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LEONARD DAVIS INSTITUTE of HEALTH ECONOMICS

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Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2026-D-1256

Introduction and Background

We appreciate the opportunity to offer comments on the Draft Guidance for Industry, "*Considerations for the Use of the Plausible Mechanism Framework to Develop Individualized Therapies that Target Specific Genetic Conditions with Known Biological Cause.*" We are faculty members at leading research institutions, including academic centers advancing the field of individualized therapeutics.[1] Our professional backgrounds span law, clinical research, medical practice, and bioethics. Collectively, we bring expertise in FDA law and policy, research ethics, genetic medicine, and innovation policy.

We have followed the plausible mechanism framework closely since Commissioner Makary began to discuss the idea in April 2025. We analyzed FDA's November 2025 commentary published in the *New England Journal of Medicine (NEJM)*, sharing our perspective in a series published in *Health Affairs Forefront* (Part 1, Part 2), as no docket had yet been opened to receive public comment given that no draft guidance had yet been published. We noted the importance of the plausible mechanism framework to resolve critical challenges to developing individualized genetic medicines for n-of-1/n-of-few disorders. However, we also flagged concerns about the scope of the proposal and FDA's approach to announcing the new policy via journal article, in contravention of the agency's Good Guidance Practices regulation (21 CFR 10.115).

Upon review of the draft guidance, we are supportive of its goal of facilitating FDA approval of n-of-1/n-of-few therapies and further clarifying how such a framework may be operationalized by the agency. However, additional clarifications and changes are needed in a final guidance to achieve the framework's aim of bringing safe and effective individualized therapies to patients who need them, while minimizing the likelihood of extending the framework in ways that would inappropriately lower FDA's regulatory standards or lead to unintended consequences.

Scope Constraints

The plausible mechanism framework is well-suited to individualized products designed to treat n-of-1/n-of-few genetic variants. The draft guidance includes language indicating that the framework's scope will be limited to these exceptional circumstances, for example, requiring sponsors to justify why a randomized controlled trial is infeasible and document that the targeted variant is unique to the patient. However, this language is in tension with public statements by FDA leadership. For example, the NEJM article suggested that the plausible mechanism "pathway" would be "also available for common diseases" with unmet need. More recently, CDER Director Tracy

[1] Institutional affiliations are provided for identification purposes only. The views expressed in this comment represent the personal views of the signatories in their individual capacities and do not necessarily represent the views of any institutions, grant funders, or individuals with which they are affiliated.

Beth Høeg stated that FDA would "not limit this [framework] to ultra-rare diseases," while CDER's Office of Neuroscience Director, Teresa Buracchio, explained that although this draft guidance is specific to individualized therapies, "you might be able to use the principles of the plausible mechanism framework to approve other therapies." The final guidance should clearly resolve this ambiguity regarding scope in favor of narrow application.

The history of drug development includes many biologically plausible interventions that failed to demonstrate effectiveness in controlled clinical trials. The plausible mechanism framework should therefore be available only when a traditional prospective clinical investigation is genuinely infeasible, not merely inconvenient or difficult; this will be obvious for n-of-1/n-of-few variants. Relatedly, because randomization is not always needed to confidently determine a drug's benefit (e.g., when disease presentation is relatively homogeneous, the natural history is clear, and an intervention's effect size is expected to be substantial), the framework should be available not only when a randomized controlled trial is infeasible but more narrowly when any appropriately designed traditional prospective investigation would be infeasible. In addition, FDA should further clarify – with public input – when traditional prospective studies will be considered infeasible in rare disease.

Finally, the draft guidance appropriately states that investigation results should be "robust" to support approval under the plausible mechanism framework. However, it does not specify what type of outcomes would fail to meet that standard or how the agency will respond to ambiguous or negative outcomes. Particularly given the pressure that FDA often experiences to approve drugs despite uncertain evidence, especially in the context of rare disease, it would be helpful to include examples of what outcomes will and will not be approvable under the framework.

Recommended Revisions:

- ***Limit scope explicitly.*** *Clarify that the plausible mechanism framework is not available to products intended to treat common diseases/conditions that reasonably could be subjected to traditional prospective investigation.*
- ***Require a stronger showing of infeasibility.*** *Add an expectation for sponsors to describe why it is infeasible to conduct any traditional prospective investigation (not only a randomized controlled trial), such that the plausible mechanism framework offers the exclusive pathway to approval. These explanations should be shared publicly as part of FDA's commitment to transparency.*
- ***Clarify standards of infeasibility.*** *With the input of advisory committees, clarify when traditional prospective investigations will be considered infeasible in rare disease.*
- ***Elaborate the robustness standard.*** *Provide further discussion of what FDA means by "robust" results under the plausible mechanism framework and how FDA will respond to results that fall short of that threshold.*

Manufacturing Challenges

The plausible mechanism framework will hopefully attract commercial developers to invest in n-of-1/n-of-few individualized therapies. Academic developers will also be important given the likely insufficiency of commercial interest to develop these therapies for all patients who could benefit. However, some academics have suggested that, in practice, the manufacturing expectations described in the draft guidance may effectively foreclose academic developers from utilizing the framework.

FDA's recent steps to increase flexibility in manufacturing requirements for cell and gene therapies, such that they build in intensity as the product approaches approval, are helpful and recognize the difficulty of meeting stringent chemistry, manufacturing, and control (CMC) standards from the start of clinical development. Under the plausible mechanism framework for individualized therapies, however, the first-in-human study is simultaneously contemplated to be the pivotal study, posing challenges to a staged CMC approach.

Importantly, the concern is not that academic developers of n-of-1/n-of-few therapies will never be able to achieve the stringent CMC standards applicable to approved products. Instead, it is that imposing those standards from the start of the research designed to support approval of individualized therapies under the plausible mechanism framework often would be so resource-intensive that academic developers may not be able to begin that research at all, absent an industry partner. Grant or other funding, such as public-private partnerships, may help address these resource challenges and FDA should work with partners across HHS to encourage this support. However, grants are likely to be insufficient to address the concern in all cases, given limited funds and substantial timing gaps between application and funding, among other reasons.

Thus, FDA should consider both whether and, if so, what CMC flexibility for academic developers of individualized therapies may be appropriate to allow them to utilize this framework independent of commercial developers when necessary. In doing so, FDA should recognize the potential harms to patient access of relegating academic developers exclusively to use of unreimbursable approaches, such as the Expanded Access pathway or perpetual IND-status for n-of-1/n-of-few therapies, which will not be practical, sustainable, or in the interest of patients. Approaches that would encourage payers to reimburse unapproved individualized therapies should also be avoided, given concerns about how that reasoning might problematically extend more broadly outside the framework.

We recognize the importance of strong CMC standards to protect study participants and patients, alongside the risk that limiting the plausible mechanism framework to commercial developers will substantially constrain its impact. This is a challenging problem, but we encourage FDA to examine the concerns facing academic developers of individualized therapies, consider whether appropriate and limited CMC adjustments may exist to address these concerns, and commit to working with relevant stakeholders, including HHS partners and Congress, to address resource constraints that may prevent academic developers from using this framework. FDA should also encourage – or if feasible, require – sponsors to share data, manufacturing processes, validated assays, and the like once CMC standards have been met for a product/platform under the plausible mechanism framework, to minimize the need for continued CMC flexibilities as the field develops.

Recommended Revisions:

- ***Acknowledge the academic developer challenge.*** *Consider whether appropriate adjustments both exist and can be made to allow academic developers of individualized therapies to feasibly meet manufacturing standards during research studies needed to secure approval under the plausible mechanism framework.*
- ***Solicit public input on potential solutions.*** *To inform the agency's consideration, FDA should solicit public input, through an advisory committee or other public meeting, on the CMC challenges facing academic developers of individualized therapies and possible solutions that could be applied under the plausible mechanism framework.*

- ***Address resource support.*** *Work with HHS and other partners to consider how resources could be provided to support academic developers in meeting CMC standards under the plausible mechanism framework.*
- ***Encourage sharing across programs.*** *Evaluate approaches to encourage or require sponsors using the plausible mechanism framework to share data, processes, validated assays, and the like to minimize future challenges meeting manufacturing standards.*

Approval Reach

The draft guidance does not clearly define the scope of the individualized product that will be granted approval under the plausible mechanism framework or explicitly explain which variants will be included in the initial or subsequent approvals. However, it indicates that, following approval, sponsors wishing to treat a patient with a new variant not included in the original trial must provide in vitro data to address editing activity at the target site and off-target editing. The draft guidance does not specify what FDA's process and anticipated timeline for reviewing those data will be, nor does it address whether alternatives to pre-submission/pre-approval might suffice. Importantly, the approach contemplated by the draft guidance appears to differ materially from a "process approval" model, such as that being developed in the UK, in which all future modifications of the individualized therapeutic are encompassed within the original approval.

Although the "backbone" of the individualized therapeutics contemplated to be approvable under the plausible mechanism framework can remain the same across individual patient variants, it is important for developers to test individualizations for new variants to ensure safety and effectiveness. The question is not whether testing is needed but rather what sort of oversight of that testing is needed and how oversight can avoid impeding the utility of the plausible mechanism framework.

If pre-approval from FDA is required before each patient with a new variant may be treated with an otherwise approved product, it is unclear that FDA will have the capacity to respond quickly enough to meet patient treatment needs, given anticipated growth in these submissions. As an alternative to pre-approval of further individualizations of the approved product, FDA should consider whether a less formal clearance or notification process could suffice, perhaps as a condition of enforcement discretion. Another option would be for FDA to prespecify in vitro assays that must be performed before intervening on a patient presenting with a new variant but without requiring pre-submission or pre-approval by FDA, perhaps with annual or more frequent public reporting requirements of these changes. Relatedly, it might be feasible to credential treatment sites to follow a prespecified process for adding patients with new variants or to follow a process analogous to predetermined change control plans for medical devices in which such plans are part of the product's marketing authorization. If these approaches are not available under existing statutory authority, FDA should consider seeking appropriate amendments from Congress.

Finally, we note that the scope of the individualized product granted approval under the plausible mechanism framework, including subsequent additions, has important implications for the scope of associated market exclusivities. Given the potential implications of these exclusivities for patients with different variants to access care across centers, the final guidance should explicitly address how they will apply.

Recommended Revisions:

- ***Define the scope of the approved product.*** *Explicitly define the product and state the scope of approval granted under the plausible mechanism framework when applied to individualized therapies, as well as how exclusivities will apply to the product and its associated variants.*
- ***Clarify testing expectations.*** *Clarify appropriate tests that should be conducted prior to using the approved individualized therapy to treat a patient with a new genetic variant.*
- ***Clarify the regulatory process for adding new patient variants.***
    - *Consider whether alternatives to pre-submission and/or pre-approval could be appropriate for oversight of further individualization of products approved under the plausible mechanism framework, such as clearance, notification, reporting, and prespecified tests or processes included in the marketing authorization.*
    - *If information must be provided to FDA before adding a new product variant after approval under the plausible mechanism framework, clarify how that information will be handled (e.g., pre-approval, notification, etc.) and on what anticipated turn-around time from FDA.*
    - *Require public transparency when new variants are added to approved individualized therapies under the plausible mechanism framework.*

Post-Approval Requirements

Given the limited evidence available for approval, it is important to ensure appropriate postmarket evidence generation for products under the plausible mechanism framework. The final guidance should therefore strengthen postmarketing expectations, regardless of whether a product is approved under regular or accelerated approval. For accelerated approvals, however, the final guidance should explain what a confirmatory study will look like in these n-of-1/n-of-few circumstances and how it could be initiated before approval, given stated expectations. The final guidance should also clarify how FDA's existing guidance on long-term follow-up for gene therapy products applies in this context.

Plausible mechanism approvals should come with postmarketing requirements (PMRs) – not postmarketing commitments (PMCs) – for both safety and effectiveness to enable more robust enforcement. Ideally, these would include required patient registries with minimum standardized datasets for collection, as exemplified by the Stem Cell Therapeutic Outcomes Database, managed by the Center for International Blood and Marrow Transplant Research. PMRs might also be a way to gather data on product modifications to address new patient variants without requiring pre-approval, as discussed above.

Finally, the draft guidance does not address how a serious adverse event in a patient treated with a product approved under the plausible mechanism framework may affect other patients treated with related products targeting different variants of the same gene or related genes affecting the same phenotype. FDA should describe in the final guidance how these safety considerations will be addressed, with a commitment to make public both its safety investigations and their resolution.

Recommended Revisions:

- ***Require PMRs instead of PMCs.*** *State an expectation that all products approved under the plausible mechanism framework, whether through regular or accelerated approval, will have postmarketing requirements (PMRs) for both safety and effectiveness.*
- ***Specify long-term follow-up expectations.*** *Clarify what type of long-term follow-up will be expected for gene therapies approved under the plausible mechanism framework.*

- ***Address patient registries.*** *Describe expectations for patient registries, including as PMRs, for products approved under the plausible mechanism framework.*
- ***Consider PMRs to address new variants.*** *In addition to PMRs for the initially approved product, explain whether and how PMRs may be used to extend products approved under the plausible mechanism framework to new patient variants.*
- ***Explain accelerated approval expectations.*** *Clarify the expectations for confirmatory studies when an individualized therapy receives accelerated approval under the plausible mechanism framework.*
- ***Address cross-product safety implications.*** *Describe in more detail how safety concerns presenting for products approved under the plausible mechanism framework may affect other related products and commit to sharing safety investigations publicly.*

Additional Considerations

We also note several additional issues that should be considered in developing the final guidance:

- The draft guidance states that **biomarkers** may be used to support an individualized product's effectiveness, among other functions, and calls for a variety of biomarker assessments. It is not clear, however, what validation standards will apply to biomarkers used within the plausible mechanism framework. It also remains unclear whether FDA will revisit biomarkers without established evidence of association with clinical outcomes after approval of products using such endpoints. FDA should publicly describe the strength of evidence for biomarkers used to support approval under the plausible mechanism framework and routinely review the evidence supporting association with clinical outcomes. FDA could require sponsors to generate such evidence or work in collaboration with NIH and academic partners to do so.
- The draft guidance encourages the use of **New Approach Methodologies (NAMs)** when appropriate. However, given that validation standards for NAMs have not yet been established, it is not clear that they should be encouraged under the plausible mechanism framework at this stage. More specifically, it is not clear that NAMs will save time and resources or be sufficiently accurate compared to available animal models. If NAMs will be called out in the final guidance, greater clarity should be provided regarding when and why they are likely to be appropriate.
- Like the plausible mechanism framework, FDA's **platform technology designation** assumes the possibility of leveraging information across applications to speed development. The final guidance should explain how platform technology designation will interact with products approved under the plausible mechanism framework.

Procedural Issues and FDA Resources

Finally, with regard to procedural issues and FDA resources in the context of the plausible mechanism framework, we recommend the following:

- FDA should **engage with Congress** and relevant stakeholders to determine how the plausible mechanism framework could be buttressed through statutory amendment, including mandates for post-approval registries and data sharing.
- FDA should consider moving beyond guidance to **promulgate regulations** applicable to the plausible mechanism framework. This will provide greater certainty and stability for product developers, while giving FDA stronger ability to develop requirements and appropriate enforcement for the plausible mechanism framework.

- FDA should commit to **transparent implementation** of the plausible mechanism framework, both for public accountability and to inform future development. Transparency expectations should include at least annual **public reporting** of products approved under the framework, for which conditions, why they were unable to be studied using traditional clinical investigations, postmarketing requirements, and safety actions (as well as prompt posting of approval packages as individual products are approved and amended).
- For all future policy developments relevant to the plausible mechanism framework (and otherwise), FDA should adhere to its **Good Guidance Practices regulation** and refrain from announcing new policies exclusively via press release or journal article.
- The draft guidance envisions extensive engagement between FDA and developers of individualized therapies under the plausible mechanism framework. Both to ensure proper oversight and avoid bottlenecking development, FDA must ensure the necessary resources and work environment to support an adequate number of **expert staff** to advance the framework. Given recent staffing loss, this concern must be a strong priority for resolution.

Conclusion

We hope these recommendations contribute to a final guidance that is clear, workable, appropriately bounded, and accessible, including to the academic developers of individualized therapies and patient communities that motivated it. We welcome further discussion.

Respectfully submitted,

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