Re: Docket No. FDA-2026-D-1256 — Draft Guidance: "Considerations for the Use of the Plausible Mechanism Framework to Develop Individualized Therapies that Target Specific Genetic Conditions with Known Biological Cause"

Submitted by: Elissa Gentry, JD/PhD,[1] Daniel Chen, JD/PhD,[2] & Timothy Yu, MD/PhD[3]
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I. Introduction

We respectfully submit this comment in response to the FDA's draft guidance on the use of the "plausible mechanism" framework for individualized therapies. This comment draws on our attached working paper, *Authorizing Bespoke Therapies*, which analyzes the regulatory, economic, and legal challenges posed by N-of-1 precision medicine. In particular, the article highlights the incompatibility between N-of-1 precision medicine and a population drug-based regulatory approach, the weaknesses of premarket approval without sufficient causal inference, and the importance of mandatory data sharing.

While the draft guidance represents an important and commendable step toward acknowledging that traditional evidentiary paradigms may be infeasible in the context of ultra-rare and individualized genetic conditions, the guidance does not go far enough in customizing oversight from the traditional population-based drug framework. First, in a context where significant customization is expected in subsequent patient treatment, premarket approval is both overly burdensome and under-protective. Instead, a service-based model is more appropriate, substituting ongoing monitoring for burdensome premarket approval that does not create sufficiently generalizable information. Second, due to the shared modalities of such N-of-1 therapies, data sharing can lead to significant cost reduction. Based on the barriers to voluntary licensing, such data sharing must be mandatory, not voluntary.

II. Support for Exploring Alternate Procedures

The FDA's acknowledgement that conventional clinical trials are often infeasible in this setting reflects an appropriate evolution in regulatory thinking. Reliance on this framework prevents patients from accessing potential treatments and chills innovation in this space. In particular, the importance of the emphasis on proof of concept (POC) studies and nonclinical data to support plausible mechanisms is a step in the right direction. We support the FDA's willingness to see that alternate procedures are necessary in this context.

Despite this, we worry that the proposed pathway's reliance on traditional drug development processes actually creates more safety issues than a service-based model. Specifically, we agree

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[1] Associate Professor of Law, Sandra Day O'Connor College of Law, Arizona State University
[2] Professor, Toulouse School of Economics
[3] Associate Professor of Pediatrics, Boston Children's Hospital, Harvard Medical School, The N=1 Collaborative

with the FDA that N-of-1 treatments are best characterized not as a traditional, uniform drug but as a medical treatment that requires customization for each patient. With such necessary customization, the model of premarket approval (even with post-market monitoring of adverse events) simultaneously provides insufficient oversight and delays patient access. Finally, data-sharing has the potential to reduce costs for development; however, the guidance provides insufficient incentives (or requirements) to facilitate such sharing.

II. Individualized Therapies Operate on a Customization Continuum

The draft guidance implicitly treats individualized therapies as drug development activities. However, the type of evidence underlying these interventions evince a primary focus on patient care rather than generalizable knowledge production.

This distinction can similarly be framed on a service- or a goods-based continuum. A service-based model would center a specialist physician in the development and customization of treatment per individual patient. A goods-based model instead anticipates that individualized therapies are approved, mass produced, and implemented without patient customization, much like population-based drugs. If the FDA believes that the goods-based model is the future of such N-of-1 treatments, more rigorous research strategies must be mandated, even in small populations. If the goal is generalizable knowledge production, the current reliance on predictable natural history creates a much lower level of generalizability.

Given the small number of patients afflicted with individual genetic mutations, we are skeptical of a goods-based model. If we target truly individualized therapies, it seems unlikely that approved N-of-1 treatments can be implemented without further customization to subsequent patients. If a treatment must be customized per patient, ongoing monitoring and adherence to best practices more effectively assures quality than one-time premarket approval. This distinction has important regulatory implications.

III. Continued Reliance on Premarket Authorization Is Ill-Suited to Individualized Therapies

The draft guidance continues to rely on a framework centered on premarket authorization. In contexts in which a treatment requires significant customization upon implementation, however, premarket approval is simultaneously overly burdensome and under protective.

Premarket approval creates costly delay for patients faced with life-threatening illnesses. This tradeoff is often worthwhile when the resulting evidence (from randomized, sufficiently powered clinical trials) creates evidence of general efficacy that is difficult to otherwise obtain. In the context of individualized therapies, we are skeptical that the methods employed in premarket approval are sufficient to create this generalizable efficacy.

The guidance notes the need for robust evidence supporting effectiveness but does not provide adequate information about how that will be provided. For clinical investigations, the guidance assumes that the disease will have a “well-characterized natural history in the untreated population” which will serve as a control group “if it is adequate to allow for the treatment effect

to be reasonably distinguished from natural variability in the phenotype of the disease." It is not clear to us how many of these genetic illnesses have a sufficiently defined natural history to allow for use as a control.

While the guidance allows for longer duration of follow-up or surrogate endpoints in case such variability is high, this does not provide strong evidence of general efficacy. The guidance also discusses the use of baseline data with which to compare treatment; while this is sufficient to assess patient treatment, it is not sufficient for generalizable efficacy. As the attached paper explains, pre/post comparisons without randomization or crossover designs are vulnerable to confounding from time trends, placebo effects, and disease variability.

Such a relaxation without more continuous monitoring likely reduces patient safety and potentially confidence.[4] Current adverse event monitoring by the FDA is not sufficiently systematic or enforceable to substitute for more formal monitoring.

IV. Lack of a Data-Sharing Infrastructure

As the attached paper explains, individualized therapies generate highly valuable information—such as design choices, safety data, and manufacturing experience—that can substantially reduce the cost and improve the safety of future therapies. However, because developers bear the cost of generating this information while others benefit from it, there is a predictable market failure resulting in underproduction and under-disclosure of data.

While the draft guidance acknowledges the importance of prior knowledge, platform technologies, and "larger scale data collection and sharing," including through master protocols, it does not establish mechanisms to ensure that such data sharing occurs in practice.

This is a critical omission. While companies are free to negotiate licenses with one another, there are multiple practical and theoretical barriers to negotiating a beneficial bargain. As noted by Calebresi and Melamad,[5] transaction costs such as asymmetric information prevent bargains that would benefit both parties from being successfully negotiated. In contexts like this, the social benefit from sharing data may even exceed the private benefits accruing to either party. In cases like this, encouraging data sharing is insufficient; without mandatory or incentivized disclosure, the benefits of cross-case learning will not be realized.

V. Conclusion

The FDA's draft guidance represents a significant and thoughtful step toward addressing the unique challenges of individualized therapies. To fully realize the promise of the plausible

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[4] The postmarket monitoring suggested by the guidance falls short of the type of monitoring necessary, particularly in light of the absence of other legal levers like products liability and medical malpractice. Chen, Daniel, Elissa Philip Gentry, and Tim Yu. "Authorizing Bespoke Therapies." *Arizona State University Sandra Day O'Connor College of Law Paper* 6471020 p. 34-38 (2026).

[5] Calabresi, Guido, and A. Douglas Melamed. "Property rules, liability rules, and inalienability: one view of the cathedral." *Modern Understandings of Liberty and Property*. Routledge, 2013. 139-178.

mechanism framework, however, the final guidance should move beyond a modified premarket approval paradigm and incorporate mechanisms that:

1. Create Continuous Oversight Rather Than One-Time Authorization

We recommend that the guidance shift emphasis away from marketing authorization toward:

- Ongoing compliance with standards of good practice; and
- Continuous, enhanced monitoring of safety and outcomes.

The attached paper provides a potential solution for how to accomplish this, but for the purpose of this comment it is sufficient to note that this is a missing and necessary dynamic.

2. Mandatory Standardized Data Disclosure

We recommend that rather than encouraging voluntary data sharing (with no incentives), that the policy shift to mandating reporting of:

- Both successful and unsuccessful design iterations;
- Preclinical and safety data;
- Clinical outcomes and follow-up observations.

Again, our paper proposes a way to do this, but we believe it is sufficient for the purpose of this comment to flag the ineffectiveness of voluntary measures in this context.

We believe that N-of-1 precision medicine has the potential to transform the way we approach individualized genetic interventions. We urge the FDA to consider the value of premarket approval/continuous oversight and data-sharing in this context.

Respectfully submitted,

Elissa Gentry, JD/PhD
Daniel Chen, JD/PhD
Timothy Yu, MD/PhD