

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAREPTA THERAPEUTICS, INC.,

Petitioner

v.

GENZYME CORPORATION,

Patent Owner

U.S. Patent No. 9,051,542

“Compositions and Methods to Prevent AAV Vector Aggregation”

IPR2025-01194

**PETITIONER’S SUR-REPLY IN SUPPORT OF ITS OPPOSITION TO
PATENT OWNER’S REQUEST FOR DISCRETIONARY DENIAL**

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EX1021	Verma and Somia, “Gene therapy – promises, problems and prospects,” <i>Nature</i> , Vol. 389, 1997 (“Verma”)
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EX1045	Wright <i>et al.</i> , “Recombinant adeno-associated virus: Formulation challenges and strategies for a gene therapy vector,” 8(2) <i>Current Opinion in Drug Discovery & Development</i> 2003: 174-178 (“Wright 2003”)
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EX1049	Okada <i>et al.</i> , “Scalable Purification of Adeno-Associated Virus Serotype 1 (AAV1) and AAV8 Vectors, Using Dual Ion-Exchange Adsorptive Membranes,” <i>Human Gene Therapy</i> 20.9 (2009): 1013-1021 (“Okada”)
EX1050	Venkatakrishnan <i>et al.</i> , “Structure and Dynamics of Adeno-Associated Virus Serotype 1 VP1-Unique N-Terminal Domain and Its Role in Capsid Trafficking,” <i>Journal of Virology</i> 87.9 (2013): 4974-4984 (“Venkatakrishnan”)
EX1051	Tibbetts and Giam, “In Vitro Association of Empty Adenovirus Capsids with Double-Stranded DNA,” <i>Journal of Virology</i> 32.3 (1979): 995-1005 (“Tibbetts”)
EX1052	Huyghe <i>et al.</i> , “Purification of a Type 5 Recombinant Adenovirus Encoding Human p53 by Column Chromatography,” <i>Human Gene Therapy</i> 6.11 (1995): 1403-1416 (“Huyghe”)
EX1053	Roth and Jeltsch, “Biotin-Avidin Microplate Assay for the Quantitative Analysis of Enzymatic Methylation of DNA by DNA Methyltransferases,” <i>Biol. Chem.</i> , Vol. 381, pp. 269 – 272, March 2000 (“Roth”)
EX1054	O’Riordan <i>et al.</i> , “Scaleable chromatographic purification process for recombinant adeno-associated virus (rAAV),” <i>The Journal of Gene Medicine</i> , 2.6 (2000): 444-454 (“O’Riordan”)

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EX1055	Kreilgaard <i>et al.</i> “Effect of Tween 20 on Freeze-Thawing- and Agitation-Induced Aggregation of Recombinant Human Factor XIII,” <i>Journal of Pharmaceutical Sciences</i> (1998): 1593-1603 (“Kreilgaard”)
EX1056	Auricchio <i>et al.</i> , “Isolation of Highly Infectious and Pure Adeno-Associated Virus Type 2 Vectors with a Single-Step Gravity-Flow Column,” <i>Human Gene Therapy</i> (2001): 71-76 (“Auricchio”)
EX1057	<i>Phosphate-buffered saline</i> , Cold Spring Harbor Laboratory Press (2006), https://cshprotocols.cshlp.org/content/2006/1/pdb.rec8247
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EX1065	Yeung and Tufaro, “Virus Vectors for Gene Therapy of the Nervous System,” in <i>Protocols for Neural Cell Culture</i> , 3d edition, Fedoroff and Richardson, eds., 2001, pp. 229-44 (“Yeung”)
EX1066	Grimm <i>et al.</i> “Novel Tools for Production and Purification of Recombinant Adenoassociated Virus Vectors,” <i>Human Gene Therapy</i> 9 (18) (1998): 2745-2760 (“Grimm”)
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EX1068	Schwartz, “Diafiltration for Desalting or Buffer Exchange,” <i>BioProcess International</i> , May 2003, pp. 43-49 (“Schwartz”)
EX1069	Hatano <i>et al.</i> “Immunogenic and Antigenic Properties of a Heptavalent High-Molecular-Weight O-Polysaccharide Vaccine Derived from <i>Pseudomonas aeruginosa</i> ,” <i>Infection and Immunity</i> (1994): 3608-3616 (“Hatano”)
EX1070	Monahan <i>et al.</i> , “Direct intramuscular injection with recombinant AAV vectors results in sustained expression in a dog model of hemophilia,” <i>Gene Therapy</i> (1998): 40-49 (“Monahan”)
EX1071	Oster, “The isoelectric points of some strains of tobacco mosaic virus,” <i>J. Biol. Chem.</i> 190 (1951): 55-59 (“Oster”)
EX1072	Konz <i>et al.</i> , “Development of a Purification Process for Adenovirus: Controlling Virus Aggregation to Improve the Clearance of Host Cell DNA,” <i>Biotechnol. Prog.</i> 2005, 21, 466-472 (“Konz 2005”)

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EX1074	Booth <i>et al.</i> , “Transfection-free and scalable recombinant AAV vector production using HSV/AAV hybrids,” <i>Gene Therapy</i> (2004): 829-837 (“Booth”)
EX1075	Dufour <i>et al.</i> , “Toxicity and Efficacy Evaluation of an Adeno-Associated Virus Vector Expressing Codon-Optimized RPGR Delivered by Subretinal Injection in a Canine Model of X-linked Retinitis Pigmentosa,” <i>Human Gene Therapy</i> (2020): 253-267 (“Dufour”)
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EX1077	Keeler and Flotte, “Recombinant Adeno-Associated Virus Gene Therapy in Light of Luxturna (and Zolgensma and Glybera): Where Are We, and How Did We Get Here?” <i>Annual Review of Virology</i> (2019): 601-621 (“Keeler”)
EX1078	Davidsson <i>et al.</i> , “A comparison of AAV-vector production methods for gene therapy and preclinical assessment,” <i>Scientific Reports</i> (2020): 21532 (“Davidsson”)
EX1079	T.W. Graham Solomons, <i>Organic Chemistry</i> (5th ed. 1992) (“Solomons”)
EX1080	Bates and Acree, “pH Values of Certain Phosphate-Chloride Mixtures and the Second Dissociation Constant of Phosphoric Acid From 0° to 60° C,” <i>J. Res. Natl. Bur. Stand.</i> 30.2 (1943): 129-155 (“Bates”)

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EX1081	Po and Senozan, “The Henderson-Hasselbalch Equation: Its History and Limitations,” <i>Journal of Chemical Education</i> 78.11 (2001): 1499 (“Po”)
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EX1092	<i>Genzyme Corp. v. Sarepta Therapeutics, Inc. et al.</i> , C.A. No. 24-882-RGA (D. Del.) (April 16, 2025), Plaintiff’s Initial Claim Charts on Infringement Pursuant to Paragraph 4(C) of the Default Standard for Discovery, Redacted Public Version

Sarepta's arguments are directly responsive to Genzyme's contentions regarding alleged "settled expectations" – the principal argument in Genzyme's request for discretionary denial. Genzyme should not benefit from "settled expectations" that are based on its unfair dealings with the Patent Office and prior misrepresentations to the Board. The unique circumstances here do not "vastly expand" the scope of discretionary denial disputes. Instead, Genzyme's pattern of unfair dealings weighs heavily against its request for discretionary denial, in accordance with Board precedent. Maintaining the integrity of the patent examination and IPR processes is among the best uses of Board resources. Thus, Genzyme's discretionary denial request should be denied.

I. Consideration of Genzyme's Unfair Dealings as One Factor in the Discretionary Denial Process Is Squarely in Line with Board Precedent

Sarepta appropriately relies on Board precedent for its argument that Genzyme's unfair dealings should be considered as one factor that weighs heavily against discretionary denial. In *Tessell*, the Board stated that "the Office may consider *unfair dealings as a factor* when determining whether to exercise discretion to deny institution under 35 U.S.C. § 314(a)." *Tessell, Inc. v. Nutanix, Inc.*, IPR2025-00322, Paper 14, p. 2 (PTAB June 12, 2025) (emphasis added). This statement is not restricted to the particular facts of *Tessell*, nor is it restricted to unfair dealings by *petitioners*, notwithstanding Genzyme's spurious arguments to the

contrary. Sarepta has set out in detail Genzyme's specific misrepresentations, centered around a specific piece of prior art, during the Novartis IPR proceedings. Sarepta has further pointed to Novartis's specific allegations of inequitable conduct that the District Court permitted Novartis to add to its pleadings over Genzyme's objections in a prior litigation involving the '542 patent.

Moreover, in *Tessell*, the Board stated that "the determination to exercise discretion to deny institution is based on a holistic assessment of all of the evidence and arguments presented." *Tessell*, Paper 14, p. 3. Sarepta has argued that such a holistic assessment, including consideration of Genzyme's unfair dealings as a particularly significant factor among multiple other factors, warrants denial of Genzyme's discretionary denial request. Sarepta's arguments fall squarely within Board precedent, and do not require any extension of *Tessell*.

II. Genzyme Has Repeatedly Failed to Offer Any Substantive Response Regarding Its Misrepresentations of Potter During the Novartis IPRs

As Sarepta set out in detail in its Petition, Genzyme and its expert did not "accurately" respond to Novartis's arguments regarding the disclosures of Potter during the Novartis IPR proceedings. Instead, they misrepresented to the Board that Potter discloses vector genome concentrations that are "orders of magnitude" lower than those of the claimed compositions – when the plain disclosure in Potter confirms that they are not. This misrepresentation is not an insignificant

misstatement regarding a “different section” of a “minor reference.” It is a mischaracterization that Genzyme advanced and relied on to distinguish Potter from the challenged claims and overcome Novartis’s arguments. Moreover, there is no “substantive dispute” on the technical merits, as Genzyme contends. The disclosure in Potter is clear on its face. Yet, even now, Genzyme offers no explanation for its blatant mischaracterization. This omission in Genzyme’s reply speaks volumes.

III. Inequitable Conduct Issues Weigh Against Discretionary Denial

Sarepta has neither argued that inequitable conduct is relevant to the merits of the Petition nor sought to adjudicate inequitable conduct before the Board. Instead, Sarepta’s arguments respond directly to Genzyme’s efforts to rely on settled expectations to defeat Sarepta’s Petition. The fact that the District Court in the earlier Novartis litigation allowed Novartis to amend its pleadings to add inequitable conduct allegations, over Genzyme’s objections, helps to demonstrate a pattern of unfair dealings by Genzyme that weighs heavily against discretionary denial. Moreover, it is Genzyme, not Sarepta, that seeks to expand Board precedent. Without citing any supporting case, Genzyme argues that the existence of inequitable conduct proceedings somehow weighs *in favor of* discretionary denial. This argument, which ignores Genzyme’s improper efforts to benefit from its earlier misstatements during prosecution by relying on settled expectations, is contrary to *Tessell* and should be flatly rejected.

October 22, 2025

Respectfully submitted,

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §42.6, I hereby certify that on October 22, 2025, the foregoing document, Petitioner's Sur-Reply in Support of Its Opposition to Patent Owner's Request for Discretionary Denial was served via email on the following counsel of record:

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