

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

GENZYME CORPORATION,
Patent Owner.

Case: IPR2023-00609
Patent No. 9,051,542

PATENT OWNER'S PRELIMINARY RESPONSE

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2003	Declaration of Katherine A. Helm, J.D., Ph.D. In Support of Motion for Admission <i>Pro Hac Vice</i>
2004	Declaration of Martin Christopher Davies in Support of Patent Owner's Preliminary Response ("Davies")
2005	Martyn Christopher Davies, Curriculum Vitae
2006	Xie et al., " <i>Large-Scale Production, Purification and Crystallization of Wild-Type Adeno-Associated Virus-2</i> ," 122 J. Virol. Methods 17 (2004) ("Xie")
2007	J.F. Wright et al., " <i>Identification of Factors that Contribute to Recombinant AAV2 Particle Aggregation and Methods to Prevent Its Occurrence during Vector Purification and Formulation</i> ," 12 Molecular Therapy 171 (July 2005)
2008	A.E. Smith, " <i>Gene Therapy: Where Are We</i> ," 354 The Lancet SI1 (July 1999)
2009	J.O. Konz et al. " <i>Development of a Purification Process for Adenovirus: Controlling Virus Aggregation to Improve the Clearance of Host Cell DNA</i> ," 21 Biotechnol. Prog. 466 (2005) ("Konz")
2010	Stipulation and Order to Amend Case Schedule, <i>Genzyme Corp. et al. v. Novartis Gene Therapies et al.</i> , C.A. No. 21-1736-RGA, D.I. 151 (D. Del.)
2011	October 11, 2022 Defendants' First Amended Invalidity Contentions in <i>Genzyme Corp. et al. v. Novartis Gene Therapies et al.</i> , C.A. No. 21-1736-RGA (D. Del.)
2012	June 2023 Docket Navigator Time to Trial Statistics in Patent Cases in the United States District Court for the District of Delaware
2013	Federal Judicial Caseload Statistics 2022
2014	Order Denying Plaintiffs' Motion for Leave to File the Second Amended Complaint, <i>Genzyme Corp. et al. v. Novartis Gene Therapies et al.</i> , C.A. No. 21-1736-RGA, D.I. 147 (D. Del.)
2015	Disclaimer in Patent Under 37 CFR 1.321(a) of claims 1 and 2 of U.S. Patent No. 9,051,542

I. INTRODUCTION

Petitioners, Novartis Gene Therapies, Inc. and Novartis Pharmaceuticals Corporation (“Novartis”) filed two *Inter Partes* Review (“IPR”) petitions challenging claims 1, 2, 5 and 6 (the “challenged claims”) of U.S. Patent No. 9,051,542 (Ex. 1001, the “’542 patent”) as obvious.¹ Both petitions are devoid of the most basic legal and factual proofs required to establish by a reasonable likelihood that the challenged claims are obvious.

The ’542 patent claims the results of a breakthrough in recombinant adeno-associated virus (“rAAV”) compositions for gene therapy made nearly twenty years ago by inventors at Avigen, a small biotechnology company. Administering rAAV vectors to patients for delivery to the central nervous system (“CNS”) requires “small volumes of highly concentrated vector.” Ex. 1001, 2:12-14. Development of concentrated rAAV compositions was hindered by rAAV particle aggregation, which caused loss of infectivity, biodistribution issues, and adverse immune responses. *Id.*, 2:15-39. Without an adequate solution to the

¹ Novartis also filed a parallel petition, IPR2023-00608, challenging claims 1, 2, 5, and 6 of the ’542 patent, and Genzyme Corporation (“Genzyme”) concurrently files its Preliminary Response to IPR2023-00608 and its Response to Petitioners’ Notice Regarding Multiple Petitions.

problem of rAAV aggregation, gene therapy formulations would be ineffective and unviable. Ex. 2008, SI2 (“[H]igh doses of viral vector ... are usually required to achieve measurable gene transfer”); Ex. 2007, 171; Ex. 1005 (“Huang”), S286. While this problem and its severity was documented, the ’542 patent inventors were the first to solve it. They surprisingly discovered that significant aggregation could be prevented by formulating compositions with an ionic strength greater than 200 mM. *Id.*, 7:1-21. The inventors’ innovation further allows the compositions to be isotonic and suitable for human parenteral administration by including the use of multivalent ions to increase ionic strength. *Id.*, 7:1-8.

In its Petition, Novartis stitches together its case for obviousness of claim elements by relying wholly and impermissibly on hindsight, while failing to address the claimed combination. Novartis selectively picks and chooses piecemeal art to cobble together the disclosure for individual elements, while ignoring that the field as a whole would not have led the person of ordinary skill in the art (“POSA”)² to the claimed combination. **First**, it is black letter law that establishing obviousness requires the evaluation of a claim as a whole to guard against “hindsight reasoning, using the invention as a roadmap to find its prior art

² For this Preliminary Response only, Genzyme does not challenge Novartis’s definition of the POSA. Petition, 16-17 (citing Amiji, ¶82).

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). **Second**, it is a “longstanding principle that the prior art must be considered for all its teachings, not selectively.” *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019).

Genzyme has now disclaimed claims 1 and 2 (Ex. 2015), so only claims 5 and 6 remain challenged. 37 C.F.R. § 42.107(e).³ The Petition’s Grounds fail to identify how the prior art would have motivated or given the person of ordinary skill in the art (“POSA”) a reason to develop high concentration rAAV compositions having elevated ionic strength without significant aggregation. *See, e.g., infra* §§IV.A.1, IV.B.1. For example, Novartis alleges for both Grounds 1 and 2 that a POSA would have been motivated to increase the viral vector concentrations of compositions disclosed in the primary reference of Ground 1, Liu (Ex. 1009), and Ground 2, Lochrie (Ex. 1004) despite overwhelming evidence that rAAV vector particles aggregated at viral particle concentrations exceeding 10¹³ vg/ml. *See, e.g., infra* §§IV.A.1.a, IV.B.1.a (citing Exs. 1005, 1007, 1013).

³ Claims 1 and 2 were disclaimed to streamline issues for the Board, because only claims 5 and 6 are asserted for infringement in the co-pending litigation.

Testimony by Novartis’s expert, Dr. Amiji, further exposes the hindsight basis of Novartis’s arguments. The Petition argues that a POSA would have adapted Liu’s virus purification composition to arrive at the claimed high concentration rAAV composition. Novartis makes these arguments despite Dr. Amiji’s testimony indicating that the 300 mM sodium chloride (NaCl) concentration in Liu’s compositions could cause tissue damage and pain in patients if adapted for clinical purposes. *Infra* §§IV.A.1.b, IV.B.1.a.ii (citing Amiji, ¶¶ 65, 131).

Finally, institution should be denied as a matter of discretion under the Board’s precedent in *Fintiv/NHK*. *Infra* §V. In December 2021, Patent Owner, Genzyme filed suit against Novartis for infringement of several patents by Novartis’s Zolgensma®. On February 23, 2022, Genzyme amended its complaint to assert the ’542 patent. Novartis filed this Petition nearly a year later—one day before the expiration of its one-year § 315(b) bar. Petition, 67-68. Meanwhile, the litigation has significantly progressed—the district court completed its claim constructing hearing, final invalidity and infringement contentions have been exchanged, and fact discovery closes on June 30, 2023. Opening expert reports will be served on August 4, 2023 before an institution decision is due, a jury trial is scheduled for March 2024, and the Court has expressly opposed delays. Instituting this IPR would be highly inefficient, with a district court trial occurring

approximately six months **before** a Final Written Decision. Notwithstanding the unmistakable relevance of *Fintiv*, the Petition does not even mention it and Novartis has not proffered a stipulation of any kind, much less a *Sotera* stipulation.

Novartis fails to establish a reasonable likelihood of succeeding in this Petition, much less that compelling merits favor institution as required under the Board's *Fintiv* standard. The Board should deny institution.

II. THE '542 PATENT

The inventors were able to overcome the challenge of concentration-induced rAAV aggregation, while also ensuring the resulting rAAV composition would be suitable for human parenteral administration (Ex. 1001, 5:10-20), including considerations of tonicity, pH, and the pharmaceutical acceptability of excipients, which elevated the complexity of solving the rAAV aggregation problem.

A. Disclosed Innovation

After many unsuccessful attempts at solving AAV aggregation, the inventors discovered that high ionic strength was the key to storable compositions suitable for human administration. Ex. 1001, Abstract (The '542 patent discloses "high ionic strength solutions...that are nonetheless isotonic with the intended target tissue...achieved using salts of high valency"). 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., 6:63-65, 12:33-67 (Example 3), FIGS. 1A, 1B.

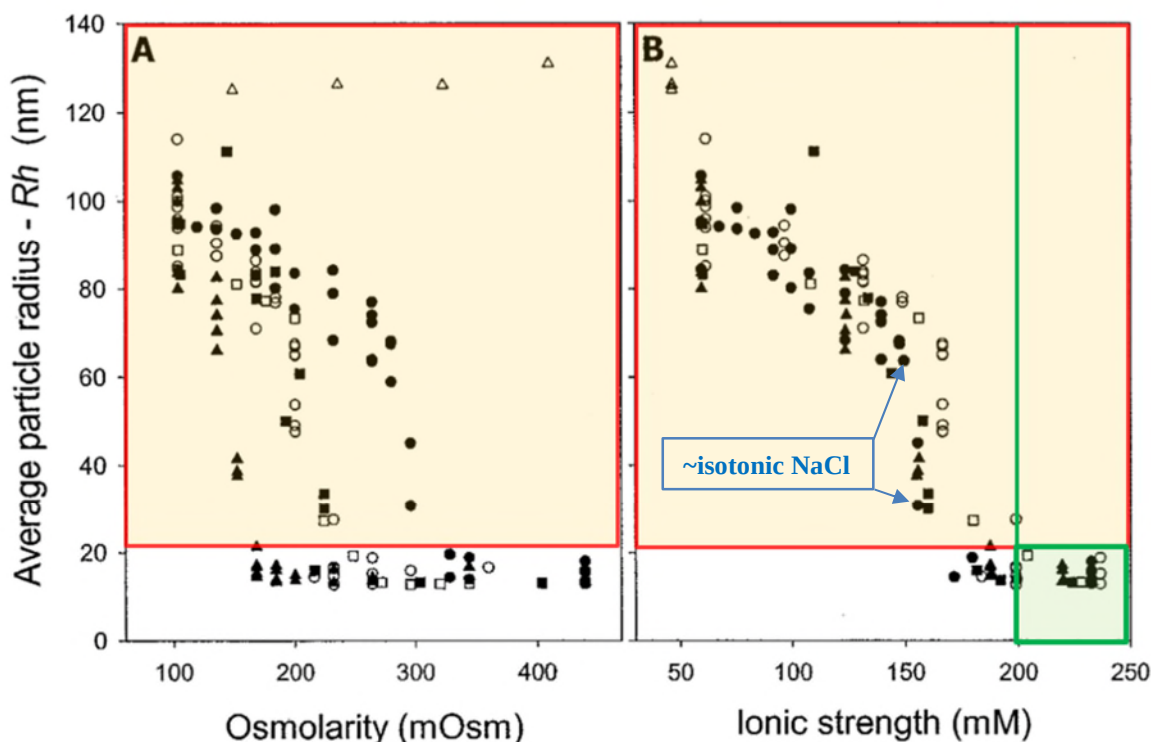
Osmolarity is a measure of the number of particles of solute per liter. For a salt that fully dissociates like NaCl there are two solute particles, one Na⁺ and one Cl⁻, for every equivalent of NaCl. Ex. 2004 (“Davies”), ¶29-37 (citing Ex. 1020, 614). Therefore, the osmolarity of NaCl, expressed in osmols, is double its molarity. *Id.*, ¶¶32, 59. For magnesium chloride (MgCl₂), which contains three particles of solute, one Mg²⁺ and two Cl⁻ ions, the osmolarity is triple the molarity of MgCl₂. *Id.*, ¶¶33, 59.

“Ionic strength is a measure of the intensity of the electrical field in a solution” and it increases exponentially as a function of an ions charge. *Id.*, ¶38. (citing Ex. 1020, 616). 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.*, ¶¶39-40. 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).

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.” Ex. 1001, 4:18-21. Given the average radius of these viral particles is approximately 13 nm, “Rh

values >20 nm are deemed to indicate the occurrence of some level of aggregation.” *Id.*, 9:25-27; Davies, ¶¶43-47.

In annotated Figures 1A and 1B below, the excipients are denoted as follows: sodium chloride (●), sodium citrate (○), sodium phosphate (▪), sodium sulfate (□), magnesium sulfate (▲), and glycerol (Δ):



Id., FIGS. 1A, 1B (annotation added). In both Figures, compositions falling within the orange shaded portion of the plots exhibited significant aggregation ($R_h > 20$ nm), whereas compositions 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 [(▲)] prevented aggregation at >200 mOsm whereas sodium chloride [(●)] required ≥ 350 mOsm to achieve a similar effect,” while glycerol (Δ) never prevented aggregation even at >400 mOsm. *Id.*, FIG. 1A, 7:1-8 (Stating that “[s]odium citrate, sodium sulfate, and sodium phosphate are intermediate in their potency to prevent vector aggregation”).

Figure 1B shows data from the same experiment “plotted as a function of the calculated ionic strength, rather than osmolarity, for each excipient.” *Id.*, 7:18-20. 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.*, 7:21-22. These data led to the breakthrough “that the ionic strength (μ) of a solution ... is the **primary factor affecting aggregation.**” *Id.*, 7:22-25. The green box in annotated Figure 1B illustrates the scope of claim 5 requiring both an “ionic strength ... greater than 200 mM” and a “an average particle radius (R_h) of less than about 20 nm as measured by dynamic light scattering.” *Id.*, 14:34-37.

The identification of ionic strength as a key to preventing aggregation unlocked the path to isotonic compositions for human parenteral administration by employing multivalent ions to adjust ionic strength. As the inventors observed,

“[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.*, 4:65-67. “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.*, 5:15-17. Thus, making a concentrated rAAV composition in NaCl would require the formulation to be hypertonic. *Id.*, 5:4-7; Davies, ¶¶34-35, 58.

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.*, 7:1-8. Davies, ¶¶32-33, 58-59. The inventors recognized and capitalized on the “exponential relationship of ionic strength with charge [v]alency ... to develop isotonic formulations with high ionic strength.” *Id.*, 5:7-10. Compositions containing multivalent ions, including pharmaceutically acceptable excipients containing citrate, sulfate, magnesium, and/or phosphate can have an ionic strength of greater than 200 mM, while remaining isotonic or minimizing isotonicity, because multivalent ions even at low concentrations have high ionic strength.

Novartis alleges that the ’542 patent “admits” that it was “known that high salt concentrations increase AAV2 vector solubility.” Petition, 7 (quoting Ex.

1001, 4:67-5:4); *see also id.* (quoting Ex. 1001, 1:52-55). Novartis, however, ignores that the cited passages of the '542 patent relate to “highly concentrated AAV2 vectors recovered from gradients ... in concentrated CsCl” (Ex. 1001, 4:67-5:7) that were understood to be unsuitable for human administration. *Infra* §IV.A.1.c; Davies, ¶106. Thus, as of the priority date the prior art lacked any indication that it was possible to make a storable composition of concentrated rAAV vector particles without significant aggregation, let alone by developing high ionic strength compositions.

Particle size detection (*id.*, 9:5-50 (Table 3), claim 5) and percent product recovery following filtration (*id.*, 7:65-8:40 (Table 2), claim 6), further confirmed that high ionic strength compositions 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.*, 11:66-12:3. In Experiment 1 the samples contained 2.5×10^{13} vg/ml vector, and in Experiment 2 the samples contained 6.7×10^{13} vg/ml vector. *Id.*, 12:4-12.

In Example 2, the exemplary formulations were filtered through a 0.22 μ m filter. *Id.*, 8:1-10, 11:53-12:29. Table 2 summarizes the results of Experiments 1 and 2, including the ionic strength of each formulation. *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 greater than 200 mM, whereas recovery from CF formulations, having ionic strength of 160 mM, was only 77% and 59% for experiments 1 and 2, respectively.

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.

TABLE 3

STABILITY OF AAV2 VECTORS								
Formulation	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 μ m 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.*, 10:29-43.

B. Challenged Claims

In this proceeding, claims 5 and 6, which depend from claim 1, remain challenged. By virtue of their dependence from claim 1, claim 5 and 6 both recite, *inter alia*:

- “A composition for the storage of purified, recombinant adeno-associated virus (AAV) vector particles, comprising: purified, recombinant AAV vector particles at a concentration exceeding 1×10^{13} vg/ml up to 6.4×10^{13} vg/ml;”
- “one or more multivalent ions selected from the group consisting of citrate, sulfate, magnesium, and phosphate;”
- “wherein the ionic strength of the composition is greater than 200 mM,”
- “and wherein the purified AAV vector particles are stored in the composition without significant aggregation.”

Claim 5 further recites:

- “wherein the purified, recombinant AAV vector particles have an average particle radius (Rh) of less than about 20 nm as measured by dynamic light scattering.”

Claim 6 further recites:

- “wherein recovery of the purified, recombinant virus particles is at least about 90% following filtration of the composition of said AAV vector particles through a 0.22 μm filter.”

III. CLAIM CONSTRUCTION

For this Preliminary Response only, Genzyme does not challenge the Petition’s alleged “plain and ordinary meaning” constructions. Petition, 17.

IV. NOVARTIS FAILS TO ESTABLISH A REASONABLE LIKELIHOOD THAT CLAIMS 5 AND 6 ARE OBVIOUS

Novartis has not established a reasonable likelihood of proving claims 5 and 6 obvious, much less established by compelling merits that claims 5 and 6 are obvious. Novartis fails to meet its burden on all Grounds for at least three claim limitations, each of which constitute an independent basis for denying institution: (1) the rAAV “concentration exceeding 1×10^{13} vg/ml up to 6.4×10^{13} vg/ml”; (2) “the ionic strength of the composition is greater than 200 mM” ; and (3) the respective aggregate limitations of claims 5 and 6.

A. Ground 1: The Petition’s Combination of Liu, Huang, and Mingozi Fails to Render Claims 5 and 6 Obvious

Liu discloses low-concentration “*temporary* storage” compositions for use “[d]uring a large-scale production/purification process,” so that it is possible to “stably stor[e] the viral vectors” to “allow time to temporarily stop the production process to test or fix the production equipment.” Liu, ¶¶ [0186], [00371]. Liu’s exemplary “temporary storage” compositions have a viral *particle* concentration of “ 3.24×10^8 vp/mL” (Amiji, ¶ 285)—several orders of magnitude below the claimed vector genome concentration of 10^{13} vg/ml. Petition, 24, 29 (citing, Liu, ¶¶ [00126], [00369]); Davies, ¶¶64-65. The Petition relies on Liu’s visual assessment that “glass tubes” containing Liu’s composition showed “showed no signs of settling or precipitation.” Petition, 34, 43 (citing Liu, [00369]). The POSA would have understood that Liu’s visual assessment would be unable to detect significant aggregation to the levels recited in claims 5 and 6. Davies, ¶66.

Huang merely highlights the problem of aggregation, stating that “at high concentrations, AAV virions form aggregates of different sizes in a range of different buffer systems and storage conditions. The size of aggregates appears to be concentration dependent.” Huang, S286. Huang states “that some of our formulations could lead to a 30-50% **reduction in the size** of aggregates,” but does not explain what this size reduction means in terms of particle radius or any other metric, does not disclose any information about its formulations, and never

suggests that its stored rAAV compositions could remain free of significant aggregation. Davies, ¶67.

Mingozzi never addresses aggregation. In fact, Mingozzi does not address rAAV formulation or storage at all. Davies, ¶68.

“[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. The Petition never establishes that the POSA would have had any motivation or reason to combine Liu, Huang, and Mingozzi in a manner that would have resulted in the compositions of claims 5 and 6. “Failure to consider the claimed invention as a whole” as Novartis 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 & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1548 (Fed. Cir. 1983).

Novartis bases its motivation argument for Ground 1 on formulating a composition suitable for “therapeutic use” delivered “via parenteral administration.” Petition, 30. The POSA, however, would not be motivated to achieve the claimed invention with Liu’s 300 mM NaCl concentration as Novartis alleges (Petition, 34), because the osmolarity of such a composition would deviate so significantly from isotonicity that it would potentially result in “tissue damage and injection pain” upon administration. *Amiji*, ¶ 131; Davies, ¶¶33-36.

Novartis also fails to establish a reasonable expectation that such a composition would be free of significant aggregation. Indeed, Novartis does not submit any evidence that the particle radius and product recovery elements of claims 5 and 6, respectively, would inherently result from the claimed combination. Each deficiency is an independent reason that Novartis fails to establish a reasonable likelihood of proving claims 5 and 6 obvious.

1. Novartis Fails to Provide a Motivation or Reason To Combine Liu, Huang, and Mingozi to Arrive at the Claimed Composition

a. Novartis Fails to Establish a Motivation to Develop a Composition Having the Claimed rAAV Concentration and Ionic Strength Suitable for Therapeutic Use

Novartis falls prey to “hindsight reasoning” that “discount[s] the value of combining various existing features or principles in a new way to achieve a new result.” *Ruiz*, 357 F.3d at 1275. Novartis fails to establish that the POSA would have been motivated to develop a composition comprising an rAAV “concentration exceeding 1×10^{13} vg/ml,” “one or more multivalent ions selected from ... citrate, sulfate, magnesium, and phosphate,” with an ionic strength “greater than 200mM.” To reach the claimed rAAV concentration, Novartis argues that the POSA would have been motivated to “increase Liu’s virus genome concentration because high concentrations of genome-containing particles are required for therapeutic use.” Petition, 30 (citing Ex.1005, S286).

Novartis's Ground 1 obviousness argument relies Liu's Example 17 (Petition, 23-25), but Novartis admits that Liu's Example 17 composition only contained an initial concentration of 3.24×10^8 vp/mL. Petition, 29 (citing Liu, ¶¶ [00367]-[00368]). Even assuming *arguendo* that all of Liu's particles contained vector genomes, the concentration (Petition, 29-30) in Liu's composition value is over **30,000 times less** than the claimed "concentration exceeding 1×10^{13} vg/mL." Davies, ¶70. But the POSA would never have assumed that all the viral particles contained vector genomes. Davies, ¶¶70-71.

In fact, Dr. Amiji's declaration indicates that the POSA **would not have assumed** that Liu's viral particle compositions were free of empty capsids, and instead would have assumed the opposite—that as many as 90% of capsids in a given composition are empty. Dr. Amiji states that "Wright [Ex. 1007] teaches that $\geq 10^{14}$ capsid particles (cp)/ml corresponds to $\geq 10^{13}$ vg/ml," indicating as much as **10-fold excess in empty capsids**. Amiji, ¶ 119 (citing Ex. 1007, 176). Lochrie (Ex. 1010) states that "**more than 80% of AAV material** created during rAAV production **may be empty capsids**." Lochrie, 4:20-23. If 80% of Liu's particles contained empty capsids and 20% viral genomes, Liu's viral genome concentration to have been **over 150,000 times less** than the claimed rAAV concentration exceeding 10^{13} vg/mL. Davies, ¶72.

Novartis cites Mingozi to argue that the POSA would be motivated to administer “doses of 3.2×10^{13} vg for a 60kg human” at a “concentration exceeding 1×10^{13} .” Petition, 30. Mingozi, however, says nothing about any formulations for AAV vectors let alone anything about ionic strength or multivalent ions. Davies, ¶76.

As of June 2004, the problem of rAAV aggregation in high concentration compositions was unsolved. Novartis acknowledges and cites references demonstrating that the POSA understood that higher viral particle concentrations caused increased aggregation. Petition, 14-15 (citing Huang, S286); Ex. 1013, 1286 (“High concentrations of protein may induce aggregate formation.”); Ex. 1007, 175 (“rAAV undergoes concentration-dependent aggregation.”); Davies, ¶¶74-75. Novartis also acknowledges that Huang disclosed that aggregation led to significant losses in infectivity in high concentration rAAV compositions, when compared to lower concentration compositions. Petition, 19, 31 (citing Huang, S286) (“when the concentration reached $5-10 \times 10^{13}$ vg/ml, gene transfer efficiency was 10 to 100-fold lower compared to the same vector administered at the same dose but having a concentration of $1-5 \times 10^{12}$ vg/ml.”).

Liu, Huang, and Mingozi, alone or in combination do not teach or suggest how to make high concentration rAAV compositions without significant aggregation. Novartis 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). The inventors were the first to overcome rAAV aggregation at “concentration[s] exceeding 1×10^{13} vg/ml” when they determined that compositions with an ionic strength of greater than 200 mM did not exhibit significant aggregation. *Supra* §II.A (citing Ex. 1001, Figs. 1A, 1B).

b. Novartis’s Motivation Theory Relies on Hindsight

Novartis fails to prove obviousness by “not explain[ing] why a POSA would be motivated” to make a composition for “therapeutic use” delivered “via parenteral administration” (Petition, 30) with the claimed rAAV concentration and ionic strength, “when doing so would necessarily involve altering the inventive concept” of the ’542 patent. *Chemours Co. FC, LLC v. Daikin Indus., Ltd.*, 4 F.4th 1370, 1376 (Fed. Cir. 2021), *cert. denied*, 142 S. Ct. 1418 (2022).

Novartis contends that the POSA would have been motivated to merely adapt Liu’s Example 17 composition to be suitable for parenteral administration, without modifying the 300 mM NaCl concentration. Petition, 25, 30, 34. In fact, Dr. Amiji’s declaration explains why the POSA would have avoided a high salt concentration of 300 mM NaCl for human parenteral administration (Amiji, ¶¶ 65, 131); the POSA would have understood such a high NaCl concentration would cause a composition to deviate significantly from isotonicity. Davies, ¶¶ 78-79 (Explaining that an isotonic NaCl solution contains ~150 mM NaCl.).

Dr. Amiji emphasizes the importance of isotonic compositions for injection to avoid tissue damage and pain. Amiji, ¶¶ 65, 131; *see also* Davies, ¶¶80-81. (citing Ex. 1001, 3:29-33; Ex. 1020, 615). Indeed, “[f]or an isotonic product, often it is **advantageous to keep the concentration of salt as low as possible.**” Ex. 1018, 187. Novartis, however, argues that the POSA would have been motivated to make an rAAV composition having an NaCl concentration of 300 mM, greatly exceeding this isotonic threshold. Petition, 34; Davies, ¶¶ 82-85. This contradiction exposes that Novartis’s case for obviousness “is only straightforward in hindsight.” *Leo Pharm. Prod., Ltd. v. Rea*, 726 F.3d 1346, 1355. (Fed. Cir. 2013).

“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). Dr. Amiji explains that for viral formulations “[i]t was well known **as of June 2004** that it is preferable to **maintain the osmolarity** of a pharmaceutical composition to be **as close to isotonic as possible, especially for parenteral administration**, to reduce injection pain.” Amiji, ¶ 65 (citing Ex.1008, 410-411; Ex.1021, 1525 (“Solutions to be administered subcutaneously **require strict attention to tonicity** adjustment.”)).

Dr. Amiji also highlights Gatlin (Ex. 1008), which “***emphasizes*** ‘*the two formulation parameters, pH and **tonicity***, that are usually associated with tissue damage and injection pain,’ and ‘provides a parenteral product development outline’ that includes guidance on ways in which pH and tonicity ‘may be modified to minimize tissue damage and pain caused by a parenteral product.’” Amiji, ¶ 131 (citing Ex. 1008, 401-402); Davies, ¶¶36-37 (citing Ex. 1008 and Ex. 1018).

Serum osmolarity is about 300 mOsm. Ex. 1020, 615. “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.” Ex. 1020, 613; *see also* Ex. 1001, 5:15-16. A 300 mOsm NaCl solution is isosmotic with 300 mOsm serum, and thus isotonic. The 5 mM MgCl₂ would further increase osmolarity by 15 mOsm. Novartis proposes a parenteral composition that contains 300 mM NaCl and 5 mM MgCl₂ (Petition, 34), which would contribute an osmolarity of 615 mOsm to the composition—more than double serum’s 300 mOsm—resulting in a hypertonic composition that the POSA would have avoided. Davies, ¶¶82-85; Ex. 1020, 615.

Neither Novartis nor Dr. Amiji explain why the POSA would have violated the principle of “maintain[ing] the osmolarity of a pharmaceutical composition to be as close to isotonic as possible, especially for parenteral administration” (Amiji,

¶65) when the hypertonic composition they proposed would cause “tissue damage and injection pain.” Amiji, ¶ 131.

In contrast to Novartis’s argument that the POSA would have adapted Liu’s Example 17 composition containing 300 mM NaCl for therapeutic parenteral administration to deliver the rAAV concentration disclosed in Huang and Mingozi, the ’542 patent applied certain multivalent ions to increase ionic strength while maintaining the isotonicity of its high concentration rAAV compositions. *Trivascular*, 812 F.3d at 1068 (Liu’s high salt concentration “would destroy [the] basic objective of” parenteral compositions for therapeutic use.); *Chemours*, 4 F.4th at 1376. Thus, Novartis only reaches the combined rAAV concentration and ionic strength claim elements using impermissible hindsight.

**c. The Prior Art as Whole Undermines Novartis’s
Motivation to Combine Liu with Huang and Mingozi**

Novartis ignores that the prior art as a whole would not have motivated the POSA to make high concentration rAAV compositions with Liu’s composition to prevent significant aggregation. Novartis does not identify any teaching or suggestion indicating that a composition containing 300 mM NaCl and 5 mM MgCl₂ would have been understood by the POSA to prevent significant aggregation. In fact, the art taught that high concentrations of NaCl were insufficient to prevent significant aggregation. *Davies*, ¶¶88-91.

Novartis alleges that the '542 patent admits “known that high salt concentrations increase AAV2 vector solubility.” Petition, 7 (citing Ex. 1001, 4:67-5:4). Novartis ignores that the '542 patent's next sentence states “[h]owever, 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.” Ex. 1001, 5:4-7. The 615 mOsm composition proposed by Novartis (Petition, 35-36) is well above 400 mOsm. *Supra* §IV.A.1.b; Davies, ¶¶86-87.

Moreover, the '542 patent's statement regarding high salt concentrations cites to the purification methods of Xie et al. (Ex. 2006). Ex. 1001, 1:52-52 (“Xie and coworkers similarly reported that at concentrations exceeding 0.1 mg/mL [1.602×10^{13} vg/ml], AAV2 vectors require elevated concentrations of salt to prevent aggregation”);⁴ Davies, ¶88. Xie explained stated that “[h]igh concentrations of AAV-2 in the ~3.3 M CsCl from ultracentrifugal purification

⁴ An AAV-2 concentration of 0.1 mg/ml corresponds to approximately 1.6×10^{13} vg/ml. rAAV genome particles have an average molecular weight of 3.746×10^3 kDa, and 0.1mg/ml is 6.022×10^{16} kDa/ml, so a concentration of 0.1 mg/ml of rAAV particles is equal to about 1.602 vg/ml. The '542 patent also notes that 0.06 mg/ml corresponds to approximately 10^{13} vg/ml. Ex. 1001, 1:58-60.

remained mostly in solution at 4°C, although there was some precipitation and adhesion to glass- and plastic-ware with time....” Ex. 2006, 22-23. Thus, even for *molar* salt solutions of CsCl having osmolarity of ~ 6600 mOsm that would be unsuitable as a parenteral formulation, AAV particle precipitation was observed. Davies, ¶89. Xie further stated that a solution of “0.25 M NaCl [250 mM] resulted in **significant loss**” of AAV. Ex. 2006, 22-23. Thus, Xie teaches that a salt concentration of 250 mM NaCl, the NaCl concentration that Novartis advocates for (Petition, 35), was inadequate to prevent significant rAAV aggregation in Xie’s solution. Davies, ¶90.

Novartis also disregards statements in another reference, Frei (Ex. 1004), which stated its compositions “must take into account the additional **threat to stability posed by the high salt concentrations.**” Frei, 19:9-14; *see also id.*, 18:19-24; 21:25-26; 21:42-22:6. In an obviousness analysis, “[e]vidence that supports, rather than negates, patentability must be fairly considered,” as the 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). References like Xie and Frei teach that high NaCl compositions were not a panacea for solving aggregation issues, and in fact could lead to potential stability issues. In contrast to Xie and Frei, Novartis fails to identify any reference tying elevated ionic strength to preventing viral particle

aggregation. Fairly considering the evidence as a whole, Novartis has failed to establish a motivation to make the claimed composition based on Liu, Huang, and Mingozi.

2. Novartis Fails to Establish a Reasonable Expectation of Success in Developing a High-Concentration rAAV Composition Without Significant rAAV Aggregation

Novartis argues that the “POSA would have reasonably expected the obvious variants of Liu’s Example 17 composition discussed above to prevent aggregation.” Petition, 34 (quoting Liu, [00369], [00371]). As explained below, Novartis’s arguments fail to establish a basis for a reasonable expectation of success.

a. Novartis Fails to Consider the Unpredictability of Liquid Biological Formulations

Novartis relies on what it alleges are similarities between viral vector and protein formulations. Petition, 8. Dr. Amiji cites Carpenter (Ex. 1018), which 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.*” Ex. 1018, 188. Considering Novartis’s own cited references, including Huang, Croyle (Ex. 1013), and Wright (Ex. 1007), the POSA would have been skeptical that a high-concentration rAAV aqueous composition without significant aggregation would have been feasible. *Supra* §IV.A.1.a; Davies, ¶¶94-95.

Novartis argues that “distinctions between adenovirus and AAV lack meaningful differences with respect to ‘proper conditions to prevent aggregation’” (Petition, 28) and “a POSA ... would have reasonably expected Liu’s compositions to provide similar, if not better stability for storing AAV particles.” Petition, 29. Novartis’s argument fails because what might work for one type of viral vector (*e.g.*, an adenovirus), does not predict what will work for another (*e.g.*, rAAV). Carpenter explains that “[e]very protein and product has unique characteristics, some of which may cause difficulty in designing stable formulations.” Ex. 1018, 134.

The Board should find here, as it has before, that a reasonable expectation of success argument that fails to deal with this unpredictability cannot prove obviousness. *Amneal Pharms. LLC v. Cubist Pharms. LLC*, IPR2020-00193, Paper 7 at 32-22 (PTAB May 29, 2020); *Sandoz Inc. v. AbbVie Biotechnology Ltd. et al.*, 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. et al. v. Bristol-Myers Squibb Co.*, IPR2015-01537, Paper 37 at 12-13 (PTAB Dec. 22, 2016).

b. Liu Does Not Support a Reasonable Expectation of Success in Preventing Significant Aggregation

Novartis cannot establish a reasonable expectation of success based on the fact that “Liu reported ‘no signs of settling or precipitation over the 7 day [storage]

period’ and ‘[n]o significant change in the number of viral particles or infectious viral particles.’” Petition, 34 (quoting Ex.1009, [00369], [00371]). Novartis fails to explain how Liu’s low concentration adenoviral compositions would have supported the POSA’s reasonable expectation of success for the claimed high-concentration composition. Davies, ¶¶96-97. The Petition cites stability testing for Liu’s Example 17 (Petition, 34 citing Liu, [00369], [00371]), which contained an rAAV vector particle concentration of 3.24×10^8 , several orders of magnitude below the claimed concentration exceeding 10^{13} vg/ml. *Supra* §IV.A.1.

As Novartis and Dr. Amiji acknowledge, the POSA would have understood that “rAAV undergoes concentration-dependent aggregation” (Ex. 1007, 17) wherein aggregation increases at concentrations above 10^{13} vg/ml. Petition, 19, 32 (citing Ex. 1005, S286); Davies, ¶97. Given the known relationship between higher concentration and increased aggregation (*supra* §IV.A.1.a), however, Novartis fails to explain how Liu’s Example 17 would have supplied the POSA with a reasonable expectation that the inclusion of an rAAV concentration of 10^{13} vg/ml in Liu’s composition would not exhibit significant aggregation (Petition, 34), particularly as required by claims 5 and 6. *Infra* §IV.A.3 (explaining the Petition’s complete failure of proof with respect to the particle size requirements.). Indeed, Xie stated that “0.25 M NaCl [250 mM] resulted in significant loss” of AAV, indicating that the POSA would not have reasonably expected a high

concentration of NaCl to prevent significant aggregation. Ex. 2006, 22-23; *supra* §IV.A.1.c.

Moreover, Liu’s visual assessment of “no signs of settling or precipitation” (Liu, ¶ [00369]) was far too insensitive to establish a reasonable expectation of success in preventing significant aggregation. The largest average particle radius detected in the aggregation studies of the ’542 patent was less than 140 nm (diameter = 280 nm) (Ex. 1001, Figs. 1A, 1B), which is magnitudes smaller than 10,000 nm the threshold for detection by the naked eye. Davies, ¶98. Thus, the POSA would not have understood Liu to support a reasonable expectation of success in preventing significant aggregation.

c. Huang, Mingozi, and Other Cited Art Do Not Remedy Novartis’s Failure to Establish an Expectation of Success Argument

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). Novartis’s statement that “based on Huang, the POSA would have reasonably expected that high-concentration AAV compositions (e.g., $5\text{-}10 \times 10^{13}$ vg/ml) could be achieved and utilized for successful gene transfer” (Petition, 40) is contradicted by Huang’s finding that high-concentration

compositions exhibited “**gene transfer efficiency [that] was 10-100 fold lower**” than lower concentration rAAV compositions. Huang, S286; *supra* §IV.A.2.a; Davies, ¶101.

Novartis’s statement that Mingozi supports its argument is similarly unfounded. Petition, 32 (citing Mingozi, 10497); *see also id.*, 37. Neither Novartis nor Dr. Amiji provide any information regarding the formulation of Mingozi’s composition, whether it contained aggregates or was even stored before administration. Davies, ¶103.

Novartis argues that “compositions capable of storing purified AAV vector particles at the claimed concentrations ‘without significant aggregation’ were described in Wright [Ex. 1007] and, therefore, cannot form the basis for patentability.” Petition, 35-36. But Wright does not provide any information about the composition, including its pH, ionic strength, and whether there were multivalent ions present. Ex. 1007, 175 (stating that the formulations are based on “unpublished data”); *KSR*, 550 U.S. at 418; *W.L. Gore*, 721 F.2d at 1548 (“Each claimed invention must be considered as a whole.”). In fact, Wright stated that the “mechanism of vector aggregation is **not well understood**, and purification conditions that **may affect aggregation include** buffer ionic strength and pH, shear and vector concentration.” Ex. 1007, 175. On a molecular level, Wright states that the “nature of the interparticle interactions that result in aggregation has **not been**

well characterized.” *Id.*, 176. If anything, Wright, having dedicated an entire section to the unknowns of the viral vector aggregation problem, stands for the proposition that viral vector aggregation was an unsolved problem in the field prior to the ’542 patent’s earliest priority date. Davies, ¶¶99-100.

It was established in the art that for rAAV composition, “[h]igh concentrations of protein may induce aggregate formation and precipitation upon freezing resulting in poor recovery of the product.” Ex. 1013, 1286. Novartis has not provided any evidence that the POSA would have reasonably expected high-concentration rAAV compositions made with Liu’s formulation to not exhibit significant aggregation by the specific requirements of claims 5 and 6. *Infra* §IV.A.3.

3. Novartis Fails to Establish that the Claims 5 and 6 Are Obvious

Both claim 5 and claim 6 relate to specific measures setting quantitative limits on aggregate formation. Davies, ¶¶104-113. Novartis, however, fails to provide any evidence that the particle size elements recited in claims 5 and 6 necessarily result from the combination of elements Novartis has alleged was obvious. Petition, 37, 39-40 (claims 1 and 5), 41-42 (claim 6). To meet the standard for inherency in the context of obviousness “[a] party must ... meet a high standard ... the limitation at issue necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art.” *PAR Pharm.*,

Inc. v. TWI Pharms., Inc., 773 F.3d 1186, 1195-96 (Fed. Cir. 2014). “Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.” *Id.* Novartis bears the burden in establishing inherent obviousness. *Knauf Insulation, Inc. v. Rockwool Int’l A/S*, 788 F. App’x 728, 734–35 (Fed. Cir. 2019) (“it was not Patent Owner’s burden to establish that the inherent result” was not inherent, “it was Petitioner’s burden to prove that every limitation in the claim was found in the prior art, either inherently or explicitly.”). Novartis failed to meet its burden.

a. Claims 5 and 6 Carry Patentable Weight

Without evidence to support its inherent obviousness argument claims 5 and 6, Novartis distorts the prosecution history and litigation record. Novartis wrongly argues that “Patent Owners admit that claim 5 [and 6] merely “provide [a] method[] of ensuring that there is no substantial aggregation.” Petition, 39, 41 (citing Ex. 1023, 72; Ex.1025, ¶¶ 60, 323). Claims 5 and 6, however, “provide[] the criteria by which the” composition for the storage of purified rAAV vector particles “is analyzed.” *In re Jasinski*, 508 F. App’x 950, 952 (Fed. Cir. 2013); see also *Vizio, Inc. v. Int’l Trade Comm’n*, 605 F.3d 1330, 1340 (Fed. Cir. 2010) (holding that claims language going to “the essence or a fundamental characteristic of the claimed invention” was “properly construed as a limitation.”)

For claim 5, the '542 patent explains that “Rh values >20 nm are deemed to indicate the occurrence of some level of aggregation.” Ex. 1001, 25-27. By analyzing average particle radius, the inventors determined that ionic strength was a key determinant of rAAV. *Supra* §II.A.

For claim 6, the '542 patent explains that the presence of aggregates can be measured through vector recovery following filtration through a 0.22 µM filter. Ex. 1001, 8:19-44. These filtration experiments allowed for the comparison of aggregate formation for the formulations CF, TF1, and TF2 having different vector concentrations. *Supra* §II.A.

Claims 5 and 6 clearly carry patentable weight, because they relate to the quantification of rAAV aggregation (or the absence of aggregates) more accurately than other methods of detection, including visual inspection and analytical methods such as A_{320}/A_{260} absorbance. Davies, ¶¶45-50 (citing Ex. 2009). Thus, claims 5 and 6 each relate to “a fundamental characteristic of the claimed invention” that should be “properly construed as a limitation” for determining whether a composition is within the scope of the claims. *Vizio*, 605 F.3d at 1340.

b. Genzyme Did Not Acquiesce to the Unpatentability of the Limitations in Claims 5 and 6

Novartis erroneously argues that Genzyme acquiesced to the Examiner’s statement by “never disput[ing] the Examiner’s conclusion that the ‘average particle radius’ limitation of claim 5 is an ‘inherent characteristic feature[] of the

purified viral composition’ disclosed in the cited references.” Petition, 39 (citing Ex. 1002). Genzyme never acquiesced to the Examiner’s incorrect inherency arguments. In fact, as Novartis acknowledges, Genzyme disputed the Examiner’s rejection. Petition, 39 n.6.

The Federal Circuit in *TorPharm, Inc. v. Ranbaxy Pharms., Inc.* rejected Novartis’s proposition that “Patent Owner’s silence constitutes a binding admission” (Petition, 39), holding instead that a “patentee is not required to fight tooth and nail every possibly adverse thought an examiner commits to paper, nor to advance redundant arguments for patentability.” 336 F.3d 1322, 1330 (Fed. Cir. 2003); *see also Woods v. DeAngelo Marine Exhaust, Inc.*, 692 F.3d 1272, 1287 (Fed. Cir. 2012) (“A patent applicant is not presumed to have conceded the presence in the prior art of every claim limitation he had no reason to dispute”). “[A]cquiescence may be found where the patentee narrows his or her claims by amendment,” which may be relevant for claim interpretation. *TorPharm*, 336 F.3d at 1330. “But these principles do not suggest that a patentee may advance during litigation only those arguments in support of patentability that were made before the Patent Office.” *Id.* Novartis adduces no evidence suggesting that Genzyme acquiesced that the elements of claims 5 and 6 were in the prior art, and thus the Board should reject its argument.

c. Novartis Fails to Establish that Claim 5 Is Inherently Obvious

Novartis alleges that “[b]ecause Liu’s claim 5 composition prevented aggregation, a POSA would have reasonably expected AAV particles stored therein” at concentrations several orders of magnitude higher (*supra* §IV.A.1) “would have an Rh of $<\sim 20$ nm measured by DLS.” Petition, 39-40. Novartis alleges that a “POSA would have reasonably expected success in minimizing particle size in view of Huang’s teaching that its optimized compositions ‘could lead to a 30-50% reduction in the size of aggregates at high vector concentrations.’” Petition 40-41 (citing Huang, S286). The POSA would have recognized that Huang’s composition still contained aggregates and that Huang provided no information about its formulation or what the purported size reduction of aggregation Huang’s statement represents. *Supra* §IV.A.2.c.

Liu’s statement that adenovirus compositions showing “no signs of settling or precipitation” is similarly irrelevant for claim 5’s radius requirement. Petition, 42; *supra* §IV.A.2.b. Liu’s visual methods would have been understood to have been far too insensitive to detect aggregation, particularly as compared to methods for detecting average particle radius. Davies, ¶106. Visible particles are magnitudes larger than rAAV particles, so eliminating or preventing visible particles does not mean that subvisible aggregates are not present. Davies, ¶42.

Novartis bears the burden in establishing inherent obviousness for claim

5. *Knauf Insulation*, 788 F. App'x at 734–35. Novartis, however, ***fails*** to produce any evidence that for the claimed composition “the purified, recombinant AAV vector particles” would necessarily and inevitably have had “an average particle radius (Rh) of less than about 20 nm as measured by [DLS].” For claim 5, Novartis cannot possibly meet the standard for inherency in the context of obviousness. *PAR Pharm.*, 773 F.3d at 1196.

d. Novartis Fails to Establish that Claim 6 Is Inherently Obvious

Novartis argues that “[t]he ’542 patent does not identify anything critical about the recited recovery rate” and argues that claim 6 is an inherent feature of the prior art. Petition, 4. The claimed percent recovery following filtration through a 0.22 μm filter, however, is a measure of the degree of aggregation within the composition (Davies, ¶¶108-109), which goes to a “fundamental characteristic of the claimed invention.” *Vizio*, 605 F.3d at 1340.

When the inventors assessed the effect of ionic strength on aggregation by measuring vector recovery after filtration through a 0.22 μm filter they found compositions having ionic strength greater than 200 mM surprisingly resulted in recoveries ***exceeding 90%***, whereas compositions having ionic strengths below 200 mM resulted in recoveries below 80%. Ex. 1001, 8:19-44. The ’542 patent explains that “[w]ithin the variability of the assays used, vector was recovered fully

at both target concentrations using TF2, **indicating that aggregation was prevented.**” Ex. 1001, 8:44-46; Davies ¶¶111-113 (citing Ex. 2009). It was known that rAAV aggregates in compositions could lead to, *e.g.*, loss of infectivity and adverse immune responses, and the POSA understood minimizing aggregation is critical. Ex. 1001, 1:15-39.

Novartis bears the burden in establishing inherent obviousness for claim 6 but provides no evidence of inherency. *Knauf Insulation*, 788 F. App’x at 734–35. Thus, Novartis cannot possibly meet the high standard for inherency relying on Liu’s Example 17, which applies only visual methods that the POSA would have understood could not determine the presence (or absence) of significant aggregation to the degree of claim 6’s product recovery following filtration requirement (Davies ¶42). *PAR Pharm.*, 773 F.3d at 1196.

B. Ground 2: The Petition’s Combination of Lochrie, Huang, Mingozi, Johnson, and Liu Fails to Render Claims 5 and 6 Obvious

Novartis fails to establish that Ground 3 renders obvious at least three elements of claims 5 and 6: (1) the rAAV “concentration exceeding 1×10^{13} vg/ml up to 6.4×10^{13} vg/ml”; (2) “the ionic strength of the composition is greater than 200 mM”; and (3) the respective particle size limitations of claims 5 and 6. “[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. Novartis fails to establish that the combination of elements in claims 5 and 6 was obvious over the Ground 2 references.

The Petition contends that “Lochrie’s Example 2 provides an rAAV composition meeting all but three of the limitations of challenged claim 1, each of which differ only slightly in value than the recited elements.” Petition, 44. Novartis fails to establish why the POSA would have gone from Lochrie, which has an rAAV vector concentration of 4×10^{12} , significantly below the claimed “concentration exceeding 1×10^{13} vg/ml,” does not address aggregation or stability for its compositions, and contains no indication that increased ionic strength suppresses particle aggregation, to the compositions of claims 5 and 6, with a reasonable expectation of success in making those compositions. Davies, ¶¶114-118. Although Novartis premises its obviousness arguments on the POSA’s motivation to make “therapeutic compositions” for “parenteral administration,” Lochrie does not contain disclosure regarding aggregation. Davies, ¶126. Lochrie is directed to “methods for producing stocks of rAAV virions with reduced amounts of empty capsids.” Lochrie, 5:1-3. Lochrie’s “methods include treating the purified AAV stock with destabilizing agents, subjecting the stock to changes in pH, and heating the stock to preferentially denature empty capsids while maintaining the viability of packaged capsids.” *Id.*, 5:15-18.

Johnson published in 1975, which was over two decades before the art identified rAAV aggregation as a significant hurdle to high concentration rAAV compositions, for example in Huang, Wright (Ex. 1007), and Croyle (Ex. 1013) published on the unsolved issue of concentration induced rAAV aggregation. Novartis relies on Johnson for a single sentence that “aggregates of virus were present at pH 7.2 and below, but at pH 7.5 no aggregates were seen.” Petition, 15, 46, 50 (citing Johnson, 589). Novartis, however, fails to identify where Johnson provides, for example, the AAV concentration or ionic strength of the Johnson composition, or how Johnson’s method of determining aggregation would have applied to claims 5 and 6. Davies, ¶132.

The many deficiencies of Huang, Mingozi, and Liu for rendering claims 5 and 6 obvious are documented in detail for Ground 1. *Supra* §IV.A. In addition, Novartis fails to provide any evidence that the particle size and product recovery elements of claims 5 and 6, respectively, would inherently have resulted from the claimed compositions developed by adapting Lochrie. Petition, 55-57. Each deficiency in the Petition is an independent reason that Novartis fails to establish a reasonable likelihood of proving claims 5 and 6 obvious.

1. Novartis Fails to Provide a Motivation or Reason to Combine Lochrie, Huang, Mingozi, Liu, and Johnson to Arrive at the Claimed Composition

a. Novartis Fails to Establish a Motivation to Develop a Composition Having the Claimed rAAV Concentration and Ionic Strength

Novartis's argument fails to establish that the POSA would have been motivated to develop a composition comprising an rAAV "concentration exceeding 1×10^{13} vg/ml," "one or more multivalent ions selected from ... citrate, sulfate, magnesium, and phosphate," with an ionic strength "greater than 200mM." Novartis's Ground 2 arguments rely on Lochrie's Example 2 (Petition, 44-47), but Novartis admits that Lochrie's Example 2 composition only contained an initial concentration of 4×10^{12} vg/mL. Petition, 47 (citing Lochrie, 29:7-9).

Novartis cites Mingozi to argue that the POSA would be "motivated to raise the concentration of Lochrie's composition to $>1 \times 10^{13}$ vg/mL to deliver increased amounts of AAV particles via parenteral administration based on the successes described in Mingozi." Petition, 47. The Board, however, must "be careful not to allow hindsight reconstruction of references . . . without any explanation as to *how* or *why* the references would be combined to produce the claimed invention." *TriVascular*, 812 F.3d at 1066.

By addressing the concentration and ionic strength elements separately, Novartis ignores the inventive combination and falls prey to "'hindsight syndrome'

by reasoning backward from the teaching of the patent itself.” *Creo Prod., Inc. v. Presstek, Inc.*, 166 F. Supp. 2d 944, 966 (D. Del. 2001), *aff’d*, 305 F.3d 1337 (Fed. Cir. 2002); *see also Rockwell Int’l*, 147 F.3d at 1364; *Jones*, 727 F.2d at 1529; *W.L. Gore*, 721 F.2d at 1548. The teachings of the relevant timeframe demonstrated that higher rAAV concentration was understood by the POSA to lead to increased aggregation, but until the ’542 patent’s invention, the art also failed to provide guidance on how to solve the aggregation issue. *Supra* §IV.A.2.c (citing Huang, S286; Ex. 1013, 1286; Ex. 1007, 175). Neither Lochrie nor Mingozi, alone or combined with the other art Novartis cites, establishes any motivation to make a composition having an rAAV “concentration exceeding 1×10^{13} vg/ml,” at and ionic strength “greater than 200 mM,” such that the result composition would be “without significant aggregation.”

i. Novartis Fails to Demonstrate the Ionic Strength Was a Recognized Result Effective Variable

According to the Petition, Lochrie’s Example 2 composition had an ionic strength of ~196 mM, below the 200 mM threshold of the claims. Petition, 51. Novartis argues that the “POSA would have been motivated to increase the ionic strength of Lochrie’s composition to prevent aggregation” because it was “known that AAV2 vectors require elevated concentrations of salt to prevent aggregation.” Petition, 52 (citing Ex. 1007, 175; Amiji, ¶¶ 362-364).

Novartis, however, mischaracterizes Wright (Ex. 1007) to support its contention that “ionic strength ... likely affects vector aggregation.” Wright stated that the “mechanism of vector aggregation is **not well understood**, and purification conditions that **may affect aggregation include** buffer ionic strength and pH, shear and vector concentration.” Ex. 1007, 175; Davies, ¶¶120. Novartis never explains how Wright’s statement that factors causing vector aggregation were “not well understood”—followed by a non-exclusive list of conditions that *may* impact aggregation—was an indication that “ionic strength ... **likely** affects vector aggregation.” *Id.*

Moreover, the POSA would have understood that adjustments to *buffer* ionic strength would not be made by adding salts such as NaCl or MgCl₂. Davies, ¶¶40-41. Buffers, which are added to modify and maintain a target pH, have their own intrinsic buffer ionic strengths. Ex. 1020, 225. For example, “50mM sodium phosphate containing 0.1M NaCl, [is] a buffer that has a relatively high ionic strength” where phosphate provides the buffering effect. Ex. 1018, 32. A “buffer of moderate ionic strength” is “10mM Tris, pH 8.5, 100 mM NaCl, 1 mM EDTA” (*id.*, 33), where Tris and EDTA provide the buffering effect. Both the moderate and high ionic strength buffer solutions have the same NaCl concentrations (0.1 M = 100 mM), so the difference in their ionic strengths is from the buffering species not NaCl. Davies, ¶41. Moreover, Wright’s adenovirus formulation contains only

25 mM NaCl (Ex. 1007, 176), which is 10-fold below the 250 mM NaCl concentration Novartis alleges was obvious. Thus, Wright also fails to teach or suggest ionic strength as a results-effective variable for rAAV aggregation.

ii. Novartis’s Motivation Theory to Increase Ionic Strength Relies on Hindsight

Novartis argues that the “POSA would have further been motivated to target the claimed ionic strength of ‘greater than 200 mM’ based on Liu, which reported ‘no signs of settling or precipitation over the 7 day [storage] period’ and ‘[n]o significant change in the number of viral particles or infectious viral particles’ after storing virus compositions having an ionic strength of ~315mM.” Petition, 52 (quoting Liu, [00369], [00371]).

Novartis, however, fails to establish that a POSA would have been motivated to modify the ionic strength of Lochrie’s compositions to arrive at the claimed high-concentration rAAV compositions based on Liu. Davies, ¶¶122-125. **First**, Liu’s viral particle concentration is several magnitudes lower than Lochrie’s concentration, which is lower than the claimed rAAV concentration. Davies, ¶123. Because the POSA understood that increased concentration causes increased aggregation, the POSA would not have relied on Liu for guidance on how to formulate a high-concentration rAAV composition. *Supra* §§IV.A.1-IV.A.1.a.

Second, Novartis states in Ground 2 that the POSA’s motivation is to develop an rAAV composition for parenteral administration (Petition, 47, 49), but

the POSA would have considered Liu's salt concentration (300 mM NaCl and 5 mM MgCl₂), which provides the composition's ionic strength, to raise the risk of tissue damage and pain when injected due to its high hypertonicity. *Supra* §IV.A.1.b; Davies, ¶124.

Third, the POSA would not have considered Liu's report of no settling or precipitation based on visual assessment to be insufficient for determining whether there was significant aggregate formation or not. *Supra* §IV.A.2.b; Davies, ¶125.

In contrast to Novartis's argument that the POSA would have increased the ionic strength of Lochrie's Example 2 by adding NaCl based on Liu, the '542 patent applied certain multivalent ions to increase ionic strength while maintaining the isotonicity of high concentration rAAV compositions. *Trivascular*, 812 F.3d at 1068 (Liu's high salt concentration "would destroy [the] basic objective of" parenteral compositions for therapeutic use.); *Chemours*, 4 F.4th at 1376. Thus, Novartis only reaches the combined rAAV concentration and ionic strength claim elements using impermissible hindsight.

iii. The Prior Art as a Whole Undermines Novartis's Motivation Arguments

Novartis alleges that the "POSA would have been motivated to increase the ionic strength of Lochrie's composition to prevent aggregation because, as the '542 patent admits, it was known that 'AAV2 vectors require elevated concentrations of salt to prevent aggregation.'" Petition, 52 (citing Ex. 1001, 1:54-55; *see also* 4:67-

5:2). Novartis ignores that the '542 patent's next sentence states "[h]owever, 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." Ex. 1001, 5:4-7. Thus, the POSA would not have avoided raising the salt concentration in manner that resulted in a hypertonic composition. *Supra* §IV.A.2.b.

Moreover, the '542 patent's statement regarding high salt concentrations cites to the purification methods of Xie et al. (Ex. 2006). Ex. 1001, 1:52-52 ("Xie and coworkers similarly reported that at concentrations exceeding 0.1 mg/mL [1.602×10^{13} vg/ml], AAV2 vectors require elevated concentrations of salt to prevent aggregation").⁵ Xie explained stated 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...." Ex. 2006, 22-23. Thus, even for *molar* salt solutions of CsCl

⁵ An AAV-2 concentration of 0.1 mg/ml corresponds to approximately 1.6×10^{13} vg/ml. rAAV genome particles have an average molecular weight of 3.746×10^3 kDa, and 0.1mg/ml is 6.022×10^{16} kDa/ml, so a concentration of 0.1 mg/ml of rAAV particles is equal to about 1.602×10^{13} vg/ml. The '542 patent also notes that 0.06 mg/ml corresponds to approximately 10^{13} vg/ml. Ex. 1001, 1:58-60.

having osmolarity of ~ 6600 mOsm that would be unsuitable as a parenteral formulation, AAV particle precipitation was observed. Davies, ¶¶121. Xie further stated that a solution of “0.25 M NaCl [250 mM] resulted in **significant loss**” of AAV. Ex. 2006, 22-23. Thus, Xie teaches that a salt concentration of 250 mM NaCl, a hypertonic composition, was inadequate to prevent significant rAAV aggregation in Xie’s solution. Davies, ¶¶121.

Novartis also disregards statements Frei stating that its compositions “must take into account the additional **threat to stability posed by the high salt concentrations.**” Frei, 19:9-14; *see also id.*, 18:19-24; 21:25-26; 21:42-22:6. In an obviousness analysis, “[e]vidence that supports, rather than negates, patentability must be fairly considered,” as the POSA has “knowledge of the entire body of technological literature, including that which might lead away from the claimed invention.” *Dow Chem.*, 837 F.2d at 473. Fairly considering such evidence, Novartis has failed to establish a motivation to make the claimed composition based on the cited references.

2. Novartis Fails to Establish a Reasonable Expectation of Success in Developing a High-Concentration rAAV Composition Without Significant rAAV Aggregation

Novartis nonetheless argues the “POSA would have reasonably expected success in achieving such concentrations, since Lochrie itself provides methods for generating high yields of AAV.” Petition, 48. This is not enough to establish a

reasonable expectation of success. 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). Novartis fails to establish that the POSA would have reasonably expected that modifying Lochrie’s stock solution to have the claimed rAAV concentration and ionic strength would have resulted in a composition without significant aggregation according to the requirements of claims 5 and 6.

Lochrie never addresses aggregation or stability for rAAV compositions. For instance, the composition of Example 2 that Novartis relies on (Petition, 51, 55, 57) is a stock solution that is then subjected to various conditions to remove empty capsids (*supra* §IV.B, citing Lochrie, 5:15-18), but Lochrie does not address whether there is significant aggregation in the stock composition of Example 2, or in any other disclosure. Davies, ¶¶126-127.

a. Novartis Fails to Consider the Unpredictability of Liquid Biological Formulations

Novartis relies on what it alleges are similarities between viral vector and protein formulations. Petition, 8. Dr. Amiji cites Carpenter (Ex. 1018), which 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.***” Ex.

1018, 188. Thus, as explained in Ground 1, the art is unpredictable and the POSA would have been skeptical that a concentrated rAAV composition would have been feasible particularly in view of the many accounts, including in Huang, Wright (Ex. 1007), and Croyle (Ex. 1013), detailing rAAV aggregation issues. *Supra* §§IV.B.2.a-IV.B.2.b; Davies, ¶128.

b. Huang, Mingozzi, Liu, Johnson, Liu, and Other Cited Art Do Not Remedy Novartis's Failure to Establish a Reasonable Expectation of Success Argument

Novartis alleges that a “POSA would have reasonably expected success in minimizing particle size in view of Huang’s teaching that its optimized compositions ‘could lead to a 30-50% reduction in the size of aggregates at high vector concentrations.’” Petition, 54 (citing Huang, S286). The POSA would have recognized that Huang’s composition still contained aggregates and that Huang provided no information about its formulation or what the purported size reduction of aggregation Huang’s statement represents. *Supra* §IV.A.2.c; Davies, ¶129.

Novartis cannot establish a reasonable expectation of success based on “Liu’s ‘demonstrat[ion] that viral vector compositions can be stably stored in the temporary storage buffers of the invention for extended periods of time’” Petition, 54 (quoting Ex.1009, [00371]). Novartis fails to explain how Liu’s low concentration adenoviral compositions would have supported the POSA’s reasonable expectation of success for the claimed high-concentration composition.

Liu's Example 17 contained an rAAV vector particle concentration of 3.24×10^8 , several orders of magnitude below the claimed concentration exceeding 10^{13} vg/ml. *Supra* §IV.A.2.b; Davies, ¶130.

As Novartis and Dr. Amiji acknowledge, the POSA would have understood that "rAAV undergoes concentration-dependent aggregation" (Ex. 1007, 17) wherein aggregation increases at concentrations above 10^{13} vg/ml. Petition, 19, 32 (citing Ex. 1005, S286). Given the relationship between higher concentration and increased aggregation (*supra* §IV.A.1.a), however, Novartis fails to explain how Liu's Example 17 would have supplied the POSA with a reasonable expectation that Lochrie's modified composition would not exhibit significant aggregation, particularly as required by claims 5 and 6. *Infra* §IV.B.3 (explaining the Petition's complete failure of proof with respect to the particle size requirements.); Davies, ¶131.

In its section on pH, Novartis alleges that in Johnson the "POSA would have reasonably expected success in raising the pH of Lochrie's composition, since Johnson demonstrated that "[a]t pH 7.5, the virus particles occurred singly and were evenly distributed." Petition, 50 (quoting Ex. 1019, 589). Neither Novartis, nor Dr. Amiji, explain why the POSA would have gleaned a reasonable expectation of success in making a high-concentration rAAV composition without significant aggregation as they do not point to where Johnson an AAV

concentration, ionic strength, or any other details about its composition. Davies, ¶132. Novartis also concludes that the claimed concentration and ionic strength elements was obvious. Petition 49, 52 (citing *Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1368 (Fed. Cir. 2012)).

For reasonable expectation of success, however, the Board should consider the claim as a whole, including elements in claims 5 and 6 that relate to the detection of aggregates. *Ruiz*, 357 F.3d at 1275 (Fed. Cir. 2004). “*Alcon Research* does not stand for the proposition [Novartis] would have it support, namely, that compositions comprising multiple components with amounts of each component falling within the recited ranges necessarily meets the functional limitations.” *Spectrum Solutions LLC v. Diagnostics*, IPR2021-00851, Paper 13 at 16-17 (P.T.A.B. Nov. 18, 2021). As in *Spectrum*, “[Novartis] provides no cogent argument for extending *Alcon Research* to stand for the proposition that all compositions meeting the recited ranges of multiple components” also meet the lack of aggregate standards of claims 5 and 6. *Id.* at 17; *Infra* §IV.B.3.

3. Novartis Fails to Establish that Lochrie, in View of Huang, Mingozi, Johnson, and Liu Render Claims 5 and 6 Obvious

Ground 2 rehashes Ground 1’s arguments relating to claims 5 and 6. Petition, 55-56 (claim 5), 57 (claim 6). Ground 2’s arguments for claims 5 and 6 fail for the same reason as Ground 1. *Supra* §IV.A.3. Ground 2 also rehashes Ground 1’s arguments for “reasonably expected success in minimizing particle size

in view of Huang and Liu.” Petition, 56 (claim 5), Petition, 57 (claim 6).

Novartis’s reasonable expectation arguments fail for the same reason as Ground 1.

Supra §§IV.A.2.b-IV.A.2.c.

The Petition makes the conclusory statements that “[t]o the extent modifications to Lochrie’s composition, beyond those described above, would be required to achieve the features of claim 5” (Petition, 56); and “to improve recovery following filtration through a 0.22µm filter, only routine optimization of the known stabilization factors already contained therein would be needed to reduce any residual aggregation” for claim 6 (Petition, 57). As explained above, however, there was no guidance in the prior art that suggested that adjusting elements of the composition, such as ionic strength greater than 200 mM, would result in a high-concentration rAAV composition without substantial aggregation. *Supra* §IV.A.1.c (Ground 1), §IV.B.1.a.iii (Ground 2); Davies, ¶134. Wright devotes a whole section to viral vector aggregates as being an unresolved and not well understood issue in the field. Davies, ¶135. The inventors’ solution to a long-time problem “is only straightforward in hindsight” based on the teachings of the ’542 patent. *Leo Pharm.*, 726 F.3d at 1355. Accordingly, Novartis has failed to establish claims 5 and 6 as obvious under Ground 2.

V. THE BOARD SHOULD DENY THE PETITION UNDER *FINTIV* AND §314(a)

The Board should exercise its discretion to deny institution of the Petition under *Fintiv* and 35 U.S.C. §314(a). *See Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 (PTAB Mar. 20, 2020) (precedential) (“*Fintiv*”); *NHK Spring Co., Ltd. v. Intri-Plex Techs. Inc.*, IPR2018-00752, Paper 8 (PTAB Sep. 12, 2018) (precedential). As the Board noted in *General Plastic Industrial Co. v. Canon Kabushiki Kaisha*, when “exercising discretion under 35 U.S.C. §314(a) and 37 C.F.R. § 42.108(a), we are mindful of the goals of the AIA—namely, to...make the patent system *more efficient*....” IPR2016-01357, Paper 19 at 16 (PTAB Sept. 6, 2017).

Institution would be highly inefficient. Novartis filed two IPR petitions challenging the same claims of the ’542 patent, neither of which will reach final decision before trial in the Litigation. *See* Ex. 2010, 2 (March 2024 trial date). Novartis has not provided a *Sotera* stipulation and intends to present the ***same issues*** to the district court first. Ex. 2011, 234-50. Claim construction briefing is complete, a *Markman* hearing was held, fact discovery will be complete by the end of June, and trial is only nine months away. Novartis delayed filing these IPRs for nearly twelve months even though Genzyme asserted the ’542 patent on February 23, 2022. Novartis’s Petitions did not even address *Fintiv* or whether the challenges present compelling merits despite the scheduled March 2024 jury trial.

These facts, combined with the weakness of Novartis’s patentability challenges, support denying institution under *Fintiv*. None of the exceptions in the Director’s Interim Procedure for Discretionary Denials (June 21, 2022) (“IP”) apply here. IP, 4-7.

A. Factor 1: No Stay Has Been Sought and None is Likely

Novartis has not sought a stay of the Litigation and has made no indication that it intends to seek a stay. *See Mylan Labs. Ltd. v. Janssen Pharmaceutica NV*, IPR2020-00440, Paper 17 at 14 (PTAB Sept. 16, 2020) (*Fintiv* factor 1 “leans towards denial of institution” where the facts “indicate that no stay is likely to be entered”).

Judge Andrews is unlikely to grant a stay, particularly in view of the upcoming trial and advanced status of the case (*supra* §V; *infra* §§V.B-V.C). *See Ansell Healthcare Prods. LLC v. Reckitt Benckiser LLC*, Case No. 15-cv-00915, ECF No. 105 (D. Del. Dec. 1, 2016) (Andrews, J.) (denying motion to stay where “[n]o IPR is sought on two of the four asserted patents” and “[t]he prospects of meaningful simplification are not great.”); *see also Collabo Innovations, Inc. v. Sony Corp. et al.*, Case No. 15-cv-01094, ECF No. 43 (D. Del. Jan. 5, 2017) (Andrews, J.) (denying motion to say where “fourth patent and its claims will have to be litigated regardless”). Factor 1 thus weighs against institution.

B. Factor 2: The Proximity of Trial Weighs Against Institution

“If the court’s trial date is earlier than the projected statutory deadline, the Board generally has weighed this fact in favor of exercising authority to deny institution” *Fintiv* at 9. A five-day jury trial is scheduled to begin on March 25, 2024. Ex. 2010, 2. The final written decision in this case (if instituted) would not be expected until September 2024. See 35 U.S.C. §§314(b)(1), 316(a)(11). The jury will reach its verdict well before the Board’s final written decision in this case. The March 2024 trial date is unlikely to change⁶, but even if it moved, trial will likely conclude long before September 2024. See *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 15 at 13 (PTAB May 13, 2020) (informative) (“*Fintiv II*”) (“We generally take courts’ trial schedules at face value absent some strong evidence to the contrary.”). Factor 2 thus weighs against institution. *Fintiv II* at 13 (factor 2 favors discretionary denial where the “District Court trial is scheduled to begin two months before [the] deadline to reach a final decision”).

The result is similar if the Board “consider[s] the median time from filing to disposition” in the district court,” which is 32 months in the District of Delaware.

⁶ Judge Andrews denied Genzyme’s request to add a patent into the suit because of his concern that it may “cause substantial delay,” illustrating that Judge Andrews is not interested in delaying the district court proceedings. Ex. 2014.

See Ex. 2012 (32 months, patent cases in Delaware); Ex. 2013, 14 (36.3 months in all civil cases). Thirty-two months from the filing of the complaint would be August 2024, still before the expected Final Written Decision.

C. Factor 3: The Parties’ Significant and Continuing Investment in the Litigation Weighs Against Institution

Factor 3, considering “the amount and type of work already completed in the parallel litigation by the court and the parties at the time of the institution decision” weighs heavily in favor of denial. *Fintiv* at 9-10. The claim constructing hearing was held in April 2023, (*Genzyme Corporation et al v. Novartis Gene Therapies, Inc. et al.*, Case No. 1:21-cv-01736, D.I. 177 (D. Del. May 5, 2023), fact discovery is two weeks from completion and opening expert reports will be served August 4, 2023. Ex. 2010, 2. Genzyme served infringement contentions, and Novartis served its amended invalidity contentions in October 2022—contentions which raise the same arguments and art in this Petition. Ex. 2011, 226-234 (asserting “Liu (2003) alone or in combination with” “Huang” and “Mingozzi”), 250-255 (asserting “Lochrie (2003) and Johnson (1975) alone, or in combination with” “Huang” and “Mingozzi.”). By the time the Board makes an institution decision, fact discovery will be complete and expert discovery nearly complete. Ex. 2010, 2.

Moreover, Novartis was aware of each prior art reference at least as early as October 2022 (Ex. 2011), even though the ’542 patent was first asserted in

February 2022.⁷ Regardless, Novartis waited to file the Petition until February 2023, the day before expiration of the one-year §315(b) bar. *See F5 Networks, Inc. v. WSOU Investments, LLC et al.*, IPR2022-00238, Paper No. 11 at 10 (PTAB May 19, 2022) (“[a]s part of this factor, we additionally consider whether Petitioner unreasonably delayed in filing the Petition in this case.”).

“Based on the level of investment and effort already expended on claim construction and invalidity contentions in the District Court,” as well as over 660,000 pages of document productions, discovery requests, responses, and disputes, *Fintiv* factor 3 weighs heavily in favor of discretionary denial. *Fintiv II* at 14; *see also Samsung Elecs. Co., Ltd. v. California Inst. of Tech.*, IPR2023-00133, Paper 10 at 15 (PTAB May 4, 2023) (factor 3 weighs in favor of denial where the “scheduling order . . . indicates that Petitioner should have already served its opening expert report on validity” and “the deadline for rebuttal experts reports [was] only days away.”).

⁷ Novartis served its amended invalidity contentions on October 11, 2022—waiting four months before filing this Petition in February 2023. *See Ex. 2011*, 279.

D. Factor 4: The Overlap in Issues Favors Non-Institution

“*Fintiv* requires that [the Board] consider whether ‘the patentability disputes before the [district court] will resolve all or substantially all of the patentability disputes between the parties.’” *SK Innovation Co., Ltd. v. LG Chem, Ltd.*, IPR2020-00991, Paper 14 at 16 (PTAB Nov. 30, 2020). Novartis does not contend the grounds raised here are any different from those asserted in the district court. Nor could it. *Supra* V; Ex. 2011, 234, 242.

Novartis has not offered a stipulation to not pursue in the Litigation Grounds it raised or reasonably could have raised in its Petitions. *See Sotera Wireless, Inc. v. Masimo Corp.*, IPR2020-01019, Paper 12 (PTAB Dec. 1, 2020) (precedential as to §II.A)). Because Novartis raises the same arguments and art and has failed to provide a *Sotera*-type stipulation, this factor weighs in favor of denial.

E. Factor 5: The Identical Nature of the Parties Favors Non-Institution

Novartis Gene Therapies, Inc. and Novartis Pharmaceuticals Corporation are Petitioners and the only defendants in the Litigation. Genzyme Corp. is the Patent Owner and a plaintiff in Litigation. This favors denial. *Fintiv* at 6; *Samsung Elecs. Co., Ltd. v. California Institute of Technology*, IPR2023-00130, Paper 10 at 20 (PTAB May. 04, 2023) (fifth factor weighs against institution where petitioner “is a defendant in the Underlying Litigation.”).

F. Factor 6: Other Circumstances

Because *Fintiv* factors 1-5 favor discretionary denial, the Board must consider whether the Petition presents a challenge with compelling merits. For compelling merits, the Board considers whether the “evidence, if unrebutted in trial, would plainly lead to a conclusion that one or more claims are unpatentable by a preponderance of the evidence.” *Id.* at 4. “A challenge can only ‘plainly lead to a conclusion that one or more claims are unpatentable’ if it is highly likely that the petitioner would prevail with respect to at least one challenged claim.” *OpenSky Indus., LLC v. VLSI Tech. LLC*, IPR2021-01064, Paper 102 at 49 (PTAB Oct. 4, 2022). The “compelling-merits challenge is a higher standard than the reasonable likelihood required for the institution of an IPR under 35 U.S.C. §314(a).” *Id.* at 49-50; *see also Commscope Techs LLC v. Dali Wireless, Inc.*, IPR2022-01242, Paper 23 at 3 (PTAB Feb. 27, 2023).

Here, the merits are weak and fall far short of “compelling.” *Supra* §§IV.A, IV.B. This factor favors denial because no ground is “sufficiently strong to override the concerns about duplication of effort by the Board and the district court.” *See Immersion Sys. LLC v. Midas Green Techs., LLC*, PGR2021-00104, Paper 15 at 16-17 (PTAB Jan. 31, 2022). Thus, the *Fintiv* factors all favor of denial, and the Board should exercise its §314(a) discretion to deny institution.

VI. CONCLUSION

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

Respectfully submitted,

Dated: June 15, 2023

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WORD COUNT CERTIFICATION

Pursuant to 37 C.F.R. § 42.24(d), I certify that this Preliminary Response contains 12,321 words (excluding the title page, table of contents, table of exhibits, this certificate, and the certificate of service), as determined by Microsoft Word.

Dated: June 15, 2023

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CERTIFICATE OF SERVICE

I certify that today in:

Novartis Gene Therapies, Inc. & Novartis Pharmaceuticals Corporation v. Genzyme Corporation, IPR2023-00609 (U.S. Patent 9,051,542)

I caused to be served a copy of:

PATENT OWNER'S PRELIMINARY RESPONSE, and
EXHIBITS

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