



Modernizing the FDA Biomarker Qualification Program: Strengthening Regulatory Clarity and Broadening Biomarker Use in Drug Development

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Executive Summary

Biomarkers and other drug development tools (DDTs) are central to modern drug development, enabling more efficient clinical trials, supporting precision medicine, and informing regulatory decision-making. As measurable indicators of biological processes and responses to therapy, biomarkers are integral to evaluating the safety and efficacy of investigational products and have the potential to improve the efficiency and success of drug development. The U.S. Food and Drug Administration (FDA) Biomarker Qualification Program (BQP) was established to provide a structured pathway for evaluating biomarkers for a defined context of use (COU), enabling their use across development programs without repeated evidentiary review. Codified under Section 507 of the Federal Food, Drug, and Cosmetic Act through the 21st Century Cures Act, the program is intended to support broader, more consistent use of scientifically validated biomarkers in regulatory decision-making.

More than a decade after its establishment, the BQP has not consistently functioned as a predictable or broadly used pathway for biomarker qualification. Relatively few biomarkers have achieved FDA qualification, reflecting both the scientific complexity of biomarker development and structural and operational limitations in the current framework. Publicly available biomarker qualification submissions and stakeholder discussions highlight several challenges affecting the effectiveness of the program, including uncertainty regarding how the FDA operationalizes qualification determinations in product-level regulatory review, misalignment between the program's stage-based structure and the iterative nature of biomarker evidence development, limited clarity around COU expansion, and limited transparency and predictability in evidentiary expectations and review timelines.

In practice, many biomarkers achieve regulatory acceptance through program-specific pathways, including Investigational New Drug based development and product-specific regulatory review. While these pathways support biomarker use within individual development programs, they often lack transparency, consistency, and mechanisms for broader adoption. They also operate largely in parallel with the BQP, with limited exchange of evidence across pathways. This fragmentation reduces efficiency, limits shared regulatory learnings, and constrains the broader impact of biomarkers.

Modernizing the BQP is therefore necessary to make qualification a more practical and relevant pathway for drug development. The goal is not to rethink the purpose of qualification, but to operationalize that purpose more effectively: connecting evolving biomarker evidence to broader regulatory use, enabling regulatory confidence to build as evidence matures, and ensuring qualification provides a clear and useful signal for decision-making across drug development programs.

To inform practical recommendations, Friends of Cancer Research convened a multi-stakeholder working group of regulatory, industry, and scientific experts with direct experience developing biomarkers and other DDTs and navigating the qualification process. The working group identified two root issues limiting the program's effectiveness: (1) misalignment between the structure of the qualification pathway and the way biomarker evidence is generated and applied in practice, and (2) uncertainty regarding whether qualification provides a clear and predictable signal of regulatory acceptance beyond a single product or review context.

This white paper outlines targeted recommendations to strengthen the BQP:

1. **Establish predictable processes and clear accountability mechanisms.** The BQP should provide consistent, actionable feedback; predictable engagement and review timelines; and greater transparency into qualification decisions. Sustained program execution will require clearer

prioritization, sufficient resourcing, and accountability mechanisms to support reliable review performance.

2. **Strengthen institutional and regulatory alignment.** Qualification should function as a clear regulatory determination that can be consistently relied upon across review divisions and product-level decision-making. Strengthening the program will require clearer articulation of the regulatory meaning of qualification, including the evidentiary basis, defined COU, and intended regulatory role of the biomarker, as well as stronger integration between qualification and product-level review.
3. **Modernize the BQP to align with evidence maturity.** The BQP should better reflect how biomarker evidence develops over time by enabling COU expansion, leveraging prior evidence and regulatory experience, and supporting risk-based evidentiary expectations. Over the longer term, Congress should consider statutory changes to support a tiered, risk-based qualification framework that allows regulatory confidence to build progressively as evidence matures.

Near-term improvements could be advanced through FDA guidance, internal policy, and structured engagement to better operationalize the intended role of qualification. These efforts should focus on making the pathway more transparent, predictable, and useful in practice, including clearer mechanisms for COU expansion, more systematic use of prior evidence and regulatory experience, and improved engagement as evidence matures. Longer-term reforms may require legislative action, particularly to support formal tiered recognition, dedicated resourcing mechanisms, and clearer accountability for program performance.

Together, these actions would help ensure qualification functions as a practical and reliable pathway for modern drug development—supporting more efficient translation of biomarker science into regulatory use and, ultimately, improved outcomes for patients.

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We thank the working group for their expertise and contributions that helped shape the development of this white paper. The views expressed here represent the collective insights from working group discussions and do not necessarily reflect the official positions of any individual organization.

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Introduction

Biomarkers and other drug development tools (DDTs) play a foundational role in drug development and regulatory decision-making. As measurable indicators of biological processes and responses to therapeutic interventions, biomarkers are widely used to support patient selection, dosage optimization, and treatment response assessment. When supported by appropriate evidence, they can reduce uncertainty in clinical development, enable more efficient trial designs, and serve as endpoints that support regulatory decision-making. Because biomarkers are inherently context-dependent, their regulatory use requires interpretation within a defined context of use (COU). As drug development continues to evolve—including the increasing use of molecularly targeted therapies, real-world data, and artificial intelligence (AI)-enabled tools—the importance of biomarkers in guiding scientific and regulatory decisions continues to expand.

The U.S. Food and Drug Administration (FDA) Biomarker Qualification Program (BQP) was developed to qualify a biomarker for a defined COU, allowing its use across multiple development programs. Congress formalized the BQP through the 21st Century Cures Act, establishing a structured process for biomarker qualification under Section 507 of the Federal Food, Drug, and Cosmetic (FD&C) Act. While the program was designed to support consistent and efficient use of biomarkers across development programs, experience over more than a decade of implementation highlights a gap between this intended role and how qualification functions in practice, with relatively few biomarkers progressing to qualification.¹

Stakeholder experience indicates the pathway has not consistently provided the clarity, predictability, and regulatory confidence needed to support broad adoption. This reflects limitations in the current framework and its implementation, rather than a lack of value in biomarker qualification itself. Structural and operational challenges—including uncertainty regarding the interpretation and application of qualification determinations, unclear evidentiary expectations, and inconsistent review timelines—have reduced the pathway's predictability, efficiency, and overall value. The FDA has described ongoing efforts to strengthen BQP operations and improve engagement with stakeholders.² Building on this progress, additional improvements are needed to ensure the pathway provides clear, transparent, and practical value for biomarker developers.

To inform practical recommendations to strengthen the BQP, Friends of Cancer Research convened a working group of regulatory, industry, and scientific experts with direct experience developing biomarkers and other DDTs and navigating the qualification process. The working group identified key structural, operational, and implementation challenges with the current approach to the BQP and developed actionable recommendations to strengthen its clarity, predictability, and regulatory value. Two focus areas emerged from these discussions: (1) aligning the qualification pathway with how biomarker evidence matures and is used in regulatory decision-making and (2) ensuring that qualification provides a clear and predictable signal of regulatory acceptance across development programs. This white paper outlines recommendations to modernize the BQP and strengthen its role in supporting efficient drug development, with principles that may also apply more broadly to DDTs used in regulatory decision-making.

Challenges with the Current Regulatory Landscape for Biomarker Qualification

The BQP Has Not Delivered on Intended Objectives

Experience under the current framework demonstrates the BQP has not consistently delivered on its intended objectives and instead has led to limited use and a lack of predictability for biomarker development. Publicly available biomarker qualification submissions and stakeholder discussions highlight

several structural and operational challenges affecting the effectiveness of the BQP.¹ Challenges including uncertainty in navigating the pathway and ambiguity in evidentiary expectations may not always be captured from public documentation alone, but they can meaningfully influence whether requestors invest in pursuing qualification. The key issues are summarized in **Table 1**.

Table 1. Structural and Operational Challenges Affecting the Current Framework of the BQP

Challenge	Key Issues and Evidence	Implications
Regulatory clarity and reliability	<ul style="list-style-type: none"> Stakeholder uncertainty regarding how the FDA interprets and applies qualification determinations in product-level review, particularly when proposed uses approach the boundaries of a qualified COU. Uncertainty in whether review divisions can rely on qualified biomarkers without additional evidentiary justification in individual submissions. 	Reduced confidence that qualification provides reliable and sustained regulatory acceptance across development programs.
Program structure and evidence lifecycle	<ul style="list-style-type: none"> The stage-based BQP framework does not align with drug development timelines or with the iterative nature of biomarker evidence generation, particularly for emerging technologies and novel biomarkers. 	The BQP's ability to accommodate evolving evidence and emerging biomarker technologies may be limited.
Operational timelines and evidentiary expectations	<ul style="list-style-type: none"> Of 61 biomarker programs entering the BQP as of July 2025, only 8 had received qualification, and approximately half had not progressed past the Letter of Intent stage.¹ Development and review timelines frequently extend beyond expected program targets, particularly for complex biomarkers such as surrogate endpoints.¹ 	Planning uncertainty may discourage requestors from pursuing qualification.
Limited incentives for biomarker development	<ul style="list-style-type: none"> The evidence generated through the BQP becomes broadly available, and costs are borne by individual sponsors or consortia, leading to misaligned incentives. In some cases, alternative regulatory pathways may offer more direct or predictable routes to biomarker acceptance. 	Limited predictability in timelines, evidentiary expectations, and resource requirements create barriers to uptake and reduces willingness to invest in developing broadly applicable biomarkers.

Alternative Pathways Provide Options but Lack Consistency

Regulatory acceptance of biomarkers may occur through several mechanisms, reflecting both the iterative nature of regulatory science and the importance of biomarkers in modern drug development. Ongoing efforts by sponsors, regulators, and the scientific community to incorporate biomarker evidence into drug development and regulatory decision-making, including both product-specific use within clinical development plans (CDPs) and broader regulatory recognition across programs, are also reflected in the FDA's framework describing pathways for biomarker integration in drug development.³ However, these approaches may operate with varying levels of transparency, consistency, and cross-program applicability. While they may support biomarker use in specific contexts, they do not consistently provide a durable mechanism for broader regulatory reuse. **Table 2** summarizes several pathways through which biomarkers may gain regulatory acceptance.

Table 2. FDA Pathways for Using Biomarkers in Drug Development.

Pathway	Regulatory Description	Benefits and Drawbacks
BQP	Establishes acceptable use of a biomarker for a particular COU in drug development and regulatory review.	Provides transparency through public disclosure and enables use across multiple development programs. However, qualification may require substantial resources and coordination across stakeholder, may involve lengthy development timelines due to evidentiary complexity, and may not ultimately result in a COU aligned with a sponsor's intended use.
Investigational new drug (IND) and product-specific regulatory acceptance	Biomarker acceptance within a singular drug development program based on review of program-specific evidence.	May allow faster development aligned with a product's clinical development timeline and protects proprietary data. When successfully used, the biomarker and its COU are reflected in public regulatory documents. However, acceptance is generally limited to the specific development program and does not establish broader regulatory acceptance across programs. Sponsors bear the full burden of evidence generation.
Early engagement and scientific collaboration pathways	FDA engagement on biomarker development and validation through informal high-level discussions such as Critical Path Innovation Meetings (CPIMs), as well as more formal feedback mechanisms such as pre-IND interactions and Letters of Support.	Facilitates early scientific dialogue and alignment with the FDA. However, these mechanisms do not establish formal regulatory acceptance, vary in scope and formality, may not be consistently utilized across review divisions, and reflect advice at a specific point in time that may evolve as additional evidence is generated.
Regulatory acceptance through scientific and regulatory precedent	Acceptance based on accumulated evidence, repeated use, or scientific and regulatory consensus over time.	May enable broader acceptance as evidence accumulates. However, the pathway is informal and less predictable, often requiring extensive data sharing and coordination across stakeholders, as seen in cases where the FDA has convened advisory committees (e.g., Minimal Residual Disease in multiple myeloma discussed at Oncologic Drugs Advisory Committee [ODAC]) ⁴ to inform consensus.

Pathways Operate in Silos

While these pathways support biomarker development and regulatory use, they do not consistently operate as part of a coordinated framework for building regulatory confidence over time. Biomarker evidence generated and refined within product-specific programs is not routinely retained, reused, or translated into broader regulatory learning, and qualification does not consistently inform how biomarkers are evaluated or relied upon in product-level regulatory decision-making. In practice, evidence generated in one context often remains siloed within individual programs, limiting opportunities to build cumulative regulatory confidence and broader regulatory utility.

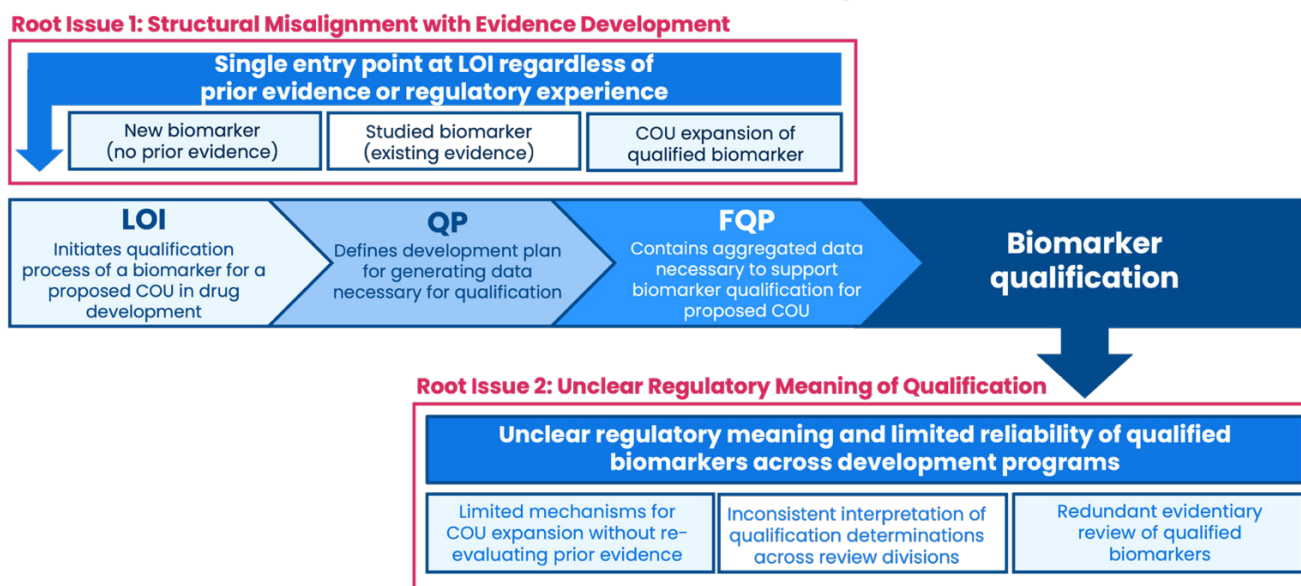
This fragmentation across pathways has important practical consequences. Biomarker insights generated in development programs that do not lead to product approval (including submissions that fail to advance within the qualification process or are withdrawn before completion) are not systematically captured or reused, even when they provide valuable evidence regarding biological relevance or measurement

performance. In some cases, negative or inconclusive trial outcomes may be attributed to the biomarker itself, even when limitations in study design, patient selection, or assay performance may have contributed. As a result, substantial scientific and regulatory learning may be lost or misinterpreted, and similar evidentiary questions may be revisited across programs rather than informed by prior evidence and experience. More broadly, without clear mechanisms to support continuity, building cumulative regulatory confidence is limited, and the validation and expansion of biomarker use may stall.

Framework for Modernizing the Biomarker Qualification Program

Strengthening coordination across these pathways—including clarifying how IND-based regulatory learning can be reused and how evidence generated across development programs can inform broader regulatory use—will be critical to addressing this fragmentation and supporting a more iterative and integrated model of biomarker development. While other pathways may support biomarker use within specific development programs, the BQP serves a distinct role as the FDA’s primary formal pathway for translating biomarker evidence into a regulatory determination applied across development programs. By doing so, it can help extend regulatory learning beyond individual programs and support broader and more consistent application across development programs.

Current Biomarker Qualification Program Structure



Abbreviations. Context of use: COU; Letter of Intent: LOI; Qualification Plan: QP; Full Qualification Package: FQP

Figure 1. Current BQP Structure and Its Implications for Regulatory Clarity and Evidence Alignment

Modernizing the BQP is therefore necessary to ensure qualification remains a practical and relevant pathway for modern drug development, connecting evolving biomarker evidence to broader regulatory use across programs. These considerations also extend beyond biomarkers to other DDTs, including clinical outcome assessments (COAs), novel endpoints, and new approach methodologies, where similar challenges related to evidence generation, regulatory consistency, and cross-program applicability arise.

As illustrated in **Figure 1**, many of the challenges stem from two root issues: (1) misalignment between the process of the qualification pathway and the way biomarker evidence develops over time, and (2) uncertainty regarding the regulatory relevance and downstream reliability of qualification.

Recommendations to overcome these challenges include:

- **Establish predictable processes and clear accountability mechanisms** to ensure predictable timelines, transparent review processes, and sustained program operation.
- **Strengthen institutional and regulatory alignment** to ensure qualification functions as a trusted regulatory determination that is consistently interpreted and applied across review divisions and integrated into product-level regulatory decision-making.
- **Modernize BQP structure and operations** to better align with how biomarker evidence develops, and ensure evidentiary expectations, COU, and lifecycle management evolve as evidence matures.

Recommendation 1: Establish predictable processes and clear accountability mechanisms.

The BQP should ensure accountability for efficient and reliable program execution, supported by sufficient resourcing and predictable, consistent engagement.

While the program is designed to support biomarker qualification through structured interaction with the FDA, variability in feedback, timelines, and expectations creates uncertainty and reduces confidence in the process. Resource constraints and inconsistent communication may limit requestors' ability to efficiently navigate the current three-stage qualification process (Letter of Intent [LOI], Qualification Plan [QP], and Full Qualification Package [FQP]) and to develop long-term evidence generation strategies. Strengthening these elements would improve predictability and usability, reinforcing the value of qualification as a trusted regulatory pathway. These key actions focus on outcomes and transparency into decision-making rather than prescribing specific operational processes, allowing flexibility in how the FDA achieves these objectives, while ensuring accountability for program performance.

Key Action: Improve Transparency and Feedback in Qualification Decisions

The FDA should provide consistent, clear, and actionable feedback when the Agency reviews biomarker submissions across BQP stages, to increase transparency and expand shared learning across stakeholders, by:

- Publishing qualification submissions and determination letters, with clearly defined and communicated timelines, in the publicly available Center for Biologics Evaluation and Research (CBER)/Center for Drug Evaluation and Research (CDER) DDT Qualification Project Search database to improve visibility into qualification outcomes.
- Ensuring completeness and consistency of publicly available materials, including expanding beyond executive summaries to provide qualification submissions
- Standardizing feedback across BQP stages, including clearer articulation of evidentiary gaps.
- Increasing transparency into the review process (e.g., publishing information requests (IRs) and applicant responses) to provide greater insight into regulatory expectations and decision-making.

Recent FDA efforts to improve transparency, such as sharing common pitfalls in COU development and providing additional guidance on LOI content, represent important steps toward greater clarity and predictability. Further expanding transparency to include IRs and applicant responses could help reduce uncertainty for developers, support more efficient resubmission of proposals, and improve understanding of evidentiary expectations associated with qualification.

Key Action: Establish Predictable Engagement and Review Timelines

Although the BQP provides opportunities for interaction with the FDA throughout the qualification process, requestors may still experience uncertainty between qualification stages regarding timelines, process status, and how feedback should inform evidence-generation plans. While target timelines exist, they are frequently exceeded, contributing to inconsistency and reduced predictability. For example, LOI and QP reviews frequently exceed FDA target timelines by approximately three months and seven months, respectively; for projects that progress to the QP stage, QP development timelines (the time from FDA's LOI determination to QP submission) take a median of 32 months for all biomarkers and 47 months for those intended for use as surrogate endpoints.¹ Greater transparency into stage-specific timelines, reasons for delay, and the distinction between FDA review time and requestor-driven development time would improve predictability and help stakeholders plan evidence-generation strategies more effectively.

The absence of predictable, transparent, and accountable timelines is a core limitation of the current BQP and undermines its utility as a development pathway. The FDA should establish a more predictable and enforceable engagement model by:

- Defining clear interaction points and expectations for engagement across qualification stages, including how and when requestors can expect feedback and engagement throughout review.
- Providing regular, structured status updates and consistent written communication throughout review, including when timelines are delayed and the reasons for those delays.
- Introducing pre-determination steps (e.g., draft qualification summaries or determination letters) to reduce late-stage uncertainty and improve alignment, allowing requestors to verify accuracy, address evidentiary gaps, and seek clarification prior to final decisions.
- Clarifying expectations for when and how requestors should re-engage the Agency as they generate new evidence or when measurement tools or analytical approaches evolve during development.

Key Action: Strengthen Prioritization, Predictability, and Resourcing

Qualification efforts require significant coordination across sponsors, regulators, and external stakeholders, yet the current framework provides limited predictability in timelines, evidentiary expectations, and resource requirements for sponsors to pursue qualification relative to program-specific approaches. In addition, the FDA may not consistently prioritize BQP activities, particularly when timelines are not enforceable, and review resources are directed toward user fee-supported programs. The FDA has acknowledged that resource constraints and competing priorities can influence BQP review timelines.² These challenges may be further amplified as biomarker development increasingly involves complex, multi-component DDTs, such as AI-enabled tools, which may require additional coordination across FDA centers and technical expertise.

The FDA should explore mechanisms to strengthen incentives and support consistent prioritization of BQP reviews, including:

- Making cross-office review processes, roles, and accountability mechanisms more transparent to requestors by building on existing governance structures.
- Aligning evidentiary expectations with the regulatory role and impact of the biomarker.
- Continuing to increase transparency around the use of qualified biomarkers, including through the public catalog of qualified biomarkers, COUs, and examples of regulatory application.

- Ensuring it appropriately prioritizes BQP activities alongside user fee-supported programs.
- Clarifying coordination across FDA centers (e.g., CDER, Center for Devices and Radiological Health [CDRH]) by building on existing subject matter experts and cross-center engagement when biomarker evaluation involves both biological and measurement components.

The FDA should also explore resourcing models to support sustained review capacity, such as dedicated funding mechanisms, user fee models, or structured review workflows aligned with existing product review processes. Greater visibility into how the FDA and sponsors use qualified biomarkers in regulatory decision-making could further reinforce the value of qualification.

Recommendation 1 Implementation Approach: These actions could be advanced through updated guidance, internal FDA policy, operational practices, and enhanced transparency under the existing DDT qualification framework. Near-term improvements could include clearer feedback and communication, more consistent public posting of qualification materials, regular reporting of stage-specific timeline performance, and greater transparency into prioritization criteria and review capacity. While Section 507 of the FD&C Act allows the FDA to prioritize submissions based on public health considerations, it does not provide dedicated resources or formal performance commitments. Going forward, achieving consistently predictable review timelines and sustained program execution may require measurable review metrics, reporting of adherence, and dedicated resourcing, including appropriations, congressionally authorized user fee models, or other mechanisms aligned to support accountability and program performance.

Recommendation 2: Strengthen institutional and regulatory alignment.

Qualification should function as a clear and consistently applied regulatory determination across review divisions and product-level decision-making.

The BQP's value depends on whether qualification provides a clear and reliable regulatory signal across development programs and FDA review divisions. While the statutory authority for qualification is well established, stakeholders may still face uncertainty regarding how the FDA operationalizes qualification determinations in product-level review, including how the defined COU informs regulatory decision-making in specific development contexts. Because COU development and interpretation often require iterative alignment between requestors and the FDA, clearer expectations are needed to ensure that qualification functions not only as a scientific determination, but as a practical regulatory signal for product-level decision-making. Strengthening institutional alignment and clarifying the regulatory meaning of qualification would help ensure qualification provides distinct and predictable value relative to other regulatory pathways.

Key Action: Clarify the Regulatory Meaning of Qualification

Qualification is intended to provide a clear and predictable regulatory signal that the FDA and sponsors can rely upon a biomarker within its defined COU. However, how the FDA interprets and applies qualification determinations across development programs remains uncertain.

The FDA should strengthen the value of qualification determinations by:

- Clearly articulating the evidentiary basis for qualification, the defined COU, and the intended regulatory role of the biomarker (e.g., enrichment, stratification) in determination letters.
- Providing more explicit and actionable feedback at earlier stages (LOI and QP), including expectations for evidentiary development and alignment with the proposed COU.

- Reinforcing that qualification determinations, once established, should not require re-evaluation of the underlying evidentiary foundation when used within the qualified COU.

Lessons can be drawn from the FDA's Medical Device Development Tool program, where qualification determinations often provide clear statements regarding the intended regulatory role of the tool, such as its use as a primary or secondary endpoint in clinical studies. Strengthening communication could help reduce uncertainty over time and guide better evidence generation.

Key Action: Promote Consistent Interpretation Across Review Divisions

Stakeholder uncertainty regarding how the FDA will interpret qualification determinations across review divisions may limit the predictability of biomarker use in regulatory submissions and create uncertainty for sponsors planning to incorporate these tools into development programs. The FDA should promote consistent interpretation and application of qualification determinations by:

- Establishing clearer internal expectations for how to interpret qualified biomarkers within their COU across divisions.
- Strengthening cross-center and cross-division coordination during qualification and product review.
- Supporting reviewer training and internal communication to ensure a shared understanding of qualification standards and implications.

Greater alignment across divisions would strengthen the credibility of qualification as a mechanism for establishing broadly applicable scientific conclusions.

Key Action: Enable Integration Between Qualification and Product-Level Development

The BQP and product-specific regulatory pathways, such as IND-based development, currently operate in parallel. Much of the evidence supporting biomarker development is generated through product-specific regulatory interactions, while qualification remains the formal pathway for establishing broader regulatory acceptance. Without clearer mechanisms for translating product-specific experience into qualification, regulatory learning may remain fragmented and underused.

To improve continuity and interpretability of biomarker-related regulatory feedback, the FDA should incorporate a structured assessment framework within IND interactions that captures its evolving view of biomarker readiness across key areas, including analytical validity, biological rationale, clinical relevance, and evidentiary gaps. Maintaining this assessment across interactions would improve transparency, reduce redundant reassessment, and allow regulatory learning generated in product-specific programs to more consistently inform qualification. In turn, qualification could provide a clearer evidentiary foundation for product-level regulatory decision-making.

Reuse of IND-based regulatory learning will require clearer mechanisms to synthesize cross-program insights, promote alignment in evidentiary expectations, and make relevant evidence available where appropriate. Product sponsors, requestors, consortia, and other data holders also have an important role in enabling this reuse through public disclosure, rights of reference, voluntary data-sharing arrangements, or consortium-generated evidence. This is particularly important when biomarker evidence generated during development is not publicly disclosed or systematically retained, limiting its broader utility. Clearer signals for when a biomarker evaluated through IND-based development may be appropriate for broader consideration through the BQP—based on repeated use across programs, consistent performance, convergence of scientific rationale, or accumulation of evidence supporting a defined COU—would help

understand when qualification may be warranted and support a more coordinated pathway from product-specific evaluation to broader regulatory acceptance.

Mechanisms to support this transition should balance the need for broader regulatory learning with appropriate protections for proprietary information. The intent is to clarify how legally permissible sources of information—including publicly available FDA reviews and labeling, advisory committee materials, published literature, rights of reference, voluntary data-sharing arrangements, aggregation or redaction where appropriate, and consortium-generated evidence—could support qualification or COU expansion. Strengthening these connections would reduce fragmentation across pathways and support a bidirectional model in which product-specific evidence can inform qualification, and qualification can provide a clearer evidentiary foundation for product-level regulatory review.

The FDA should strengthen integration by:

- Defining expectations for how qualified biomarkers could be used in regulatory submissions within their COU.
- Establishing clearer connections between the BQP and product review processes, including early involvement of relevant review divisions and incorporation of qualification conclusions into review frameworks.
- Increasing transparency regarding the use of qualified biomarkers in regulatory decision-making, including examples of their application in product reviews and labeling.
- Clarifying how evidence generated in product-specific development programs (e.g., INDs, New Drug Applications [NDAs]) may support qualification or COU expansion, where appropriate and supported by publicly available data or rights of reference.

Evidence from other qualified DDTs highlights similar challenges. For example, analyses of COAs show that, despite qualification for defined COUs, they are rarely used as primary endpoints in regulatory decision-making and are infrequently reflected in drug labeling.⁵

Recommendation 2 Implementation Approach: These actions could be advanced under FDA's existing statutory authority in Section 507 of the FD&C Act through updated guidance, internal FDA policy, reviewer training, and enhanced coordination between qualification and product review. Near-term improvements could clarify the content and structure of determination letters, expectations for interpreting qualified biomarkers within their COU across review divisions, and how qualification determinations should be incorporated into product-level regulatory review. The FDA should also clarify how the evidentiary basis for an existing qualified COU may inform the evidence needed to support related uses or COU expansion. In addition, the FDA should clarify how product-specific evidence may support qualification or COU expansion, where supported by legally permissible sources of information, including public FDA reviews and labeling, published literature, rights of reference, voluntary data-sharing arrangements, or consortium-generated evidence. Together, these changes would improve the clarity, consistency, and practical impact of qualification while preserving appropriate protections for proprietary information.

Recommendation 3: Modernize the BQP to align with evidence maturity.

The BQP should reflect how biomarker evidence develops, enabling iterative validation, lifecycle management, and risk-based evidentiary expectations.

Under the current BQP framework, applications progress through three sequential stages—LOI, QP, and FQP—with formal regulatory recognition only after completion of the full process (**Figure 1**). However,

biomarker development evolves iteratively across analytical validation, clinical validation, and expanding COUs. This misalignment highlights the need for a framework that allows regulatory confidence to develop progressively as evidence matures.

Key Action: Enable Expansion of COU

The current framework ties biomarker qualification to a specific COU, which is often narrowly defined to manage regulatory uncertainty. While appropriate during early development, this approach limits extending a biomarker's use to closely related contexts, even when much of the underlying evidence remains applicable. Expanding a COU may require additional evidence generation, often including further clinical validation, and in some cases may involve repeating substantial elements of the qualification process rather than building on prior knowledge and regulatory experience. The current pathway provides limited clarity on how requestors should initiate, structure, or support a COU expansion request, contributing to uncertainty around whether and how qualified biomarkers can evolve as evidence matures.

Importantly, COU expansion should be clearly distinguished from changes to the measurement tool or assay used to capture the biomarker. In many cases, the underlying biological concept of the biomarker remains consistent, while tools or technologies used to measure it evolve. Anchoring COU expansion to the biomarker—rather than the tool—would support broader applicability while maintaining scientific rigor. This approach should also accommodate evolution in measurement technologies (e.g., transitions from PCR-based assays to next-generation sequencing), where analytical validity may require re-establishment while the underlying clinical validity of the biomarker remains applicable.

Incremental expansion of COU could include:

- **Expanded use within the same disease setting**, based on incremental clinical validation or retrospective analyses.
- **Application in closely related disease contexts**, supported by biological plausibility, analytical validity, and clinical association.

The FDA should enable incremental and efficient expansion of COUs by:

- Allowing COU expansion based on incremental evidence that builds on prior knowledge and regulatory experience, rather than requiring redevelopment of the full evidentiary package.
- Supporting prospective planning for anticipated modifications, analogous to Predetermined Change Control Plans (PCCPs) for medical devices, where requestors define anticipated COU expansions and identify corresponding clinical evidentiary requirements upfront.^{6,7} This approach would enable predefined expansion of a qualified biomarker such that it can be deployed in multiple CDP pathways and reduce duplicative review as evidence matures.
- Clarifying evidentiary expectations for COU expansion based on the degree of contextual change and associated regulatory risk, and how existing evidence (e.g., IND-based data and prior regulatory experience) can be leveraged to support expansion and reduce duplication across both qualification and product-specific development pathway.

Key Action: Leverage Prior Evidence and Regulatory Experience

The current qualification framework may not fully leverage the growing body of evidence when evaluating new qualification proposals or COU expansions. Biomarker evidence often accumulates across multiple

sources, including clinical trials, real-world data, product-specific development programs, published literature, and prior regulatory use. A clearer framework for using this evidence would reduce duplicative evidence generation, support more efficient COU expansion, and ensure that qualification builds on established scientific and regulatory knowledge.

The FDA should build on this approach by:

- Defining when prior regulatory use or existing evidence is sufficient to support qualification or COU expansion without re-adjudication, and when additional evidence is required.
- Clarifying how evidence in product-specific development programs may support qualification or COU expansion, where appropriate and supported by publicly available or rights of reference data.
- Defining expectations for comparability across measurement tools or assay platforms, including when existing evidence supporting the clinical validity of the biomarker may be leveraged.
- Improving transparency by enhancing the public qualification database (i.e., more timely and complete posting of submissions and determinations) and by providing illustrative frameworks or examples that clarify how the Agency evaluated and applied prior evidence in qualification decisions.

Leveraging prior evidence should be grounded in the use of publicly available data or information for which sponsors have appropriate rights of reference. This approach enables broader use of existing knowledge while maintaining appropriate protections for proprietary data and sponsor confidentiality.

Key Action: Establish a Tiered, Risk-Based Qualification Framework

Under the current BQP, biomarker qualification largely functions as a single, all-or-nothing determination, requiring a complete evidentiary package before meaningful regulatory recognition. While this ensures that robust evidence supports qualified biomarkers, the approach is not well aligned with how drug development and biomarker evidence generation occur in practice.

The existing BQP framework relies on requestors providing a complete evidentiary submission package upfront, including analytical validation of the measurement tool or assay, clinical validation to demonstrate regulatory relevance within a defined COU, and supporting regulatory experience. In practice, however, biomarker evidence often accumulates iteratively across multiple CDPs, particularly for clinical validation, rather than as a complete package at a single point. In addition, measurement technologies may change over time, even when the underlying biological concept of the biomarker remains consistent.

In this context, the current framework can create uncertainty during earlier stages of development, as requestors may invest significant time and resources without clear insight into evidentiary expectations or how the FDA will evaluate emerging evidence in regulatory decision-making. It may also lead to duplicative evidence generation, as requestors assemble a complete evidentiary package rather than build progressively on prior knowledge and regulatory experience.

To address this, the FDA should establish a tiered, risk-based qualification framework that aligns evidentiary expectations and regulatory confidence with how biomarker evidence is generated, refined, and applied over time. The purpose of this framework is to make qualification a more practical and relevant pathway for modern drug development by providing clearer interim signals before full qualification, reducing development uncertainty, and enabling accumulating evidence to support continued development, future qualification, and broader regulatory use.

Operationalizing Qualification Through a Tiered Framework

This framework is not intended to replace the core purpose of qualification as a regulatory determination tied to a defined COU. Rather, it is intended to operationalize that purpose to reflect how biomarker evidence develops by aligning regulatory recognition with evidence maturity, regulatory risk, and intended use. In this model, qualification would remain anchored to a defined regulatory purpose, while enabling the FDA to recognize intermediate stages of evidence development and clarify what additional evidence would be needed to support broader, higher-impact, or cross-program use.

Within this framework, evidentiary expectations should reflect the maturity of available evidence, the regulatory risk associated with the biomarker's intended use, the novelty of the biomarker, and the availability of prior scientific or regulatory experience. Higher-risk applications, such as surrogate endpoints used to support product approval, would require more robust validation than biomarkers used for exploratory analyses. **Figure 2** illustrates how regulatory recognition could develop progressively across stages of validation. A tiered, risk-informed framework would recognize distinct stages of biomarker validation while aligning evidentiary expectations with the regulatory risk associated with the proposed use. In this framework, tiers would reflect stages of evidence maturity and regulatory recognition, while the level of evidence needed within each tier would depend on the biomarker's novelty, prior evidence, and intended regulatory role.

Biomarker classification tiers should include:

- **Tier 1: Tool Validation:** Initial measurement tool validation, demonstrating the assay or technology reliably captures the measurement of interest through analytical validation, including appropriate verification and validation, where applicable.
- **Tier 2: Exploratory Recognition:** Recognition of scientific credibility, reflecting biological plausibility, and early supporting evidence.
- **Tier 3: Development Qualification:** Clinical validation supporting defined uses, demonstrating associations with outcomes sufficient for use in clinical trials (e.g., stratification, secondary endpoints, endpoint reasonably likely to predict benefit).
- **Tier 4: Full Qualification:** Qualification for a defined COU, supported by robust analytical and clinical validation, enabling consistent use across development programs.

Role of Tool Validation

Focusing the initial tier on validation of the measurement tool could help decouple validation of the tool from validation of the biomarker itself, enabling different tools or technologies to measure the same biomarker. This approach may better reflect the distinct roles of technology developers and clinical investigators and avoid requiring demonstration of full clinical meaningfulness at early stages.

This recognition would be distinct from device regulatory pathways, such as 510(k), because the tool would not be "approved" or "cleared" as a medical device, but rather recognized as sufficiently reliable to de-risk its use in drug development within a defined COU. Establishing confidence in the measurement approach could facilitate evidence generation across programs and reduce repeated analytical validation as clinical evidence accumulates.

Importantly, a tiered approach would not preclude a requestor from submitting a single evidence package that supports both validation of the measurement tool and the biomarker.

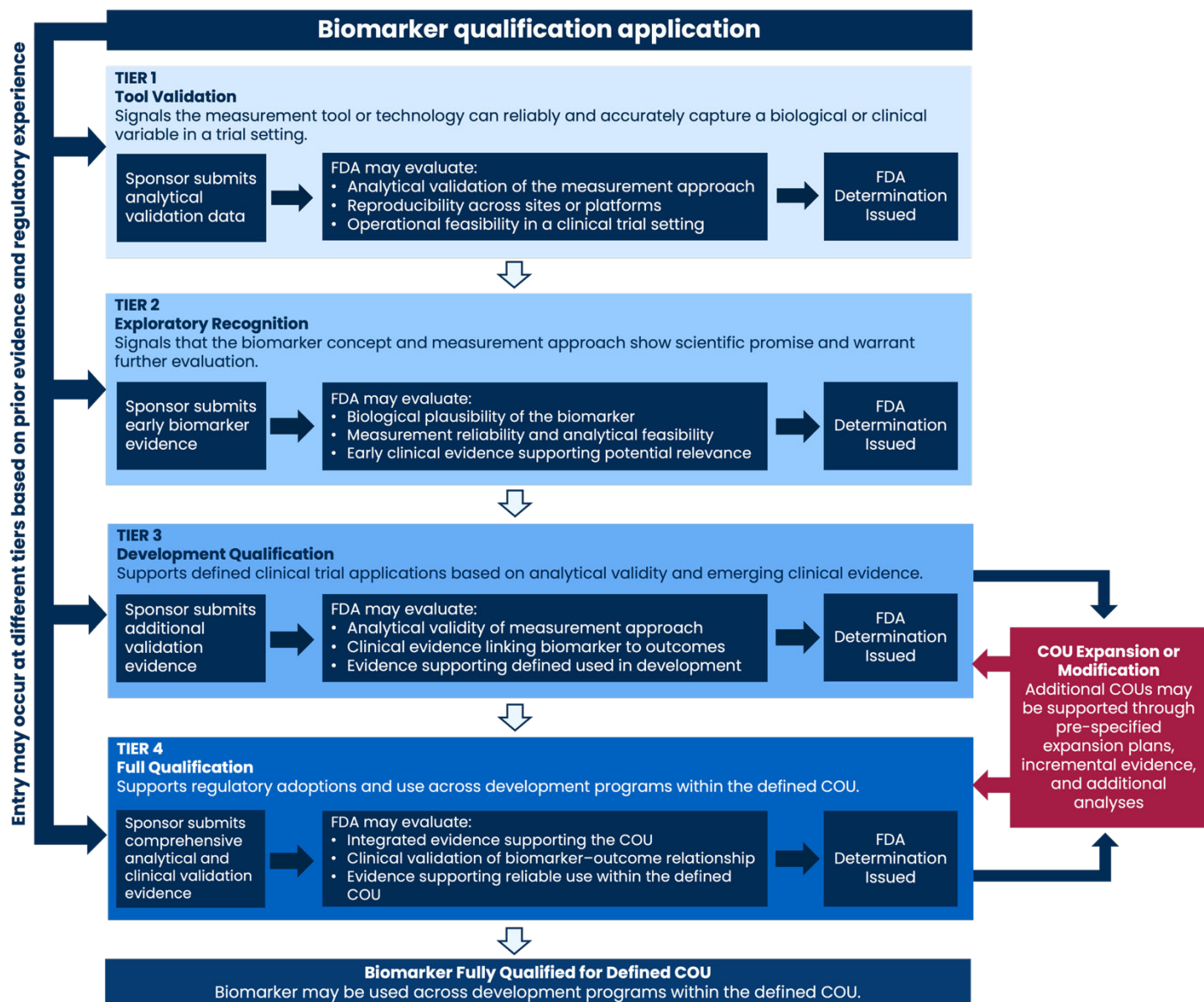


Figure 2. Tiered Framework for Biomarker Qualification.

Progression Across Tiers and COU Expansion

This framework would allow for flexible engagement, including applying for qualification based on available evidence and intended regulatory use, progressing across tiers as evidence develops, or remaining within a given tier where appropriate. The framework should also allow requestors to enter at the tier supported by the maturity of the available evidence, rather than requiring sequential progression through each tier. This approach would better align the pathway with evidence maturity, reduce duplicative administrative steps, and improve the practicality and efficiency of the program. A tiered approach could also help differentiate expected timelines, with shorter timelines for validation of measurement tools and longer timelines for full clinical validation, reflecting the differing levels of complexity and evidence required across stages. **Table 3** illustrates how evidence requirements, regulatory confidence, and potential regulatory uses could evolve across tiers. The examples shown are intended to be illustrative rather than prescriptive and would require further refinement by the FDA through implementation. In this context, prior regulatory experience, including use of a biomarker to support regulatory decision-making within an individual development program (e.g., through IND-based development or in a product-specific Accelerated Approval pathway), should be

recognized as a component of evidence maturity within the framework. Such experience should support classification at the level of Development Qualification (Tier 3), reflecting sufficient regulatory confidence for defined applications within specific programs. Recognizing this evidence would help ensure that knowledge generated in individual programs contributes to broader regulatory learning rather than remaining siloed.

Table 3. Illustrative Structure of a Tiered Biomarker Qualification Framework

	Evidence Requirements	Regulatory Confidence	Potential Regulatory Uses
Tier 1: Tool Validation	Analytical validation and/or verification and validation demonstrating the method, assay, or technology used to measure the biomarker is reliable, accurate, and reproducible	Confidence that the tool or technology provides reliable and accurate measurement of the biomarker signal to support downstream evidence generation	Use of the tool for data collection in clinical trials; exploratory endpoint generation; feasibility assessments
Tier 2: Exploratory Recognition	Initial clinical evidence supporting biological plausibility and measurement relevance, typically for biomarkers with limited prior clinical or regulatory experience	Signals scientific credibility and supports continued evidence generation	Exploratory analyses, hypothesis generation, and early clinical decision support to guide further development
Tier 3: Development Qualification	Clinical evidence demonstrating association with outcome of interest, often supported by prior scientific or regulatory experience and sufficient to support a defined use within a specific development program.	Provides sufficient confidence to support defined applications within specific development programs	Application across development programs for lower- to moderate-risk biomarker uses (e.g., enrichment, response, or safety biomarkers) and use within specific development programs for higher-risk biomarker uses (e.g., reasonably likely surrogate endpoints), including product-level regulatory decision support within the proposed COU.
Tier 4: Full Qualification	Analytical and clinical evidence supporting broader use across development programs for a defined COU, informed by the level of validation, consistency of performance across studies or populations, and prior scientific or regulatory experience needed for consistent application in higher-risk regulatory uses.	High level of regulatory confidence supporting consistent application across development programs	Use across development programs without re-establishing the evidentiary foundation, including broader application of higher-risk biomarker uses (e.g., intermediate, surrogate, or reasonably likely surrogate endpoints; high-impact safety biomarkers) to support regulatory decision-making within a defined COU.

This framework would also allow requestors to expand a biomarker’s COU within a given tier when the proposed use is supported by a similar level of evidence and regulatory risk. For example, a lower-risk

biomarker application could be extended within Tier 3 to related settings, or a qualified Tier 4 biomarker could be expanded to a new COU that remains within Tier 4 or aligns with Tier 3, depending on the additional clinical validation and regulatory risk associated with the proposed use.

How a Tiered Framework Improves on the Current Model

A tiered framework would offer several advantages over the current qualification model, including clearer regulatory signaling, reduced development uncertainty, better alignment of evidentiary expectations with regulatory risk, and more efficient pathways for COU expansion as evidence matures.

Similar principles can be applied within IND-based development, where biomarker evidence and regulatory experience accumulate progressively across programs. Enabling a risk-based, progressive approach to biomarker evaluation within IND interactions could support continuity in evidence generation and strengthen alignment between product-specific development and the qualification pathway.

Recommendation 3 Implementation Approach: Some actions could be advanced within the current statutory framework through FDA guidance, internal policy, and clearer communication practices. Near-term actions could include clarifying how COU expansion may be pursued, how incremental or bridging evidence may support expansion, how prior scientific evidence and regulatory experience may be incorporated into qualification decisions, and how interim feedback can provide greater clarity as evidence matures. The FDA should also define how predefined evidentiary pathways, including PCCP-like approaches, may support anticipated COU modifications while maintaining appropriate evidentiary standards.

Formal implementation of a tiered framework with tiered regulatory recognition would require statutory revision to Section 507 of the FD&C Act. The current statute defines qualification as a single determination based on a complete evidentiary package for a defined COU and establishes the sequential LOI, QP, and FQP process. As a result, Congress should revise statutory authorities to support staged or incremental recognition of biomarker evidence, tiered evidentiary pathways aligned with the biomarker's regulatory role and associated risk, and more flexible entry into qualification review based on the maturity and completeness of the available evidence. If statutory changes are enacted, FDA guidance should further define evidentiary thresholds for each tier, expectations for progression across tiers, mechanisms for COU expansion, and how tier assignments, evidentiary gaps, and associated regulatory uses are communicated to requestors.

Conclusions and Path Forward

The FDA's BQP was designed to enable broad, cross-program use of qualified biomarkers; however, more than a decade of experience demonstrates it has not consistently functioned as a predictable or broadly used pathway for biomarker qualification. Its limited use reflects a combination of factors, including scientific complexity, evidence-generation timelines, uncertainty around COU development and expansion, resource constraints, and limitations in transparency, alignment, and predictability.

Addressing these challenges does not require rethinking the purpose of qualification but rather modernizing how it's operationalized. To that end, this paper outlines recommendations to strengthen the conditions for qualification to function as intended: institutional alignment, transparent and predictable processes, adequate resourcing, and a structure that reflects how biomarker evidence develops over time. Together, these changes would support a more flexible, risk-based, and iterative approach to biomarker development.

Modernizing the BQP presents an opportunity to move toward a more integrated evidence ecosystem—one in which data generated in development programs can inform qualification, and qualification can in turn

support broader and more consistent application across programs. Enabling this bidirectional flow of evidence is critical to ensuring regulatory frameworks keep pace with scientific innovation.

Recent FDA activities reflect increasing attention to biomarker evidence generation, including efforts to improve BQP engagement and transparency and broader regulatory science initiatives to aggregate biomarker data across development programs.^{2,8} The next phase of modernization should translate this momentum into practical improvements within the BQP, particularly in areas that can be advanced through guidance or internal policy. These include enhanced transparency in feedback and communication, clearer mechanisms for COU expansion, more systematic use of prior evidence and regulatory experience, and improved engagement and timeline communication as evidence matures.

Multi-stakeholder forums could help refine these concepts and translate them into practical approaches. Discussions involving the FDA, requestors, patient advocates, technology developers, consortia, and other stakeholders could identify use cases, clarify evidentiary expectations, and develop shared principles for COU expansion, prior evidence, lifecycle management, and interim milestones as evidence matures. These forums could also help distinguish improvements that can be advanced through guidance or internal policy from those that require statutory change.

Near-term improvements should be paired with longer-term reforms where current authorities may be insufficient. Formal staged recognition, user fee mechanisms, or modifications to the statutory LOI-QP-FQP structure would require legislative action. Congress should consider targeted statutory changes to support tiered evidentiary pathways, dedicated resourcing, and clearer accountability mechanisms where needed to achieve predictable and durable program modernization.

Taken together, these actions would strengthen the role of the BQP as a practical and reliable pathway for biomarker development—helping to ensure that advances in biomarker science translate more efficiently into regulatory use and, ultimately, improved outcomes for patients.

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