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Critical Path Institute aims to bring scale to individualized medicines

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FDA's plausible mechanism framework aims to accelerate and expand drug development for patients with rare genetically driven diseases, but ambition alone won't deliver. The intellectual and institutional scaffolding needed to move from an artisanal to an industrial approach to individualized medicines is missing.

With its current leadership, staffing and resources, FDA cannot create that scaffolding.

The Critical Path Institute, a public-private partnership, is launching the One to Millions initiative to fill the gap between idea and action. Its goal is to build shared infrastructure for individualized therapies at scale, helping overcome barriers to deploying treatments for genetically driven diseases.

"We're at a point where science can deliver these therapies, but the system can't absorb them," said Klaus Romero, CEO of C-Path. The failure of regulatory systems to keep up with scientific advances has confined individualized treatments to isolated, one-off cases. What is needed, he said, is a repeatable development paradigm that captures lessons across programs.

The One to Millions initiative has support from FDA Commissioner Marty Makary and other agency leaders, Romero told BioCentury.

"THIS IS NOT SOMETHING THAT CAN BE SOLVED CASE BY CASE. WE NEED A SYSTEM."

JANET WOODCOCK, FORMER FDA ACTING COMMISSIONER

FDA has already quietly moved to incorporate external advice into the plausible mechanism concept. The role of outside experts and FDA career staff is visible in the evolution of the plausible mechanism concept. It began with a November New England Journal of Medicine paper announcing the pathway that was vague and untethered from legal or regulatory precedent. By contrast, the February draft guidance explicitly anchors the pathway in the "substantial evidence of effectiveness" standard, describing considerations for generating such evidence alongside safety data for individualized therapies.

One to Millions will begin with the lowest-hanging fruit, antisense oligonucleotides (ASOs), and plans to continue with gene editing and other genetic medicines.

The apparent successes of a handful of well-publicized n-of-1 treatments, such as the creation of a therapy for baby KJ last year, inspired FDA to create the plausible mechanism framework. These cases suggest that the science exists to improve the lives of patients with rare diseases, but it takes too long and costs too much to create individualized therapies.

Each case is treated as a standalone effort, requiring bespoke manufacturing, preclinical testing, and regulatory engagement. There is little reuse of data or methods, and no standardized pathway for translating one success into many.

If it is successful, the One to Millions project will illuminate business models that could allow biopharma companies to enter the space. Industry engagement could exponentially increase the number of patients treated, and in the long-run pioneer approaches to evidence development that could be applied more broadly, including to rare subsets of common diseases.

Creating an infrastructure for individualized medicines

FDA's plausible mechanism framework draft guidance acknowledges that traditional standards, including randomized-controlled trials, are often infeasible for ultra-rare conditions. Instead, it opens the door to approvals based on mechanistic understanding supported by limited clinical data.

But the framework stops short of defining how such evidence should be generated, evaluated, or reused.

C-Path's answer is to build the missing infrastructure.

The central premise of the One to Millions initiative is that individualized therapies should not be regulated as discrete products, but as part of a system. Rather than evaluating each therapy independently, C-Path is proposing a shift toward something that could be considered process-based regulation.

It intends to convene stakeholders to create approaches to defining standardized approaches to development, manufacturing, and evidence generation that can be applied across multiple therapies targeting different patients.

Former FDA Acting Commissioner Janet Woodcock, who helped launch the initiative, likens the model to blood banking, where regulators approve processes rather than each individual unit.

The initiative is designed to create what Romero describes as "reusable, regulatory-grade evidentiary frameworks," supported by integrated datasets spanning industry, academia, and clinical care.

In practice, that means pooling data across programs to generate shared tools that define structure–toxicity relationships, exposure–response models, benefit–risk frameworks, and standardized outcome measures.

One to Millions plans to create a centralized, regulatory-grade data platform that integrates preclinical, clinical, and real-world evidence; manufacturing standards and quality systems; quantitative regulatory tools and biomarkers; and longitudinal patient registries.

These tools would enable regulators to evaluate therapies in context, drawing on accumulated knowledge rather than starting from scratch for each patient.

Houston, we've got a data sharing problem

Woodcock frames the challenge bluntly. The scientists and regulators trying to turn the dream of large-scale individualized medicines into reality are flying blind.

Data from n-of-1 therapies, including both ASOs and emerging gene editing approaches, are fragmented across institutions, often unpublished and rarely standardized. There is no regulatory requirement for academic teams to report outcomes systematically, and even dramatic clinical responses may not be captured in a form regulators can use.

"One of the startling things we've heard from clinical reviewers is that they don't see evidence these therapies are working," Woodcock said. "Not because they don't work, but because no one is submitting the data."

The result is a feedback loop that undermines both regulatory confidence and scientific progress. Without aggregated data, FDA reviewers lack the basis to establish precedents. Without clear precedents, developers face uncertainty. And without a predictable pathway, investment remains limited.

C-Path's answer is to create a precompetitive data ecosystem in which companies, academic centers and nonprofits contribute data to a secure shared environment. Practically, this means measuring outcomes consistently across patients and diseases, turning fragmented or anecdotal observations into structured datasets that regulators and researchers can use to identify broader patterns.

Companies participating in the initiative will contribute data to a secure platform managed by C-Path. C-Path will use aggregated insights to develop tools that all participants can benefit from without accessing one another's data.

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KLAUS ROMERO, CRITICAL PATH INSTITUTE

Many of the questions the initiative could answer are highly specific, but could have major effects on development time and cost.

For example, Woodcock suggested it could define standards for the amount and type of toxicology data required for intrathecal ASOs. FDA currently requires three months of toxicology data. At a recent workshop convened by the Duke Margolis Center and FDA's Rare Disease Hub, Lauren Black, distinguished scientist at Charles River Laboratories International Inc. (NYSE:CRL), reported that one month may be sufficient and that extending studies yields little additional information.

If regulators adopt insights like this, development timelines and costs could fall materially.

Over time, Woodcock said, One to Millions could evolve into a standards-setting organization tackling issues that slow or derail development.

C-Path could help define "standards with a capital S," Julia Vitarello, founder and CEO of Mila's Miracle Foundation, told BioCentury, including expectations for toxicology, manufacturing, delivery methods and clinical endpoints.

Vitarello said those standards should not be imposed top-down, but derived from aggregated data and updated over time, more like systems in other areas of medicine where independent bodies refine best practices based on real-world evidence.

Although the initiative will begin with ASOs, which offer a relatively mature dataset and a tractable entry point for cross-program evidence building, Romero said it will need to extend to gene editing, gene therapies, RNA-based treatments and other modalities targeting genetically defined diseases. In each case, the goal is to establish repeatable regulatory precedents for what constitutes sufficient evidence of safety and efficacy when traditional trials are not possible.

The regulatory consensus One to Millions is trying to create could eventually extend beyond rare monogenic diseases, Romero believes. Even within common diseases, patients who share a diagnosis may have distinct genetic drivers.

Filling a gap FDA can't, creating a business model

Although FDA has signaled openness to new regulatory paradigms, Woodcock emphasized that the agency lacks the capacity to lead the kind of cross-cutting effort required to operationalize them.

"The agency isn't staffed or really assigned to do this kind of cross-cutting work anymore," she said, pointing to a loss of expertise over the past 14 months.

Historically, FDA has helped aggregate data and shape standards in emerging fields. But the scale and complexity of individualized therapies, spanning preclinical development, manufacturing, clinical evidence, and postmarket surveillance, require a level of coordination that exceeds the agency's current mandate and resources.

C-Path, with its experience running public-private consortia and developing regulatory science tools, is positioning itself to fill that gap. "This is not something that FDA can do on its own, and this is not something that a single company can do on its own," Romero said.

Beyond regulatory uncertainty, individualized therapies face a more fundamental obstacle: creating a viable model for biopharma companies. "If you have to develop each therapy as a separate product, there is no business model," Romero said.

Vitarello said the barrier is not scientific, but systemic. The current paradigm — one drug, one disease, one approval — does not work for the long tail of genetic conditions affecting very small numbers of patients. The alternative, she said, is a shift from product-by-product approval to process approval.

The One to Millions initiative can help put some of the essential pieces in place for process approvals, Vitarello said.

Where the U.K.'s MHRA is advancing rapidly towards this goal, FDA has resisted calls to explicitly support process approvals.

Instead of evaluating each therapy individually, Vitarello said patients would be grouped "horizontally," based on shared biological mechanisms, such as mutation type or therapeutic modality, rather than vertically by disease. This would allow a single validated process to generate treatments for dozens or even hundreds of conditions.

Reusing validated methods, datasets and regulatory frameworks across many therapies could reduce costs and increase predictability enough to draw industry into the field.

Industry participation will be essential to achieving that scale.

C-Path is engaging biopharma companies, academic centers and nonprofit groups to support and help fund the initiative, with the goal of moving individualized therapies beyond extraordinary, often unsustainable academic efforts and toward routine use.

The plausible mechanism framework has the potential to transform product development for rare genetic diseases, former FDA Commissioner Scott Gottlieb stated in a JAMA Health Forum article. He called on the agency to do the work necessary to turn its "forward-looking framework into durable reforms that keep pace with advances in science."

C-Path's initiative is designed to fill in some of the missing pieces he identified. For example, Gottlieb wrote that FDA should "articulate a clear and efficient framework for manufacturing these personalized therapies so that products tailored to individual patients can be produced under a common, well-defined set of quality standards."

He also noted that the draft guidance recognizes that individualized therapies can be modular but does not clearly define how multiple genetic variants can be grouped under a single approval rather than treated as separate products. One to Millions could help by defining boundaries for when therapy remains the same product and making the regulatory pathway more predictable.

From one to millions

For now, the immediate stakes are in rare disease.

Millions of children worldwide suffer from genetically driven conditions, the vast majority of which have no effective treatments. Many are never diagnosed.

Only a few dozen have received n-of-1 therapies. In the absence of initiatives such as One to Millions, the numbers won't change much.

"This is not something that can be solved case by case," Woodcock told BioCentury. "We need a system."

For families, the promise of such a system is straightforward. They will get access to therapies without having to assemble ad hoc teams of scientists, clinicians and advocates.

For industry, it offers a pathway to making individualized medicine not just scientifically feasible, but economically viable.

And for FDA, the success of initiatives like One to Millions may ultimately determine whether its plausible mechanism framework becomes a cornerstone of a new regulatory paradigm or just a talking point for podcasts.

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