Standard rAAV stock solution on page 421. Davies, ¶¶164-166. Dr. Kay's supporting testimony for the rAAV concentration and ionic strength elements never explains why a POSA would assume the elution solvent is present in Potter's National Reference Standard rAAV preparation. EX1005, ¶¶388-389, 393-399. Indeed, Auricchio describes

taking its high NaCl eluate and “adjust[ing] the NaCl concentration to physiological levels.” EX1007, 2; *supra* §IV.A.1.b.

Thus, the Kay Declaration’s opinion for these issues is “conclusory and unsupported, adds little to the conclusory assertion for which it is offered to support, and is entitled to little weight.” *Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Paper 9 at 15 (PTAB Aug. 24, 2022) (precedential) (citing 37 C.F.R. § 42.65(a)).

iv. A POSA Would Not Have Considered Potter’s Electron Microscopy Analysis to Accurately Detect rAAV Aggregation

Sarepta also alleges that Genzyme “incorrectly characterized the analytical method, electron microscopy” as not being useful to detect aggregates. Petition, 15. But a POSA would not have considered Potter’s electron microscopy analysis focused on characterizing monomeric particles as useful for detecting aggregates in an rAAV preparation. Davies, ¶¶54-61, 168-169. The Petition alleges that “Potter discloses electron microscopy studies showing that the rAAV stock formulation did not exhibit any observable aggregation.” *Id.*, 6; *see also id.*, 16, 54 (citing EX1009, 16-17, Fig. 5). Potter, however, did not use electron microscopy to detect aggregates. Potter used electron microscopy to “confirm the structure of infectious and noninfectious particles.” EX1009, 17; Davies, ¶169. A POSA, therefore,

would have understood Potter's use of electron micrographs to detect full, partial, and empty rAAV particles, but not aggregation. *Id.*, 16-17, Fig. 5; Davies, ¶169.

To confirm particle structure, Potter magnified a small sample of only hundreds of particles that was not representative of the preparation from which they were isolated. Davies, ¶172. Thus, the sample size and degree of magnification in Potter's figure was not useful for detecting the presence or absence of aggregates. *Id.*

To visualize rAAV particles, Potter also conducted several steps that drastically changed the surrounding environment of those particles. *Id.*, ¶¶173-176.

First, “[t]o confirm the structure of infectious and noninfectious particles [by electron microscopy], two peaks from the continuous iodixanol gradient are concentrated by POROS HPLC chromatography.” EX1009, 17. Iodixanol is an iodine-containing non-ionic radiocontrast agent. Potter explains that a “continuous gradient of iodixanol ... is formed by mixing virus with 30% iodixanol prepared in PBS containing 0.9 M MgCl₂. The sample is transferred into a quick-sealing tube, placed in a Ti-70 rotor, and spun at 70,000 rpm for 8 hr at 15°. After centrifugation, the sample is fractionated by puncturing the tube at the bottom and collecting 1 ml fractions.” EX1009, 14. Then that sample further undergoes POROS chromatography. *Id.*, 17. **Second**, “[f]ollowing chromatography, [electron microscopy] analysis of concentrated samples is performed ... by placing 5 µl of

purified virus stock on support films of Formvar/Carbon 400 mesh copper grids ... for 1 min.” *Id.* **Third**, the sample is then “stained with 5 µl of 2% uranyl acetate for 10 sec[onds].” *Id.*

The separation, isolation, staining, and mounting of the sample significantly altered the chemical environment in which the rAAV is present from the stock solution. Davies, ¶177. Thus, the conditions under which electron microscopy was conducted was not representative of the solution from which the sample was drawn, and therefore not useful for determining whether Potter’s rAAV preparation underwent significant aggregation. Davies, ¶178. Neither the Petition nor Kay Declaration addresses this issue.

Accordingly, even if a POSA were to know the conditions of Potter’s stock solutions, Potter’s electron microscopy studies would not have been considered useful for detecting whether rAAV aggregates had formed in that solution. Thus, a POSA would not have been motivated to use Potter’s purification method to minimize aggregation.

d. The Prior Art Directed a POSA Away from Preparing Purified rAAV Preparations with High NaCl Concentrations

As with Ground 1, Ground 2 fails to address the many reasons why a POSA would have been motivated **not** to use a high concentration of NaCl to achieve a high ionic strength. *Supra* §IV.A.1.d; Davies, ¶179. Sarepta’s failure to address

these issues is even more glaring because the rAAV preparation that the Petition points to has 500 mM of NaCl, which is double the uppermost value of Evans at 250 mM.

i. A POSA Would Have Understood that Potter's Purified rAAV Preparation Comprising 500 mM NaCl Is Hypertonic and Likely to Cause Tissue Damage and Pain

As explained for Ground 1, a POSA would have understood that therapeutic preparations should be close to isotonic (280-400 mOsm). *Supra* §IV.A.1.d.i. The high salt buffer disclosed in Evans that Sarepta relies on for the ionic strength element is hypertonic, with an osmolarity of 515 mOsm. The 500 mM NaCl buffer that Sarepta points to in Ground 2 for Potter (Petition, 57), would have an osmolarity of 1000 mOsm accounting for the added NaCl alone, rendering it extremely hypertonic. Davies, ¶¶180-181.

Sarepta fails to prove obviousness by not explaining why a POSA focused on making formulations suitable for clinical use nonetheless would have been motivated to make a formulation having a salt concentration that high, resulting in a hypertonic solution. *See Chemours*, 4 F.4th at 1376 (Fed. Cir. 2021). Neither Sarepta nor Dr. Kay explain why a POSA would have violated the principle of maintaining isotonicity when a POSA would have considered such an issue central to formulation development. Davies, ¶¶184-186.

Sarepta reaches the claimed multivalent ion and ionic strength claim elements only using hindsight. Despite the evidence showing that isotonicity was an important consideration in developing therapeutic preparations, Sarepta argues for making a preparation having an NaCl concentration of 250 mM, which greatly exceeds this isotonic threshold. Petition, 57-58. This contradiction exposes that Sarepta's case for obviousness "is only straightforward in hindsight." *Leo*, 726 F.3d at 1355.

ii. High Salt Concentrations Were Observed to Promote Precipitation of rAAV Particles

Solutions with high salt concentrations were also observed to cause instability of rAAV particles. *Supra* §IV.A.1.d.ii; Davies, ¶¶182-183. As explained, Xie disclosed that an AAV preparation containing of "0.25 M NaCl [250 mM] resulted in **significant loss**" of AAV. EX1028, 7. Thus, a POSA would not have been motivated to use Evans' 250 mM NaCl solution out of concern for rAAV stability. *Contra* Petition, 58. A POSA would have been less motivated to use Potter's 500 mM NaCl buffer (*id.*, 57), which has twice the NaCl concentration of Evans. Davies, ¶187.

2. Sarepta's Ground 2 Fails to Establish a Reasonable Expectation that an Ionic Strength of at Least 200 mM Would Prevent rAAV Aggregation

For the same reasons explained for Ground 1, Sarepta fails to establish a reasonable expectation, based on Potter and Konz, that an rAAV preparation with

an ionic strength of at least 200 mM would prevent aggregation. *Supra* §IV.A.2.

The POSA would have found it unpredictable prevent aggregation in purified high-concentration rAAV preparations. *Supra* §IV.A.2.a; Davies, ¶188. As explained, Konz's aggregation and stability studies did not address the unique challenges of formulating **high-concentration** rAAV preparations that do not exhibit significant aggregation when stored. *Supra* §IV.A.2.b.

Sarepta fails to establish that Potter's stock solution has an ionic strength of at least 200 mM. *Supra* §IV.B.1.c.ii; Davies, ¶189. Potter does not even disclose basic information about the pH, ionic strength, or preparation of the stock solution from the purified fractions. The Petition merely speculates, without supporting evidence, that the buffer system in the stock solution is the same as used for purification. *Supra* §IV.B.1.c.ii. Further, a POSA would not have considered Potter's electron microscopy analyses as accurately measuring the extent of aggregation in Potter's stock solution. *Supra* §IV.B.1.c.iv Davies, ¶190. Therefore, Potter lacks any disclosure regarding both ionic strength and aggregation that a POSA would need to determine whether elevated ionic strength decreased aggregation. Davies, ¶¶189-190.

Thus, Sarepta fails to point to any disclosure in Potter, Konz, or Evans that would have supplied a POSA with a reasonable expectation that preparations comprising rAAV particles at concentrations $>10^{13}$ vg/ml and an ionic strength of

at least 200 mM would not result in significant aggregation. Sarepta has failed to meet its burden.

V. CONCLUSION

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

Respectfully submitted,

Dated: October 8, 2025

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WORD COUNT CERTIFICATION

Pursuant to 37 C.F.R. § 42.24(d), I certify that this Preliminary Response contains 13,930 words (excluding the title page, table of contents, table of exhibits, this certificate, and the certificate of service), as determined by Microsoft Word.

Dated: October 8, 2025

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I certify that today in

Sarepta Therapeutics, Inc., v. Genzyme Corporation, IPR2025-01195

I caused to be served a copy of:

**PATENT OWNER'S PRELIMINARY RESPONSE
EXHIBITS 2015-2029, 2031-2032**

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Date: October 8, 2025

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