



When the Gene Editing Guide is the Drug

The rapid evolution of gene therapies and gene editing modalities in particular is challenging how personalised medicines are developed and evaluated. Many rare genetic disorders consist of numerous disease-causing variants, each of which requires a distinct therapeutic intervention. While advances in gene editing are making such treatments increasingly feasible, conventional development pathways are difficult to apply when patient populations are extremely small and individual mutations may be encountered only rarely. Requiring a complete development package, toxicology programme and clinical evidence package for every variant-specific therapy would make novel treatments impractical to develop.

In recognition of this challenge, the US Food & Drug Administration (FDA) issued a draft guidance in February 2026 describing a plausible mechanism framework for individualised therapies targeting specific genetic conditions with known biological cause (docket: FDA-2026-D-1256).¹ Rather than treating every variant-specific therapy as an entirely new product, the framework explores how evidence may be generated and leveraged across therapies that share a common biological cause.

The framework relies on several components: identification of a known causal genetic or molecular lesion; an understanding of untreated disease progression; evidence that the therapy engages with its intended target; and finally, demonstration that clinical outcomes reflect correction of the underlying genetic defect. With this approach, the FDA framework acknowledges that personalised therapies may be developed in settings where the first-in-human study also contributes pivotal evidence supporting effectiveness.

From Named Diseases to Causal Lesions

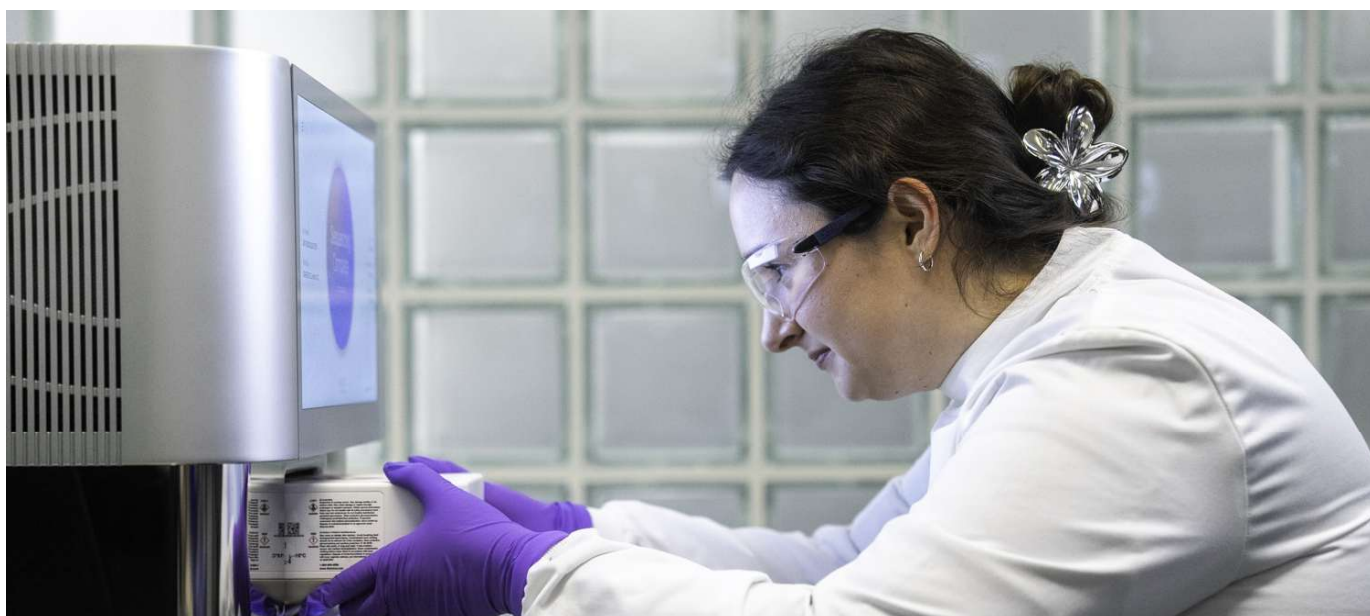
Gene editing is particularly well suited to the FDA's plausible mechanism framework because modern editing systems are increasingly modular. In this case, the therapy is comprised of a shared editor and delivery chassis plus a patient-specific guide. As such, much of what defines the therapy remains unchanged as the genomic target changes. Under these circumstances, the drug is no longer a unique molecular entity for each genotype. The drug is a platform, while the guide is the variable. This created the opportunity for the first economically coherent route to ultra-rare gene editing, with guide on- and off-target activity (OTA) being the key parameters requiring further investigation.

Rare Diseases as Case Studies

The practical value of this approach is most evident in rare genetic diseases, where hundreds of pathogenic variants may exist across relatively small patient populations. Generating a complete development package for every variant-specific therapy would often be economically and scientifically impractical.

The treatment of an infant with a metabolic disorder caused by severe CPS1 (carbamoyl-phosphate synthetase 1) deficiency using a customised lipid-nanoparticle base editing therapy in 2025 demonstrated the promise of highly personalised genome editing and the limitations of existing development models.² Repeating a full Investigational New Drug (IND) package for the next private allele would have been scientifically redundant and economically fatal. The guidance converts that one-off into policy.

A useful study showcasing how the FDA's framework might operate in practice took place at the University of Pennsylvania and Children's Hospital of Philadelphia programme developing therapies for seven infantile-onset urea-cycle disorders (UCDs).³ These conditions are well suited to the plausible mechanism





framework; the molecular causes are well known, disease progression is well characterised and treatment outcomes can be assessed via measurable biochemical endpoints, i.e., ammonia, glutamine and urea. Rather than developing a standalone therapy for each disease variant, the researchers proposed a customisable prime-editing platform using a common development strategy to help achieve a therapeutic effect across all seven UCDs.

As an initial proof of concept, the team focused on the ASS1 c.1168G>A (p.Gly390Arg) mutation, a recurrent cause of citrullinemia type 1. The proposed product was a two-component prime-editing platform: an AAV8 vector that expresses a patient-specific prime-editing guide RNA (pegRNA) and nicking guide RNA, plus a lipid nanoparticle (LNP) carrying mRNA for a compact prime editor. In this case, transient editor expression limits the off-target window while persistent guide expression allows for repeat LNP dosing. Candidate pegRNAs were first prioritised using the OptiPrime machine-learning platform and subsequently screened experimentally to identify an optimal editing configuration.

In humanised mouse models carrying the variant, the platform achieved efficient correction of the pathogenic allele, with whole-liver editing levels reaching approximately 30–40%, well above the threshold predicted to provide therapeutic benefit (i.e., 5–10%).

This programme provided an experimental basis for pre-IND discussions with the FDA. The proposal focused on an “umbrella-of-umbrellas” clinical trial model under which a shared prime-editing platform, supported by common biodistribution and toxicology data, could be expanded through the addition of new variants for all seven UCDs via IND amendments.³

Framework Strengths and the Gaps That Will Decide the Field

Even though the framework is still a draft and pre-IND advice is nonbinding, its strengths are real. It keeps the statutory effectiveness standard and changes only the permitted form of the evidence. It separates platform risk (biodistribution, immunogenicity, vector toxicity and manufacturing) from sequence risk. It also welcomes cell-based and *in silico* New Approach Methodologies (NAMs) which are defined by the FDA as “innovative testing methods and strategies used to assess the safety, efficacy and quality of FDA-regulated products”.

While the FDA framework provides opportunities to leverage platform-level evidence across multiple therapies, it does not eliminate the need for variant-specific data. Using the UCD study as an example, each guide RNA entered by IND amendment would still require variant-specific optimisation and safety assessment via the characterisation of any unintended insertions or deletions (indels) at both the on-target and off-target sites in the genome. In the framework, off-target method recommendations are explicitly deferred. FDA “intends to provide additional recommendations on nonclinical studies using NGS-based methods... in the near future.” Until then, sponsors are interpolating between this draft and the January 2024 genome-editing guidance, which already asked for two orthogonal nomination methods, one of them unbiased and genome-wide.^{1,4}

Additionally, if IND Phase 1/2 data are to support a biologics license application (BLA), chemistry, manufacturing and controls must look like a commercial product: locked process, inspection-

ready site, validated assays, stability on every individualised lot and a potency method that can be adapted to the next spacer. Research groups cannot meet that bar alone. According to the authors of the UCD study, an abbreviated path to approval “appears to be dependent on a sponsor’s ability to apply the strict requirements ordinarily reserved for late-stage clinical trials to an early-stage clinical trial.”³

The most consequential sentence in the framework is the one that allows a mutation never studied in patients to be added to a BLA based on *in vitro* activity plus an off-target assessment. The intellectual integrity of “plausible mechanism” now depends entirely on what that assessment is.

The Bottleneck is the Challenge of Off-target Assessment

Legacy approaches to off-target analysis were largely developed during a period when genome editing was dominated by nuclease-based systems designed to induce double-stranded DNA (DSB) breaks. For example, biochemical methods, such as CHANGE-seq, have proven valuable for identifying candidate off-target sites and informing risk assessment. However, many of these approaches operate outside the cellular environment in which therapies ultimately function and may not fully capture the influence of chromatin structure, epigenetic state or cell-specific DNA repair processes on editing behaviour.

These challenges are also relevant to more complex gene editing modalities including base and prime editors, which introduce alternative off-target mechanisms that legacy approaches were not designed to address, including off-target DNA nicking and bystander DNA deamination.⁵

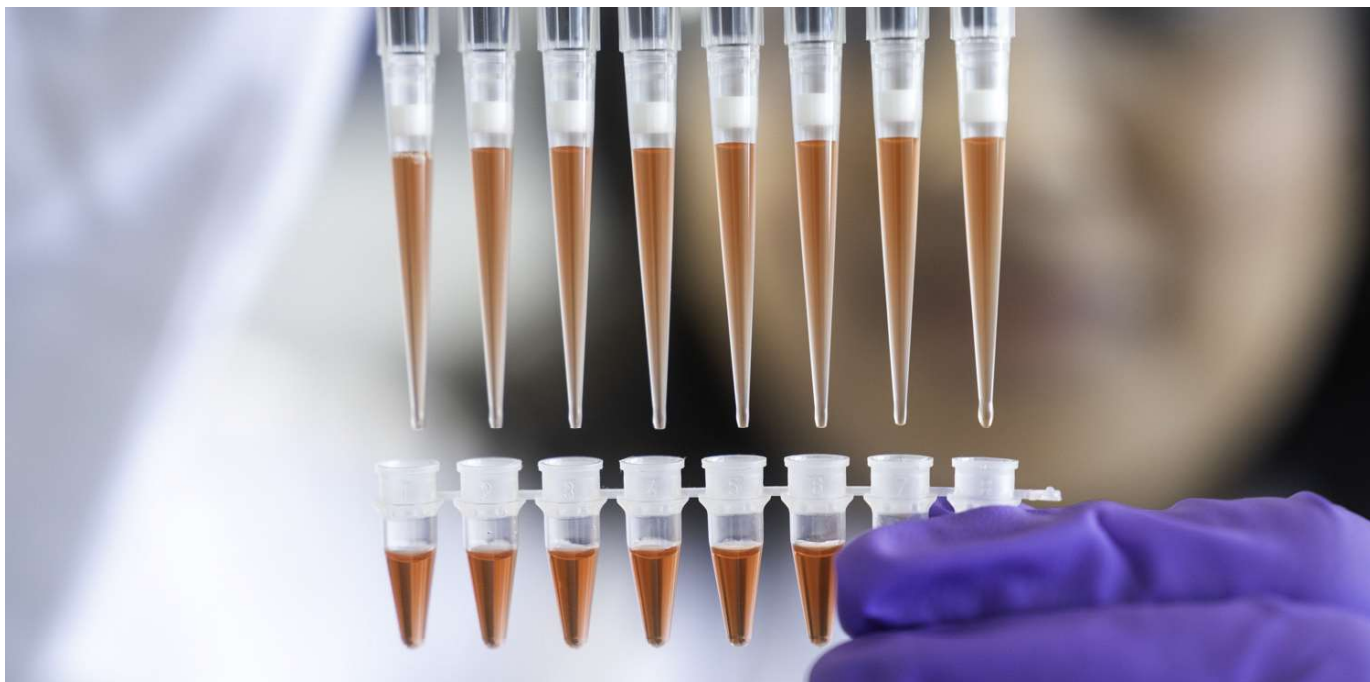
Moving Toward Effective Off-target Assessment for Novel Therapeutic Modalities

Addressing these challenges will require approaches that move beyond indirect measurements and cell-free assays towards the direct, genome-wide characterisation of DNA break formation in biologically relevant cells. As gene therapy programmes become increasingly customisable, the demands on the quality and quantity of off-target data grow. The future of screening must deliver what legacy methods cannot and will be determined by whether it can generate sufficiently comprehensive and quantitative datasets to support guide-specific safety decisions.

While *in silico* approaches remain important for guide design and risk prioritisation, they are inherently limited to sites predicted by existing algorithms. As a result, there is growing emphasis on unbiased, genome-wide methods capable of identifying editing activity irrespective of its genomic location.⁶

Equally valuable is the cellular context in which those measurements are made. Assays that directly detect editing events in intact cells can provide a more representative picture of therapeutic activity than methods based solely on cell-free DNA substrates, capturing the influence of chromatin accessibility, epigenetic state and DNA repair processes on editing outcomes.

The quality of off-target data also depends on the ability to quantify editing events accurately. PCR-dependent workflows can introduce amplification bias that distorts the apparent frequency of editing events, particularly when rare outcomes must be measured against a large background of unedited



molecules. Methods that eliminate amplification bias therefore offer advantages when quantitative comparisons are required across candidate guides or editing platforms. There is also an increased value in workflows being capable of assessing both on-target and off-target activity simultaneously, which provides a more complete picture of editing behaviour and simplifies interpretation of candidate performance.

Finally, off-target assessment needs to inform programme decisions during guide selection and lead optimisation, rather than just as part of an IND package. Approaches that can be implemented in-house and generate actionable results within days are becoming more valuable as developers evaluate larger numbers of candidate guides while maintaining control of proprietary data and development timelines. Methods that address these requirements, such as INDUCE-seq, can provide the genome-wide, cell-based evidence needed to support guide-specific safety assessments under the FDA's plausible mechanism framework.⁶ They do not replace the need for orthogonal nomination methods, integration analyses, toxicology studies or long-term follow-up, but rather complement the broader body of evidence required to support clinical development.

Make the Pathway Executable

The FDA's plausible mechanism framework is the first regulatory document that treats modular genome editing as modular, offering a potential route to bringing personalised therapies to patients whose needs would often be neglected by conventional development programmes. That is its strength. Its weakness is that it still needs evidence equal to the claim it is making.

The UCDs study demonstrates that platform-level knowledge may be leveraged across programmes, but confidence in guide-specific safety remains essential. As personalised gene therapies expand, technologies capable of generating accurate, genome-wide assessments of editing outcomes in biologically relevant cells are likely to become increasingly important. A PCR-free, cell-based map of DSBs, paired with a nick-adapted readout of base-editor engagement, is the natural contents of that file.

Combined with computational approaches that help prioritise candidates, such methods could provide the evidence needed to support efficient therapeutic development that makes the plausible mechanism framework executable.

REFERENCES

1. U.S. Food and Drug Administration. Considerations for the Use of the Plausible Mechanism Framework to Develop Individualized Therapies that Target Specific Genetic Conditions with Known Biological Cause: Draft Guidance for Industry. FDA, (2026).
2. Musunuru K, Grandinette SA, Wang X *et al.* Patient-specific *in vivo* gene editing to treat a rare genetic disease. *New England Journal of Medicine*, 392(22), 2235-2243 (2025).
3. Feirman ER, Whittaker MN, Quigley A *et al.* Implications of the FDA's new plausible mechanism framework for the development of a personalized *in vivo* prime editing platform. *The American Journal of Human Genetics*, 113(5), 891-899 (2026).
4. U.S. Food and Drug Administration. Human Gene Therapy Products Incorporating Human Genome Editing: Guidance for Industry. FDA, (2024).
5. Fiumara M, Ferrari S, Omer-Javed A *et al.* Genotoxic effects of base and prime editing in human hematopoietic stem cells. *Nature Biotechnology*, 42(6), 877-891 (2024).
6. Dobbs FM, van Eijk P, Fellows MD *et al.* Precision digital mapping of endogenous and induced genomic DNA breaks by INDUCE-seq. *Nature Communications*, 13, 3989 (2022).



Simon Reed

Simon Reed is co-founder and chief scientific officer of Broken String Biosciences. He is an honorary professor and former co-director of the Division of Cancer and Genetics at the School of Medicine at Cardiff University. With more than 25 years' experience in the field, Simon is a leading expert in genome stability and has developed genomic tools used widely by industry partners. He was a Fulbright Scholar at the Southwestern Medical Centre in Dallas, Texas and a former chair of the UK Genome Stability Network.