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TREND REPORT

Regulatory Trends in the World of AAV Gene Therapies and Rare Disease

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INTRODUCTION

Adeno-associated virus–based gene therapies occupy a paradoxical position in rare-disease medicine. AAVs are a modular gene delivery technology capable of addressing many different diseases through small modifications to existing AAVs. However, each new therapy has traditionally been regulated as an independent product despite significant homogeneity to its already-approved predecessor. Developers must therefore repeat substantial portions of manufacturing, analytical, nonclinical, and clinical work even when a new program uses a previously characterized capsid, transgene, production process, route of administration, or target tissue. For rare diseases affecting only a handful of patients, this product-by-product model can make development economically and operationally impractical. Regulatory policy is beginning to move away from that model. Initiatives announced or advanced in 2026—particularly in the United States and United Kingdom—reflect a broader shift toward platform-based development, reliance on prior knowledge, flexible evidence standards, earlier regulator engagement, and lifecycle evidence generation. These reforms do not eliminate the need to establish product quality, safety, and effectiveness. Instead, they seek to concentrate new testing on the elements that materially differ among related therapies.

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THE BGTC MODEL: TURNING AAV DEVELOPMENT INTO A REPEATABLE PROCESS

The Foundation for the National Institutes of Health's Accelerating Medicines Partnership Bespoke Gene Therapy Consortium, or AMP BGTC, is one of the clearest expressions of this platform-oriented approach. The consortium brings together the National Institutes of Health, the U.S. Food and Drug Administration, life-sciences companies, academic researchers, and nonprofit organizations to facilitate AAV gene therapies for rare genetic diseases whose populations are too small to support conventional commercial development. Its central objective is to create a standardized operational and regulatory playbook using up to eight clinical-trial test cases.

The BGTC Regulatory Playbook includes templates for INTERACT and pre-investigational-new-drug meetings, IND modules, clinical protocols, informed-consent documents, and nonclinical summaries. It also publishes selected regulatory submissions and FDA responses, addressing a longstanding problem in gene-therapy development: regulatory experience is frequently treated as confidential program-specific knowledge rather than reusable scientific infrastructure. The underlying concept is that AAV is not simply a collection of unrelated products. Its performance is strongly influenced by recurring variables—including capsid, dose, route of administration, manufacturing process, expression cassette, target tissue, and immune response. Where these elements remain sufficiently comparable, existing CMC, biodistribution, toxicology, immunogenicity, or clinical information may help answer questions for subsequent products. The BGTC describes its platform approach as leveraging prior knowledge from related AAV products and establishing standardized minimum requirements while preserving appropriate safety thresholds.

This does not mean that changing a transgene is automatically risk-free. A new transgene may alter potency, tissue-specific expression, cellular stress, immunogenicity, or toxicity, while changes to capsids, promoters, doses, or manufacturing processes may undermine comparability. The emerging regulatory principle is therefore selective reuse rather than blanket extrapolation: sponsors should identify what is genuinely shared, what has changed, and why prior evidence remains applicable.

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PLAUSIBLE MECHANISM AS AN EVIDENTIARY FRAMEWORK

A second important development was the FDA's February 23, 2026 draft guidance on the "Plausible Mechanism Framework" for individualized therapies targeting genetic conditions with a known biological cause. The framework is intended for situations in which randomized trials are infeasible because patient populations are extremely small. FDA's proposed evidentiary structure includes identification of the disease-causing abnormality, demonstration that the therapy addresses the causal defect or a proximate biological pathway, confirmation of successful target engagement or editing, natural-history evidence, and clinical outcomes or predictive biomarkers.

As summarized by the American Society of Gene & Cell Therapy in its March 2026 Advocate newsletter, the framework could support substantial evidence through a combination of mechanistic rationale, biomarkers, natural-history information, and targeted molecular effects. ASGCT connected the proposal to an "interventional genetics" model in which the therapeutic destination may change while the underlying development and regulatory infrastructure remains repeatable across a platform.

The framework is particularly significant because FDA acknowledges that a first-in-human study may also serve as the pivotal investigation and that a single adequate and well-controlled study, together with confirmatory evidence, may support approval in an appropriate case. It also contemplates master protocols and a common application covering product variants directed at different mutations within a gene. A strongly supported mechanism could potentially help justify adding variants not represented in the original clinical dataset.

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Nevertheless, the February guidance is a draft, contains nonbinding recommendations, and is framed principally around genome-editing and RNA-based therapies—not conventional AAV gene-addition products. FDA left open its possible application to other individualized modalities that directly address the underlying disease cause, but AAV applicability will require further clarification. ASGCT's April 27 comments supported the framework's emphasis on biological plausibility but requested greater flexibility. The Society argued that FDA should avoid implying that every evidentiary element is mandatory in every case, particularly where the mechanism is compelling, unmet need is severe, and the treatment effect is large. It also requested clarification concerning natural-history comparators, new approach methodologies, pediatric treatment before symptom onset, and the framework's applicability beyond genome editing and RNA therapeutics. For AAV developers, the plausible-mechanism concept may ultimately complement rather than replace platform regulation. A platform framework can establish confidence in the vector, process, analytics, and delivery system, while a plausible-mechanism framework can address why a disease-specific payload is expected to produce clinical benefit.

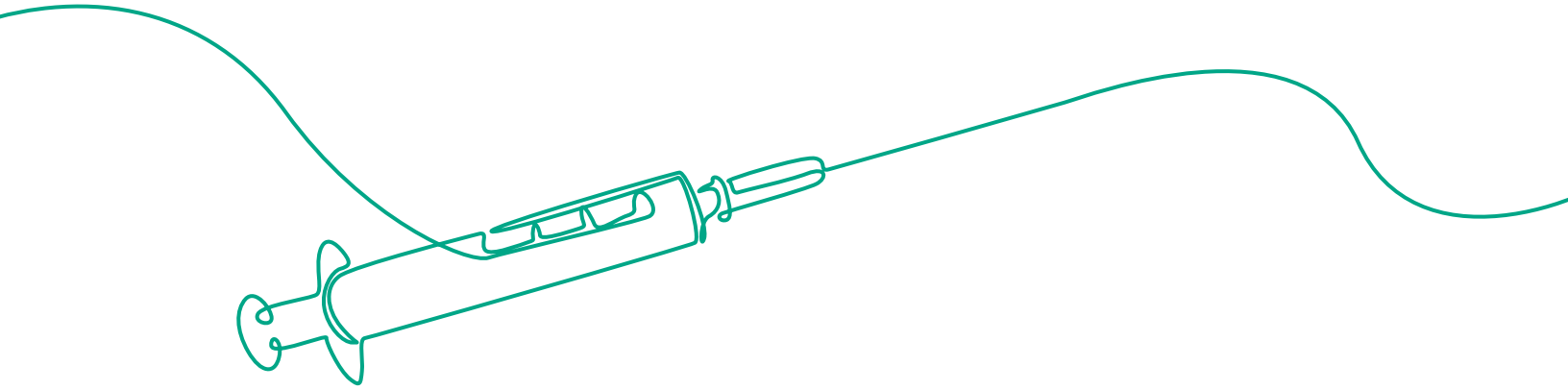
ADDITIONAL U.S. STREAMLINING MEASURES IN 2026

Other FDA actions in 2026 reinforce this direction. On January 11, FDA described a more flexible approach to CMC requirements for cell and gene therapies. The agency stated that investigational specifications may remain permissive while knowledge accumulates, validation can follow a product-lifecycle approach, and minor manufacturing changes may be supported through appropriately justified comparability packages rather than unnecessarily onerous datasets. FDA also acknowledged that small CGT populations may not generate enough commercial-scale lots to establish specifications through conventional statistical approaches. On June 2, FDA issued draft guidance on leveraging prior knowledge in human gene-therapy products incorporating genome editing. It expressly permits consideration of public and platform knowledge across CMC, nonclinical, and clinical development, provided that the sponsor presents a scientific rationale for its applicability to the new product. FDA identified rare, serious, and life-threatening diseases as settings in which this approach may be particularly valuable and encouraged early discussion through INTERACT and pre-IND meetings.

2026 FDA Streamlining Measures

- Jan 11: Flexible CMC for cell/gene therapies
- Jun 2: Prior knowledge guidance for genome editing

Although this guidance is also directed primarily toward genome editing, its regulatory logic closely resembles the BGTC model: characterize a platform deeply, document its boundaries, and avoid repeating studies that do not resolve a meaningful new uncertainty. NIH's PaVe-GT program similarly reported in February 2026 that target product profiles, early FDA engagement, shared templates, and transparent regulatory packages can transform bespoke AAV programs into more reproducible development pathways. FDA also tentatively accepted the possibility of using capsid-related biodistribution and anti-drug-antibody data across later relevant products, subject to program-specific review.



THE UNITED KINGDOM'S LIFECYCLE-BASED PROPOSAL

The United Kingdom advanced a parallel but more expansive proposal on May 21, 2026. The Medicines and Healthcare products Regulatory Agency's draft Rare Disease Therapies Regulatory Framework is technology-agnostic but expressly encompasses advanced therapies and individualized medicines. It is designed primarily for conditions affecting approximately one person in 50,000 or fewer when conventional development or approval is obstructed by measurable barriers.

Its central innovation is a proposed Investigational Marketing Authorisation: a single, continuously reviewed authorization that could combine clinical investigation with controlled patient access while real-world and clinical evidence continues to mature. The framework would permit adaptive trials, prior knowledge, surrogate endpoints, predictive modelling, real-world evidence, modular assessment, and risk-proportionate data requirements. Full implementation of the authorization would require legislative change.

The UK proposal also illustrates an important global trend: streamlining is increasingly paired with stronger lifecycle oversight. Earlier access would be balanced by predefined monitoring, periodic reassessment, ongoing consent, transparent patient communication, and structured post-authorization evidence generation. The MHRA additionally seeks alignment with international standards so that data may be reused across jurisdictions.

OUTLOOK

The direction of travel in AAV regulation is clear even though the frameworks remain under development. Rare-disease regulation is shifting from rigid replication toward justified reliance on shared knowledge; from large, sequential trials toward smaller and adaptive evidence packages; and from a single preapproval decision toward continuing lifecycle evaluation.

For AAV programs, success will depend on rigorous platform definition. Developers will need harmonized assays, controlled manufacturing, clear comparability strategies, high-quality natural-history datasets, and transparent documentation of where one product is sufficiently similar to another. Streamlining will be most persuasive when sponsors can distinguish reusable platform knowledge from product-specific uncertainty.

The likely endpoint is not a lower evidentiary standard, but a more targeted one: repeatedly test what is new, leverage what is already well established, and maintain long-term surveillance for irreversible or durable therapies. If operationalized consistently, the BGTC, FDA's 2026 guidance initiatives, and the MHRA framework could make AAV development viable for diseases that are currently too rare for the traditional one-product, one-program model.

Need regulatory insights for your AAV rare disease program? Reach out to TKD Solutions.

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