



FDA- 2025-N-4622: Immunology and Microbiology Devices; Reclassification of Nucleic Acid-Based Test Systems for Use with a Corresponding Approved Oncology Therapeutic Product; Proposed Amendment; Proposed Order; Request for Comments

To Whom It May Concern:

Friends of Cancer Research (*Friends*) powers advances in science and policy that speed life-saving treatments to patients. *Friends* is committed to accelerating cutting-edge cancer care that extends and improves quality of life for patients. To accomplish this, we leverage groundbreaking collaborations, generate scientific evidence, and integrate patient input to shape public policy.

Friends appreciates the opportunity to provide comments on the U.S. Food and Drug Administration's (FDA) proposed order to reclassify nucleic acid-based test systems for use with a corresponding approved oncology therapeutic product from Class III to Class II. This proposed rule represents an important step toward aligning regulatory requirements with accumulated scientific and clinical experience for these devices. Establishing a Class II framework with special controls has the potential to maintain appropriate safeguards while facilitating more efficient development and review, ultimately supporting timely access to diagnostic tools that inform oncology treatment decisions.

As the FDA finalizes this rule, we offer several considerations that may help clarify evidentiary expectations, support consistent implementation across development programs, and sustain innovation in areas where sample availability is limited, including rare cancers.

Clinical Validity and Alternative Evidence Sources

We appreciate the FDA's recognition that clinical performance data remains an important element of device evaluation under a Class II framework. Clear expectations for how clinical validity may be demonstrated will ensure consistent implementation across development programs, including in settings where access to clinical trial-derived samples is limited. In situations where sponsors cannot obtain sufficient quantities of samples from the pivotal clinical trial because the assay was proprietary, archived materials were depleted, or the biomarker-positive population was small, bridging studies to the trial assay may not be feasible. These circumstances are common in oncology, particularly in rare cancers where eligible patients and available tissue are inherently limited. In some cases, reliance on direct bridging to a single FDA-authorized companion diagnostic may further limit the ability of additional developers to enter the market, particularly when access to proprietary methods or materials is constrained.

In these contexts, sponsors have used alternative sample sources that remain scientifically and clinically meaningful. In our recent analysis of companion diagnostic approvals in lung cancer, we found that every diagnostic test associated with a rare biomarker relied on alternative sample

sources rather than trial-derived specimens.¹ These approaches included retrospective samples, biorepository tissues, and other clinically relevant materials. Additionally, consistent with FDA's existing guidance on the use of real-world data and real-world evidence for medical devices, real-world evidence may, in appropriate circumstances, support understanding of test performance. The FDA has demonstrated flexibility in accepting these alternatives when analytical performance and clinical relevance were adequately demonstrated, and this experience has been important for advancing diagnostics in rare cancers and other low-prevalence settings where conventional validation approaches may not be feasible.

To support consistent application under the proposed Class II framework, we recommend that the FDA clarify, through guidance, case studies, or illustrative examples, how existing evidentiary standards may be met using scientifically valid alternative approaches when traditional validation pathways are impractical, including:

- Situations in which alternative sample sources may be used when access to trial-derived material is limited or not feasible, including in rare cancers and low-prevalence molecular subsets;
- Examples of acceptable alternative sample sources (e.g., retrospective samples, banked specimens, biorepository collections) and how they may be scientifically justified within a validation strategy; and
- Expectations for demonstrating clinical relevance when alternative sample sources are used, including considerations for analytical performance, patient selection, or bridging to available evidence.

Providing this clarification would help sponsors design scientifically rigorous and feasible validation programs while enabling development of adequate tools for rare cancers and other settings where sample availability is inherently constrained. Clear evidentiary expectations will be particularly important for newer developers navigating the 510(k) pathway, where compressed review timelines heighten the importance of predictable submission requirements.

Role of Reference Datasets

We appreciate the FDA's acknowledgement of the extensive evidence supporting the proposed reclassification and the maturity of nucleic acid-based technologies. As clinical validation strategies evolve, reference datasets may play an increasingly important role in supplementing evidence generation, particularly when access to clinical samples is limited or bridging to the original trial assay is not feasible. Curated datasets can provide a consistent basis for method comparison across development programs, support reproducibility, and help minimize variability across tests intended for the same clinical use.

In a Class II framework that relies on substantial equivalence determinations, reference datasets could offer a consistent evidentiary foundation for comparing analytical performance

¹ [Companion Diagnostic FDA Review Flexibilities: An Assessment of CDx for NSCLC to Support Aligned Approaches for Validation | Therapeutic Innovation & Regulatory Science](#)

across assays intended to detect the same biomarker. To support predictable implementation, we recommend that the FDA provide additional guidance to:

- Describe how reference datasets may support validation by providing a consistent basis for evaluating performance across multiple devices and assays;
- Outline minimum expectations for dataset curation, including provenance, traceability, and representativeness of the intended-use population; and
- Encourage coordination among sponsors, academic partners, and other stakeholders to support the development and maintenance of datasets that are robust, well-annotated, and reflective of real-world clinical populations.

Establishing high-level principles, rather than prescriptive criteria, would help ensure transparency and consistency while allowing flexibility for innovation. Looking ahead, well-curated reference datasets could help streamline validation and serve as an important component of special controls under a Class II framework, providing a shared evidentiary resource for demonstrating substantial equivalence in 510(k) submissions, including for emerging diagnostic modalities such as digital pathology and AI-enabled tools.

If FDA were to establish a clear process by which diagnostic tests could utilize reference datasets for validation—including parameters for acceptable reference sets—it could meaningfully reduce the burden of individual validation programs while improving consistency, comparability, and overall quality assurance for tests used in clinical practice.

Transparency and Interpretability Across Assays

If the proposed reclassification is finalized, the FDA may also wish to consider how transparency regarding test performance is maintained as oversight transitions from a PMA-based framework to Class II review. Publicly available summaries of validation approaches and performance characteristics have historically supported clinician understanding and confidence in companion diagnostics. Additional clarity regarding how key performance information may be communicated under a 510(k) framework in a consistent and interpretable manner could help support comparison across assays intended for the same use, particularly as multiple tests may have the same clinical uses.

Broader Relevance to Emerging Diagnostic Technologies

The proposed reclassification represents an important step toward aligning regulatory requirements with technology maturity and real-world experience. Although the proposed order focuses on nucleic acid–based tests, the framework it establishes has broader relevance for emerging diagnostic technologies. An increasing number of devices used to inform treatment decisions leverage AI–enabled image analysis, digital pathology algorithms, and multimodal platforms. These tools share several characteristics with the devices addressed in this rule: they guide therapeutic selection, incorporate evolving evidence, and may depend on curated datasets rather than a single, fixed assay run on trial specimens.

As these technologies advance, developers and reviewers will face similar questions regarding appropriate pathways, evidentiary standards, and how to evaluate performance when direct access to trial material is limited. We recommend the FDA consider whether the principles articulated in this reclassification may help inform regulatory approaches for emerging modalities. Additional clarity could:

- Support consistent evaluation of devices that generate treatment-relevant information using evolving data sources;
- Streamline development by reducing uncertainty around acceptable evidence sources and comparators; and
- Facilitate efficient review of technologies that will increasingly be used to identify patients for molecularly targeted therapies.

Such alignment would be particularly valuable as oncology moves toward more complex diagnostic strategies that integrate imaging, molecular information, and algorithmic interpretation to support individualized treatment decisions.

Friends appreciates the FDA's leadership in modernizing diagnostic regulation. The proposed reclassification represents an important step toward aligning regulatory requirements with accumulated experience, supporting efficient development, and maintaining appropriate safeguards for patients. We believe that additional clarity on the use of alternative sample sources, evidentiary expectations, and the role of curated reference datasets will help ensure consistent application and successful implementation of the Class II framework, particularly in areas where clinical material is inherently limited. We look forward to continued collaboration with the FDA to advance timely, reliable access to diagnostic tools that support optimal oncology treatment decisions and ultimately benefit patients.

On behalf of Friends of Cancer Research

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