



Biotechnology Innovation Organization
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September 1, 2026

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: Docket No. FDA-2026-D-1257: Leveraging Prior Knowledge in the Development of Human Gene Therapy Products Incorporating Genome Editing

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments regarding the Agency's draft guidance, 'Leveraging Prior Knowledge in the Development of Human Gene Therapy Products Incorporating Genome Editing.'

BIO is the premier biotechnology advocacy organization representing biotech companies, industry leaders, and state biotech associations in the United States and more than 35 countries around the globe. BIO members range from biotech start-ups to some of the world's largest biopharmaceutical companies – all united by the same goal: to develop medical and scientific breakthroughs that prevent and fight disease, restore health, and improve patients' lives. BIO also organizes the BIO International Convention and a series of annual conferences that drive partnerships, investment, and progress within the sector. Learn more at bio.org.

BIO and its members strongly support FDA's efforts to establish a science-based framework that enables sponsors to appropriately leverage prior knowledge and experience across product development programs. We believe this guidance represents an important step toward reducing unnecessary duplication of data generation, increasing regulatory efficiency, and facilitating timely patient access to innovative cell and gene therapies (CGTs), particularly for rare and serious diseases. We broadly agree with the Agency's recognition that prior knowledge may appropriately support Chemistry, Manufacturing and Controls (CMC), nonclinical, bioinformatics, and clinical development activities when scientifically justified. However, BIO encourages the FDA to further clarify its evaluation criteria and expectations to enhance regulatory predictability, facilitate efficient sponsor-Agency interactions, and support the development of scientifically sound leveraging strategies across programs.

We appreciate FDA's acknowledgment that many of the principles described in this draft guidance may be applicable beyond genome editing products. Accordingly, BIO recommends broadening the scope of the final guidance and revising the title to reflect its applicability across cell and gene therapy products. BIO also recommends that FDA provide a risk-based framework for assessing



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product similarity, clarify expectations for bridging confirmatory and verification data, as well as address the application of prior knowledge across the full product lifecycle, including post-approval changes and continual improvement. We also encourage FDA to have a public process when prior knowledge changes, including providing clarity around how changes to prior knowledge would change existing approvals. This inclusion would help sponsors develop more predictable and scientifically justified leveraging strategies, as well as ensure clarity continues over time as the science continues to evolve.

Additional examples and discussion of FDA's decision-making considerations would help improve consistency and implementation of the framework. BIO also recommends clarifying the relationship between the prior knowledge framework and other regulatory initiatives, including the 'Generally Accepted Scientific Knowledge' (GASK), Platform Technology Designation and related guidances. Finally, expanding the clinical section with practical examples illustrating how prior clinical data and experience may be leveraged would help sponsors design more efficient development programs while maintaining scientific rigor and patient safety.

Additional considerations for the Agency, include clarification on the management of updates to leveraged bioinformatics tools and next-generation sequencing (NGS) analysis pipelines during development, including expectations for bridging assessments, documentation, and IND reporting requirements, as well as consideration of a risk-based approach to long-term follow-up requirements for non-integrating genome editing products delivered through rapidly cleared modalities such as lipid nanoparticles.

BIO appreciates FDA's leadership in advancing regulatory frameworks that support the efficient development of innovative cell and gene therapies. We believe the recommendations outlined below as well as our line-by-line table edit suggestions, will promote broader and more consistent application of scientifically justified prior knowledge, increase regulatory efficiency and predictability, and ultimately accelerate patient access to transformative therapies while maintaining FDA's high standards for safety, quality, and effectiveness.

We thank the Agency for its consideration of these comments and look forward to continued collaboration as FDA finalizes this important guidance.

Sincerely,

/s/

E'Lissa Flores, Ph.D.

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Biotechnology Innovation Organization



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BIO Key Recommendations

1. Broaden the Scope of the Guidance Beyond Genome Editing Products

BIO members believe the principles described in the guidance are applicable across a broad range of cellular and gene therapy products and are not unique to genome editing technologies. Many of the underlying considerations related to manufacturing platforms, analytical methods, nonclinical testing strategies, clinical trial design, comparability assessments, and lifecycle learning are shared across CGT modalities.

Accordingly, BIO recommends that FDA broaden the scope of the final guidance and consider revising the title to "Leveraging Prior Knowledge in the Development of Cell and Gene Therapy Products."

We also suggest the FDA clearly articulate which recommendations are applicable to non-genome-editing modalities and provide examples demonstrating their application across a broader range of CGT products.

2. Establish a Risk-Based Framework for Similarity Assessments

Throughout the draft guidance, the ability to leverage prior knowledge depends on the similarity of products, manufacturing processes, formulations, delivery systems, and other attributes. However, the guidance would benefit from adding more information on how sponsors should evaluate, document, and justify similarity.

BIO recommends that FDA provide a risk-based decision framework or set of guiding principles to help sponsors determine when products, or aspects of products, may be considered sufficiently similar to support leveraging activities. Such a framework could include considerations related to:

- Product structure and composition
- Editing components and mechanisms
- Manufacturing processes
- Formulation and delivery systems
- Route of administration
- Intended clinical use
- Product-specific versus platform-specific attributes

Providing these factors would improve predictability, consistency, and efficiency during regulatory interactions.



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3. Clarify Expectations for Bridging and Confirmatory Evidence

While the draft guidance states that bridging studies, confirmatory studies, or verification activities may be needed when leveraging prior knowledge, BIO encourages the Agency to provide more details regarding the expected scope of such activities.

Specifically, we recommend the inclusion of illustrative examples describing:

- Minimal confirmatory packages
- Reduced verification approaches
- Circumstances where full requalification or redevelopment is necessary
- Product-specific and platform-level scenarios

Examples involving modified gRNA sequences, alternative donor templates, different target genes, new cell sources, or manufacturing changes would be particularly valuable for sponsors.

4. Clarify Application of Prior Knowledge Across the Product Lifecycle

BIO believes the final guidance would be strengthened by explicitly discussing how prior knowledge may be applied throughout the entire product lifecycle, including post-approval as it currently focuses primarily on product development.

Sponsors increasingly rely on accumulated manufacturing, analytical, clinical, and real-world experience to inform:

- Specification refinement
- Process optimization
- Scale-up activities
- Comparability assessments
- Post-approval changes
- Continuous process verification
- Manufacturing capacity expansion and scale-out

BIO recommends the inclusion of a dedicated section describing lifecycle management principles and the role of prior knowledge in supporting ongoing product improvement using a risk-based framework. BIO also recommends that FDA clarify how accumulated manufacturing and clinical experience may support post-approval specification refinement, including examples of evidence that may be appropriate to support specification changes for marketed CGT products.

BIO recommends that FDA clarify how prior knowledge generated for a product may be leveraged across therapeutic areas throughout the product lifecycle. Where the product, manufacturing process, mechanism of action, and safety profile remain unchanged, sponsors should be able to



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use accumulated clinical, nonclinical, manufacturing, pharmacovigilance, and real-world evidence to inform dose optimization, clinical trial design, safety monitoring, endpoint development, and post-market evidence generation in new indications. FDA should provide examples illustrating when prior knowledge from one therapeutic area (e.g., oncology) may support development in another (e.g., immunology), including through integrated safety analyses, shared long-term follow-up studies, common pharmacovigilance programs, registries, and real-world evidence sources.

5. Improve Regulatory Predictability Through Additional Examples & Decision-Making Factors

BIO members support FDA's recommendation for early engagement through INTERACT and pre-IND meetings. However, many key determinations in the draft guidance are deferred to future discussions with the Agency and securing INTERACT meetings continues to be a challenge as identified by our members. While early FDA engagement can be valuable, the guidance should provide sufficient clarity and specificity to enable sponsors to make informed development decisions without necessarily requiring an INTERACT meeting to interpret FDA's expectations. To facilitate such understanding, FDA should provide additional examples, decision matrices, and descriptions of the factors reviewers may consider when evaluating leveraging proposals. Greater transparency regarding FDA's expectations would help sponsors develop more focused regulatory strategies and reduce uncertainty across development programs. We also encourage the agency to remain receptive to discussions on the use of prior knowledge through other meeting formats, including Type C and Type D meetings, throughout product development.

6. Clarify Terminology and Relationship to Existing Regulatory Frameworks

BIO appreciates FDA's acknowledgment that the use of the term "platform" in this guidance differs from the statutory concepts of "platform technology" and "designated platform technology" under Section 506K of the FD&C Act. However, the use of similar terminology for distinct regulatory concepts may create confusion. For instance, FDA has referred to "platform-like approaches" in public forums, yet that term is not used in the guidance. Therefore, BIO recommends that FDA more clearly distinguish these concepts through consistently applied terminology and definitions, explain when sponsors should leverage prior-knowledge approaches versus pursuing platform technology designation, as well as clarify how this guidance interfaces with existing regulatory frameworks and guidances, including:

- Platform Technology Designation
- CMC Flexibilities for Cell and Gene Therapies
- Safety Assessment of Genome Editing Using Next-Generation Sequencing
- ICH Q12 principles
- Relevant real-world evidence and natural history study guidances



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Additional cross-references and illustrative examples would improve implementation and consistency.

7. Expand Clinical Development Examples

BIO members support FDA's recognition that prior knowledge may inform clinical trial design, dose selection, monitoring strategies, and other aspects of development. However, compared to the CMC and nonclinical sections, the clinical section contains relatively few examples describing how actual clinical data may be leveraged across programs.

BIO recommends that FDA provide additional examples illustrating circumstances where prior clinical data may support:

- Streamlined development programs
- Optimized assessment schedules
- Safety monitoring approaches
- Dose selection strategies
- Use of external or historical data sources

Such examples would help stakeholders better understand FDA's expectations regarding clinical data leveraging.

BIO Line-by-line Table Suggestion Edits

Line from*	Line to*	Section	Comment and rationale	Proposed changes / recommendation
20	27		FDA says the guidance may be particularly helpful for genome-editing products intended for rare, serious, and life-threatening diseases, and the broader 2026 FDA “plausible mechanism” framework also discusses the use of well-characterized natural history to help distinguish treatment effects when randomized trials are not feasible.	We kindly suggest to explicitly address whether natural history data, external controls, and real-world evidence can be leveraged as clinical prior knowledge.
30	33		This change will more clearly underscore the applicability of this guidance to modalities outside of genome editing and ensure the recommendations have a broader impact on the CGT field and developmental efficiencies through leveraging prior knowledge	We recommend the following edit change to " <u>...the recommendations in this guidance, when finalized, are intended to be broadly applicable to other CGT products</u> , such as adeno-associated viral (AAV) vectors, nanoparticle-based GT products, and ex vivo-modified cell-based GTs that do not incorporate GE."
31	34	I	The principles described in the draft guidance are very much applicable to other CGT products that do not incorporate GE; this passage seems to understate the value of this guidance more broadly to cellular and gene therapy products.	As discussed in above letter, kindly consider widening the scope of this document and change the title to encompass more than only genome edited products.
48	50	II	The guidance states, "This prior knowledge may be scientifically appropriate to leverage in product development programs to streamline submissions and subsequent review of regulatory applications, and to expedite product development." The background does not recognize the potential for prior knowledge to support changes in the post approval setting.	"This prior knowledge may be scientifically appropriate to leverage in product development programs to streamline submissions and subsequent review of regulatory applications, to expedite product development and regulatory approval of changes in the post-approval setting "
53	58		The current definition may unintentionally limit public knowledge to long-standing scientific principles and broadly accepted information. A broader definition would better reflect the rapidly evolving nature of cell and gene therapy development, where scientifically relevant evidence may emerge from recent publications, publicly available datasets, manufacturing experience, or collaborative research efforts. This revision maintains scientific rigor by placing responsibility on sponsors to justify the relevance and applicability of the	~~"Public knowledge" or "generally accepted scientific knowledge" refers to medical or scientific information that is generally accepted by experts qualified by scientific training and experience in the relevant field including FDA experts (e.g., certain data and 56 information published in rigorous peer-reviewed publications). Generally, "prior knowledge" or "generally accepted scientific knowledge" is based on widely accepted scientific principles that are typically long-standing.~~ Public knowledge refers to publicly available medical or

			information to their specific development program rather than relying on the age or source of the information alone.	~~scientific information that may inform product development or regulatory decision-making.~~ Instead, we suggest the following edit, “Public knowledge may include established scientific principles, peer-reviewed literature, publicly available datasets, consensus recommendations or standards, information generated through collaborative research efforts, and other publicly accessible sources of scientific evidence. Such information may be considered public knowledge when qualified experts, including FDA experts, would reasonably consider the information relevant to the scientific question under consideration. Sponsors seeking to rely on public knowledge should provide a scientific rationale supporting the relevance, reliability, and applicability of the information to the proposed application.”
59	67	II.A	Platform Governance and Traceability	FDA could consider revising where the draft guidance defines platform knowledge and describes how platform information may be submitted or cross-referenced. The guidance should clarify expectations for platform governance, lifecycle controls, version control, documentation standards, and traceability from each leveraged dataset to the source product, study or report, quality attribute, and applicability rationale. For example, sponsors could maintain a platform summary and traceability table identifying the source product, study report, analytical method, PPQ run, stability study, comparability assessment, applicable platform element, authorization status, version history, and rationale for applicability to the current product
100	134	II	Similarity Assessment	FDA could consider revising where the draft guidance describes scientific soundness and similarity factors for leveraging prior knowledge. The guidance would benefit from minimum similarity considerations and an illustrative similarity matrix to support consistent sponsor justification across molecular structure, manufacturing process, formulation, delivery system, and mechanism of action. For example, the matrix could compare editor type, gRNA or target sequence, cell source, vector or LNP composition, formulation, manufacturing site, equipment train, critical process parameters, CQAs, and intended biological activity to

				determine whether prior knowledge may be leveraged fully, partially, or only with bridging data.
108	114		The guidance states that scientific soundness depends on similarities between products and diseases, but for clinical programs that is still fairly broad. The guidance identifies factors that may inform the ability to leverage nonclinical data for ex vivo GE products and in vivo GE products, but it does not provide comparable specificity for other emerging CGT modalities that may rely on conserved platform characteristics. Additional guidance would help sponsors determine when prior nonclinical platform studies may be leveraged for products such as in vivo CAR-T therapies and when targeted product-specific studies are warranted. This clarification is particularly important where there are limited or no fully pharmacologically relevant animal species, and where humanized models, in vitro systems, new approach methodologies, or other scientifically justified approaches may provide more relevant information than repeating traditional animal studies.	Kindly define what constitutes sufficient “similarity” for clinical leveraging. For in vivo GE products, the similarities and differences between the products, manufacturing process, final formulation, route of administration (ROA), proposed clinical dosing regimen, and dose levels will inform the ability to leverage data. Similar considerations may apply to other emerging CGT modalities, including in vivo CAR-T products. For such products, the ability to leverage prior nonclinical platform studies may depend on whether the relevant nonclinical question is driven primarily by conserved platform characteristics or by product-specific features such as the therapeutic transgene or CAR construct. Sponsors should consider similarities in delivery system, vector or non-viral delivery characteristics, promoter or regulatory elements, manufacturing process, formulation, ROA, dose range, biodistribution, persistence, integration biology, off-target transduction potential, cell-type specificity, and the availability and limitations of pharmacologically relevant species. Where available animal species are not fully pharmacologically relevant, prior platform knowledge, humanized models, in vitro systems, new approach methodologies, or other scientifically justified approaches may be used to address specific nonclinical questions. Prior platform studies may be appropriate to leverage where changes are limited to the CAR construct or are expected to maintain or increase cell-type specificity, while targeted product-specific studies may be warranted where changes could alter biodistribution, persistence, pharmacologic activity, species translatability, or safety profile.
114	114		The guidance notes that for in vivo GE products, the ability to leverage prior knowledge depends in part on route of administration, proposed dosing regimen, and dose levels.	We request clarifying how prior knowledge can support dose selection, sentinel strategies, dose-escalation intervals, and regimen optimization.

116	120		The guidance says the appropriateness of leveraging clinical data depends in part on the phase of clinical studies and whether the purpose is to support a new clinical trial or a future licensing application, but it does not appear to define clear thresholds or examples of what level of similarity is sufficient for each regulatory use case.	We would encourage the FDA to clarify the evidentiary threshold for leveraging clinical prior knowledge at different milestones: IND initiation, dose escalation, pivotal design, and BLA
116	120		The guidance states that scientific soundness depends on similarities between products and diseases, but for clinical programs that is still fairly broad.	Request to Define what constitutes sufficient “similarity” for clinical leveraging.
116	120		FDA says the guidance may be particularly helpful for genome-editing products intended for rare, serious, and life-threatening diseases, and the broader 2026 FDA “plausible mechanism” framework also discusses the use of well-characterized natural history to help distinguish treatment effects when randomized trials are not feasible.	Recommend explicitly address whether natural history data, external controls, and real-world evidence can be leveraged as clinical prior knowledge.
116	120		Genome-editing products raise long-term safety questions, and the new NGS safety guidance highlights continuing attention to off-target and genome integrity issues. Ask the FDA: Clarify whether long-term follow-up intensity can be risk-adjusted based on prior platform or clinical knowledge.	We suggest the Agency to define what constitutes sufficient “similarity” for clinical leveraging.
122	127		Expand the type of data that will likely be shared across a product in a facility and provide more definitive answer that where justified sponsors may leverage such unit operations across multiple CGT products.	"...developers <u>should</u> consider whether the knowledge applies to independent or dependent attributes of the component or product. Knowledge pertaining to attributes independent of the specific product (e.g., an analytical method, <u>facility qualification, equipment operating parameters</u>) is <u>generally appropriate for leveraging with scientific justification alone, without the need for bridging studies</u> . Knowledge pertaining to <u>dependent attributes</u> (e.g., product activity/potency or identity) may require product-specific verification."
129	135		The guidance says the appropriateness of leveraging clinical data depends in part on the phase of clinical studies and whether the purpose is to support a new clinical trial or a future licensing application, but it does not appear to define clear thresholds or examples of what level of similarity is sufficient for each regulatory use case.	Request to please clarify the evidentiary threshold for leveraging clinical prior knowledge at different milestones: IND initiation, dose escalation, pivotal design, and BLA
129	135		FDA says the guidance may be particularly helpful for genome-editing products intended for rare, serious, and life-threatening diseases, and the broader 2026 FDA “plausible mechanism”	We recommend explicitly addressing whether natural history data, external controls, and real-world evidence can be leveraged as clinical prior knowledge

			framework also discusses the use of well-characterized natural history to help distinguish treatment effects when randomized trials are not feasible.	
129	135		Genome-editing products raise long-term safety questions, and the new NGS safety guidance highlights continuing attention to off-target and genome integrity issues.	We encourage the FDA to kindly clarify whether long-term follow-up intensity can be risk-adjusted based on prior platform or clinical knowledge.
131	135	II	The guidance states, "Furthermore, it may be possible to leverage additional knowledge throughout the product lifecycle as product specific experience and knowledge in the field is gained. However, in all cases, when leveraging any kind of prior knowledge, a sponsor should provide a justification for the applicability of the data being leveraged." FDA should more clearly emphasize that prior knowledge can and should be leveraged from any phase of drug development to another, so long as it is scientifically appropriate and justifiable."	We suggest the following edit to, "Furthermore, it may be possible and is encouraged for sponsors to leverage additional knowledge throughout the product lifecycle as product specific experience and knowledge in the field is gained. However, in all cases, when leveraging any kind of prior knowledge, a sponsor should provide a justification for the applicability of the data being leveraged."
137	142		Genome-editing products raise long-term safety questions, and the new NGS safety guidance highlights continuing attention to off-target and genome integrity issues.	We recommend clarifying whether long-term follow-up intensity can be risk-adjusted based on prior platform or clinical knowledge.
151	162	II.A	Similarity Assessment:	FDA could consider revising where the draft guidance describes scientific soundness and similarity factors for leveraging prior knowledge. The guidance would benefit from minimum similarity considerations and an illustrative similarity matrix to support consistent sponsor justification across molecular structure, manufacturing process, formulation, delivery system, and mechanism of action. For example, the matrix could compare editor type, gRNA or target sequence, cell source, vector or LNP composition, formulation, manufacturing site, equipment train, critical process parameters, CQAs, and intended biological activity to determine whether prior knowledge may be leveraged fully, partially, or only with bridging data.
169	188	III.A.1	Evidence Boundaries and Product-Specific Justification:	FDA could consider revising where the draft guidance addresses platform analytical methods, lot release specifications, process characterization/PPQ, and bridging or confirmatory data. The guidance should more clearly define the boundaries for using bridging or confirmatory data, platform CQAs, potency assays, and PPQ reliance while preserving product-specific justification for identity, potency,

				specifications, validation, and lifecycle control. For example, platform analytical validation data may support selected method attributes, but product-specific verification may still be needed for a new gRNA sequence, cell source, matrix, or potency mechanism. Similarly, platform PPQ data may support reduced PPQ only where site, scale, equipment, process parameters, and relevant CQAs remain comparable.
199	202		You may consider leveraging non proprietary public knowledge to support the use of analytical methods that have been validated in scientific literature, performing bridging studies as needed to confirm suitability for their specific product and manufacturing context	We suggest that the guidance encourage sponsors to utilize pharmacopeial methods when possible.
204	244	III.A.2.	The guidance should incorporate information pertaining to how prior knowledge can be leveraged to inform modification to lot release (e.g., expanding the specification parameters)	FDA could provide recommendations regarding what types and level of information is acceptable to support a post-approval change in specification request, particularly focusing on individualized therapies (e.g., CAR-T).
205	232	III.A.2	Evidence Boundaries and Product-Specific Justification:	FDA could consider revising where the draft guidance addresses platform analytical methods, lot release specifications, process characterization/PPQ, and bridging or confirmatory data. The guidance should more clearly define the boundaries for using bridging or confirmatory data, platform CQAs, potency assays, and PPQ reliance while preserving product-specific justification for identity, potency, specifications, validation, and lifecycle control. For example, platform analytical validation data may support selected method attributes, but product-specific verification may still be needed for a new gRNA sequence, cell source, matrix, or potency mechanism. Similarly, platform PPQ data may support reduced PPQ only where site, scale, equipment, process parameters, and relevant CQAs remain comparable.
212	219	III.A.2.a.i	In the context of genome editing, it is understandable that gRNAs would be cited as an example for leveraging prior knowledge for specification setting. However, in emphasizing GE components, the broader applicability of this passage to DS and DP specifications may be lost.	Kindly provide a second example, citing similarities between DSs or DPs as an opportunity to justify similar lot release specifications across the same platform.
230	231		Although you may be able to leverage some information for identity and potency, such as the analytical method, testing for these attributes is intended to be product specific	Also consider that an identity test must also distinguish a product from others manufactured in the same facility.

233	233	III.A.2.a.i ii	Recommend adding more specificity to last sentence “...knowledge for these product dependent attributes.”	Draft proposed text: “Leveraging prior knowledge of potency-related CQAs may be part of the sponsor’s comprehensive potency assurance strategy, aligned with FDA Guidance for “Potency Assurance for Cellular and Gene Therapy Products”. For example, it may be appropriate to use prior knowledge of a related in-vivo gene editing product with a shared editing mechanism to assist in initial specifications where lot release data may be limited. Implementation of progressive, phase appropriate specifications should be based on method capability and manufacturing history to ensure that each lot will achieve the intended therapeutic effect.”
235	244		Current text is highly specific to ex vivo. This section can be expanded to include or exclude vector-based therapies, not just specifically ex vivo. Infectious titer, residuals etc. would be a helpful addition	For example, standardized potency assay designs such as mechanism-of-action based assays, or cytotoxicity assays for CAR-T cells may be considered for leveraging across similar products within the same therapeutic class. <u>For in vivo approaches, infectious titers, residuals, and other CQAs may also be leveraged with appropriate justification.</u>
278	281		It is understood that supportive commercial shelf life data can be leveraged from prior stability knowledge. However the statement “prior knowledge is not intended to replace long-term, real-time product stability data in a BLA submission” does not address whether any reduction in the number of batches, testing frequencies/conditions can also be considered when leveraging prior knowledge information. Additionally, it would be helpful to address whether prior knowledge can reduce annual stability requirements. These recommendations expand scope of considerations for stability data to ensure that platform data may supplement real-time data and enable efficiencies for real-time stability data required for BLA filing. This will expedite stability requirements for subsequent applications.	“Prior knowledge of stability may be considered to support a commercial shelf life in addition to real time stability data of primary product lots. However, prior knowledge is not intended to replace long-term, real-time product stability data in a BLA submission. <u>Platform stability trending data may be used to supplement real-time data and may support a reduced duration of real-time stability data at the time of BLA filing for subsequent products on the same platform. This data may also be able to reduce annual stability requirements.</u>

278	283	III A.3.iii	Section III.A.3.iii establishes that prior knowledge cannot replace long-term real-time stability data in a BLA submission, but then adds that “flexibility may be given for critical components.” The use of prior knowledge to support long-term stability, including critical components for ex vivo GE products, can have a significant impact on product development particularly where direct product manufacturing experience is limited. Additional clarity on 1.) the circumstances under which prior stability data alone would be adequate for critical components and 2.) the aspects of the data package would help both the Agency and Industry better align on the appropriateness of relevant prior knowledge. In turn, this would support the Agency’s review of long-term, stability-related submissions that leverage prior knowledge.	The Agency should clarify the circumstances under which prior stability data alone would be considered adequate for critical components. In addition, the Agency should expand on the aspects of the data package that would be needed to support this approach.
282	283		This sentence is vague: “Additionally, flexibility may be given for critical components for manufacture of ex vivo GE products.”	Please clarify what kind of flexibility it refers
289	289	III.A.3.a.i v	The regulatory status of a delivery device should not have any bearing on the ability to leverage prior stability/compatibility data between a product and that delivery device. If a platform product were compatible with an IDE device and another platform product later utilized that same device, the subsequent approval of the device would not render the stability data any less relevant.	We suggest to omit "regulatory status"
291	291	III.A.3.a.i v	Recommend additional example after “...(like route of administration and flow rate).”	Draft proposed text: “For example, leveraging prior knowledge of an in-vivo gene editing product infusion compatibility studies for a related product which uses identical formulation may be appropriate.”
333	371	A.5	Recommend adding a bullets to state: 1) Shipping: prior knowledge maybe be used to support transportation characterization and shipping validation studies 2) Extractables and Leachables (E/L): prior knowledge maybe be used to support understanding of E/L	Draft proposed Text: “Data from shipping studies may be considered for leveraging between products that use similar shipping conditions, transportation nodes, and product configurations (e.g., similar container closer system).Data from E/L studies may be considered for leveraging between products that use similar configurations (e.g., similar container closer system and formulation).”

334	370	III.A.5	Evidence Boundaries and Product-Specific Justification:	FDA could consider revising where the draft guidance addresses platform analytical methods, lot release specifications, process characterization/PPQ, and bridging or confirmatory data. The guidance should more clearly define the boundaries for using bridging or confirmatory data, platform CQAs, potency assays, and PPQ reliance while preserving product-specific justification for identity, potency, specifications, validation, and lifecycle control. For example, platform analytical validation data may support selected method attributes, but product-specific verification may still be needed for a new gRNA sequence, cell source, matrix, or potency mechanism. Similarly, platform PPQ data may support reduced PPQ only where site, scale, equipment, process parameters, and relevant CQAs remain comparable.
335	336		Clarify that process characterization data may be leveraged to support scale-up. This is a critical aspect that will ensure sponsors can leverage efficiencies as products move from early to later phase studies or commercial supply.	Proposed line edits to "Process characterization data may be considered for leveraging between products or components that use the same platform manufacturing process to determine criticality of process parameters, define proven acceptable ranges of these parameters, and to develop overall microbial control and potency assurance strategies. <u>Such data may also be leveraged to support manufacturing scale-up (e.g., from laboratory scale to clinical or commercial scale).</u> "
352	358	5.c	Can you leverage enough prior knowledge to not do a PPQ run. If there is sufficient justification for a highly similar CAR-T product or critical raw material like LVV, does Applicant still need to do run another PPQ.	Proposing Agency to provide guidance on this approach and whether this would apply to not just rare disease platform.
352	358		As aligned with recent FDA flexibilities (https://www.fda.gov/media/192321/download), the guidance should enable sponsors, particularly in the rare disease space, to have the option to justify fewer PPQ runs. The guideline could also benefit from more specific direction regarding whether reduction in number of PPQ batches can be considered when transferring to a new site, or scale out of a previously established process, as this could fall in a prior knowledge category.	Proposed line edits to "Process performance qualification (PPQ) study data from a GE component or product may be considered for leveraging to support manufacturing process validation of multiple GE components or products that use the same manufacturing process platform at the same or a different manufacturing site. Platform process validation data may be considered to inform a new PPQ study design such as determination of the number of PPQ runs needed and sampling strategies. <u>In many cases, with the use of supportive platform PPQ data, a reduced number of PPQ batches (e.g., one PPQ batch) may be justified.</u> "

370			An important CMC use case not currently reflected in the guidance is the use of accumulated manufacturing knowledge to support post-approval manufacturing changes, including site-to-site transfers, manufacturing scale-up, and capacity-expansion activities. For products such as autologous cell therapies, sponsors may have extensive experience demonstrating process robustness, comparability, and consistent control of product quality across numerous manufacturing runs. This accumulated knowledge can inform the scope of data needed to support increases in throughput, transfers between manufacturing sites, and other scale-up activities, helping to ensure adequate supply while maintaining product quality and process control.	Propose to add a new paragraph, “Prior knowledge may be considered for leveraging to support manufacturing changes across the product lifecycle, including site-to-site technology transfers, scale-up activities, process development, validation, and manufacturing capacity expansion. When a manufacturing process is transferred to a new site using equivalent platform processes, equipment design principles, and control strategies, prior process characterization, validation, and comparability data generated at the original site may help inform the scope of studies conducted at the receiving site. Similarly, prior knowledge generated at one manufacturing scale may inform process development and validation at a larger scale. For example, platform data establishing proven acceptable ranges for critical process parameters at laboratory or pilot scale may support operating range selection and risk assessments at commercial scale. Prior knowledge derived from commercial manufacturing experience, process characterization activities, and lifecycle management may also support comparability assessments associated with capacity expansion, including increases in manufacturing throughput, additional production capacity operating under comparable process conditions, or other modifications intended to expand supply while maintaining control of critical quality attributes.”
390	390	III B	The guidance describes leveraging information across the scope of development but this sentence ends considering the nonclinical information “needed to enter into a clinical trial”. As some leveraging may be possible through the time of BLA, and additional nonclinical evidence may be required than for FIH studies, reference to BLA here would be more inclusive in scope.	Proposed edit to “... should inform the nonclinical program, including kind, duration, and scope of nonclinical testing needed to enter into a clinical trial or support a future BLA.”
485	488	III B ii	Leveraged biodistribution studies can allow a sponsor to select human cell types to evaluate on and off target editing though focusing the evaluation on the target tissue with the highest in-vivo exposure is the most applicable when product consistency can be demonstrated.	Proposed text, “If a product contains a previously evaluated editor, delivery vehicle, formulation, and manufacturing process and has demonstrated on-target editing activity in target tissues and absence of off-target editing in non-target tissues, off-target analyses may be limited to cell types representative of the target tissue(s).”

489	490	III B ii	Archival of “all tissues” from in vivo biodistribution studies is not practical or necessary. Some guidance or additional clarity on collection of key tissues would be helpful.	Proposed text: Comprehensive archiving of tissues consistent with ICH S12 and/or relevant for the product’s mechanism of action should be conducted for in vivo BD studies for possible future assessment.
498	498		Simply states LNPs without stating if leveraging genotoxicity data implies LNPs that share the same physiochemical properties.	Incorporate properties of LNPs that may qualify for leveraging genotox data across products similar to lines 471-472 and lines 530-531
498	501	III B iii	Genotoxicity leveraging appears twice, briefly in lines 498-501 and again with further context in lines 521-542. To minimize redundancy we recommend removing the mention of genotoxicity in lines 498-501 and moving any needed text into the broader explanation of genotoxicity considerations.	To minimize redundancy, we recommend removing the mention of genotoxicity in lines 498-501 and moving any needed text into the broader explanation of genotoxicity considerations.
501	507		Separate impact on DART studies in a separate paragraph iv (general tox, LNP genotoxicity and vector DART mixed in a single paragraph	iv. BD data indicating no distribution to the gonads may be considered for leveraging to forgo developmental and reproductive toxicities (DART) and germline transmission studies for a product with a similar delivery vector. The potential for leveraging DART or germline transmission data when editing is observed in the gonads should be discussed with the FDA.
530	531	III.B.c.ii. 1	Recommend an additional example.	Draft text: Add “phospholipid” to sentence “...lipid components, including ionizable lipids, cholesterol, phospholipid and PEG-lipids, are identical in type and ratio.”
552	563	III.B.1.c.i ii	With regards to applicability beyond genome editing components, the language in this passage regarding changes to transgene between platform products seems to contradict the spirit of the guidance written in Section III.B.1.b.iii. Lines 492-507 state that if BD profile and product characteristics are sufficiently similar between products, general toxicology data may be considered for leveraging, and additional nonclinical studies focusing on the cargo may be adequate. But lines 552-563 state that a change to the transgene can make it challenging to leverage nonclinical data, even if the vector backbone and expression cassette remain the same. It is not clear why a change only to the transgene of a platform in vivo vector could	Reconcile the language between sections 1.b.iii and 1.c.iii; enable the leveraging of platform vector tox data if supplemented by cargo-specific nonclinical data.

			not leverage prior tox data so long as it was supported with cargo-focused nonclinical studies.	
611	613	2.a.ii	The guidance says parameters may be leveraged "when the intended on-target edit rates achieved by different drug products are similar," but gives no quantitative or qualitative threshold for similarity.	Request a defined range (e.g., percentage difference in editing efficiency) or at least examples of what FDA would consider similar versus dissimilar, since this determination affects whether assay parameters like starting material amount or culture conditions can be reused without re-assessment.
634	666	III.B.2	The guidance does not address how leveraging determinations should be handled when a previously leveraged bioinformatics pipeline or tool component is subsequently updated (e.g., a new aligner version, an updated reference genome build, or an updated tool dependency).	Given that NGS analysis pipelines are routinely revised over the course of a development program, FDA's clarification is requested on the following: 1. Whether updating a previously leveraged pipeline component requires a bridging assessment confirming relevant performance characteristics are unchanged. 2. Criteria for distinguishing substantive updates from those unlikely to affect pipeline output. 3. Whether such updates require an IND amendment or may be documented at the next planned submission or regulatory interaction.
644	647	2.c.i	The guidance acknowledges that target sequence and mismatch parameters "may need to be modified" when applying a leveraged pipeline to a new product, but doesn't specify what level of supporting justification or documentation FDA expects once these parameters are changed.	Does adjusting the target sequence and mismatch parameters represent a substantive change to the analysis that warrants its own performance assessment or is this considered an expected, routine input change for a pipeline whose underlying logic and performance have already been established on prior products? Clarification on FDA's expectations here would help sponsors determine the appropriate scope of supporting documentation when reusing a pipeline across products targeting different genomic loci.
689	689		Cross-reference potential delivery genotoxicity effects	Kindly suggest adding a sentence: "genotoxicity risk linked to the delivery method should be addressed or leveraged separately (as listed in c.ii.2)"
724	725	III C 3	It has been challenging to secure an INTERACT meeting with the FDA for some early phase gene editing programs. There have been recommendations to proceed directly to Pre-IND though these programs have had only preliminary evidence available. The guidance doesn't acknowledge this reality and instead continues to steer Sponsors toward requesting meetings that may not be granted.	Proposed change: "Sponsors planning to leverage clinical data or general prior knowledge are encouraged to engage with FDA in the early stages of product development through available opportunities such as INTERACT or pre-IND meetings or Type C/Type D meetings."

730	731		This will align with FDA's ongoing clinical trial reform initiatives to enable more seamless early-stage study designs and efficiencies such as multiple related products under a shared protocol.	"...sponsors should consider how the characteristics of the platform technology may impact the clinical evaluation of the product. <u>Sponsors may also consider platform or basket trial designs that evaluate multiple GE products targeting different genes within a shared clinical protocol.</u> "
751	760	III.C.2.a	If there are scenarios in which clinical data from one platform product could be leveraged to justify trial design, conduct, or analysis, some examples of these scenarios would be especially valuable to the reader.	Provide 1-2 examples where clinical data could be leveraged.
772	780		We agree that this is an appropriate flexibility that will help ensure LTFU studies are appropriately tailored to the evidence generation needs of a product and may evolve as the understanding and profile of a product or modality becomes better characterized. This flexibility helps address the fact that currently there is significant patient and healthcare system burden that occurs for long-term safety follow-up in both clinical and commercial settings. Accordingly, while flexibility around LTFU is beneficial to clinical patients as written here, we recommend FDA adopt a similar approach to post-market requirements and post-approval safety study on the same basis of accumulated safety evidence and prior knowledge.	Sponsors should refer to current guidance on long-term follow-up specific to the type of therapy. The FDA remains open to reconsider the type of data collected, frequency and duration of follow up monitoring based on the cumulative safety data and any emergence of new safety signals to reduce unnecessary burden on the patients and the Sponsors. <u>For example, a genome editing product may initially have a 15-year follow-up requirement, that is proposed to be modified when either the sponsor, or a group of sponsors across a shared modality, compiles data to present to the FDA that supports a modification to the duration of this study or events collected. Such an approach will also be applied in the post-approval setting when considering the totality of evidence collected across the clinical and commercial setting when determining the scope (e.g. duration, AEs of interest) or potential modification to post-market requirements and post-approval safety studies. Sponsors are encouraged to discuss long-term monitoring plans with appropriate justification throughout product development and when appropriate, in the post-approval setting.</u>
787	797	IV	Evidence Boundaries and Product-Specific Justification section	FDA could consider revising where the draft guidance addresses platform analytical methods, lot release specifications, process characterization/PPQ, and bridging or confirmatory data. The guidance should more clearly define the boundaries for using bridging or confirmatory data, platform CQAs, potency assays, and PPQ reliance while preserving product-specific justification for identity, potency, specifications, validation, and lifecycle control. For example, platform analytical validation data may support selected

				method attributes, but product-specific verification may still be needed for a new gRNA sequence, cell source, matrix, or potency mechanism. Similarly, platform PPQ data may support reduced PPQ only where site, scale, equipment, process parameters, and relevant CQAs remain comparable.
797	797		This will ensure that the ability to leverage prior knowledge and associated bridging studies are proportionate to the differences between the products under investigation. For example, where significant elements of the product are conserved, bridging studies may not need to be as extensive as when there are more notable product differences (e.g. differences in vector design, regulatory elements, delivery approach)	Proposed text: "Supply bridging or confirmatory data as appropriate, <u>proportionate to the degree of difference between the leveraged product and the current product</u> "
798	812	IV	Platform Governance and Traceability:	FDA could consider revising where the draft guidance defines platform knowledge and describes how platform information may be submitted or cross-referenced. The guidance should clarify expectations for platform governance, lifecycle controls, version control, documentation standards, and traceability from each leveraged dataset to the source product, study or report, quality attribute, and applicability rationale. For example, sponsors could maintain a platform summary and traceability table identifying the source product, study report, analytical method, PPQ run, stability study, comparability assessment, applicable platform element, authorization status, version history, and rationale for applicability to the current product.
800	800	IV	We appreciate the reference to a Master File (MF) as a mechanism to provide the FDA with platform information. Establishing a platform requires data from multiple products to be compared and analyzed which may be more suitable for a MF than in an individual IND. Current draft MF guidance refers to Module 4 data related to characterizing an excipient or impurity but this does not cover the type of data (e.g. biodistribution, on-target editing, off target editing, general toxicology, DART, etc.) related to the product as a whole that would support a platform. Openness to a MF covering a platform evidence across all modules (CMC, Nonclinical, and Clinical) would be useful.	Platform information and data may be provided directly in the IND submission, a new platform Master File (MF), or it may be referenced to a previously submitted IND or a Master File.
811	813	IV	Sponsor's are instructed to include the justification for leveraging information in the IND but there is not guidance on	Suggested edit: "Regardless of whether the platform information and data are being provided directly in the IND

			“where” or in which module this should be included. A multiple-module information amendment (e.g. 1.11.4) could be appropriate as this could span multiple disciplines but if the FDA would prefer that this justification be included in a Module 2 summary or as a standalone document in Modules 3-5 then additional clarity on this point would be beneficial.	submission or is cross-referenced, the justification for why the knowledge is applicable to the current product should be provided as a multiple module information amendment or as a standalone report within the appropriate Module (3-5) in the IND for that product.”
825	827		Minor change to ensure FDA-sponsor engagements on the use of prior knowledge provide actionable feedback for sponsors as they create development plans on the basis of leveraging prior knowledge and ensuring such approaches do not introduce delays to regulatory interactions.	Proposed text: “...we recommend that they discuss this with FDA as early as possible in the product development lifecycle (e.g., INTERACT and pre-IND meetings). <u>FDA intends to provide written feedback on leveraging proposals within the standard meeting response timelines.</u> ”
829	833	IV	Consider adding a column to Table 1 regarding in vivo GE products. If the Agency opts to broaden the scope to include other non-GE products, this table could be further expanded as needed (i.e., in vivo gene therapies, ex vivo gene-modified cellular therapies, etc.)	We suggest adding column(s) to the table, consistent with the scope of the final guidance document.
105, foot note 7	105	II	Recommend including mention of the lipids or AAV vector as one of the gene editor “components”. Because the guidance defines a component as “any material that is essential for the intended genomic modification”, and without these components there is not the appropriate biodistribution, internalization, and pharmacologic activity, they are vital to achieving the desired genetic modification.	Suggested text: “GE components may include, but are not limited to, the editor, DNA targeting elements (i.e., elements used to dictate the target DNA sequence, such as guide RNA) and a donor DNA template (i.e., DNA sequence provided to repair the target sequence), and the individual lipids or viral vector present in the drug product, as applicable.”