FRIENDS of CANCER RESEARCH

PARKER INSTITUTE FOR CANCER IMMUNOTHERAPY

Regulatory and Operational Considerations for Cell-Based Therapies

Issue Brief | 2026

Executive Summary

Cell-based therapies, including genetically modified products, are transforming treatment paradigms across oncology and rare diseases. Advances in underlying technologies and development strategies have accelerated innovation, and while the U.S. Food and Drug Administration (FDA) has emphasized flexibility for these complex products, sponsors frequently encounter uncertainty in how those principles translate to specific development decisions. Variability in how risk-based principles are applied across development stages can increase costs, delay patient access, and shift early-phase research outside the U.S.

This issue brief highlights three areas where targeted dialogue and greater clarity could enhance development efficiency and regulatory predictability:

1. Early-phase clinical development and strategy:

Unclear expectations of the types and applications of flexibility during investigational new drug (IND) application preparation and protocol design can lead to delays, repeated revisions, and duplicative data generation. Sponsors may re-establish common clinical trial elements despite precedent, while operational complexity and regulatory uncertainty can contribute to more first-in-human trials occurring outside the U.S. A framework that identifies protocol elements where sufficient precedent supports greater consistency, while retaining product-specific flexibility where warranted, could reduce sponsor uncertainty and improve the efficiency and predictability of early-phase development.

2. Chemistry, manufacturing, and controls (CMC) expectations and lifecycle management:

Manufacturing processes for cell-based therapies evolve significantly over time yet sponsors often face uncertainty in how the FDA applies regulatory flexibility for CMC across clinical development stages. In response, sponsors may take overly conservative approaches, such as premature specification setting or delayed process improvements, which increase cost and complexity. Lifecycle-based frameworks that incorporate staged specifications, flexible comparability approaches, and clearer validation expectations could improve predictability while maintaining safety and quality standards.

3. Clinical trial design and evidentiary expectations:

Cell-based therapies such as CAR T-cell products were initially approved based on data from single-arm trials in high unmet need settings. Following this success, these therapies are now moving into earlier lines of treatment where the FDA typically expects randomized trial designs. This shift towards randomized trials introduces significant operational and design challenges—particularly around comparator selection, feasibility, and ethical considerations—given the unique manufacturing and delivery constraints of these therapies. Greater clarity on evidentiary expectations, including when alternative clinical trial designs or novel early endpoints may be appropriate, could support efficient and predictable late-stage development.

This brief identifies specific barriers to efficient cell-based therapy development and proposed targeted proposals that could help address them. Translating these concepts into practice will require continued collaboration across regulators, sponsors, clinicians, and other stakeholders, and in some cases pilot programs or further policy development. Improving clarity, consistency, and transparency in how regulatory flexibility is applied can reduce unnecessary iteration, support more efficient development, and ultimately improve timely patient access to cell-based therapies.

Working Group Members

We thank the working group members for their expertise and contributions that helped shape the development of this issue brief.

Ben Beneski, Allogene Therapeutics

Marc Better, Pharmefex

Chris Cabanksi, Consultant

John Connolly, Parker Institute for Cancer Immunotherapy

Lola Fashoyin-Aje, Independent Consultant

Patrick Hanley, Children's National Hospital

Kristen Hege, Independent Advisor

Jonathan Jazayeri, Kite, A Gilead Company

Michael Kalos, Next Pillar Consulting

Kerry Jo Lee, Novartis

Elena Levi-D'Ancona, Friends of Cancer Research

Deepu Madduri, Johnson and Johnson Innovative Medicine

Ingrid Markovic, Novartis

Nancy Nair, Johnson and Johnson Innovative Medicine

Raj Puri, Iovance Biotherapeutics

Travis Quigley, Kelonia Therapeutics

Rosanna Ricafort, Bristol Myers Squibb

Nicholas Richardson, Precision for Medicine

Alexandra Beumer Sassi, AstraZeneca

Nirali Shah, National Cancer Institute

Mark Stewart, Friends of Cancer Research

Chris White, *Friends* Advisory Advocate

Table of Contents

Introduction

Cell-based therapies,[a] including those that are genetically modified, are transforming treatment paradigms across oncology and rare diseases and show great potential in other therapeutic areas. Advances in gene editing, vector engineering, and manufacturing technologies continue to expand their clinical potential. As innovation accelerates, regulatory and operational frameworks must evolve in parallel to ensure the safe, efficient, and predictable development of these products.

Recent U.S. Food and Drug Administration (FDA) communications emphasize the Agency's commitment to regulatory flexibility for cell and gene therapies,[1,2] acknowledging that traditional development paradigms may not always align with products characterized by limited preclinical predictability, multifactorial mechanism of action, complex and evolving manufacturing processes, or development in small or highly selected patient populations. Across the development lifecycle, from early-phase trial design through manufacturing evolution to late-stage evidence generation, uncertainty persists about how to operationalize risk-based principles in practice, particularly with respect to how and when the FDA may allow flexibility in sponsor proposals.

Closing the gap between flexibility in principle and clarity in practice is critical to realize the full transformational promise of cell-based therapies for patients with unmet medical needs. In many cases, the challenge is not the absence of regulatory guidance, but rather variability in how sponsors interpret existing frameworks, apply them across programs and development stages, and, in some cases, whether those frameworks fully align with the scientific and operational realities of these products. When expectations are unclear or appear to be applied inconsistently across programs with similar risk profiles, developers may respond by front-loading data generation, repeatedly revisiting protocol elements, and defaulting to more conservative approaches (e.g., when selecting starting doses, generating non-clinical data packages beyond what phase-appropriate development would require) that may be time and cost intensive and not scientifically justified or required from a regulatory perspective. These dynamics can increase development complexity, delay patient access to promising therapies, and, in some cases, influence where and how sponsors initiate early-phase clinical development.

Meaningful opportunities to better operationalize regulatory principles in a risk-based manner exist within current statutory authorities. In that context, a better understanding of how the FDA applies regulatory principles across early development, chemistry, manufacturing and control (CMC) lifecycle management, and evidentiary standards could enhance clarity of expectations while preserving rigorous safeguards for safety, purity, and potency. As cell-based therapies continue to advance rapidly, ongoing dialogue across regulators, developers, clinicians, policymakers, and patients will be important to ensure regulatory frameworks evolve and support innovation while maintaining patient safety and product quality.

This issue brief outlines three areas where targeted dialogue may improve operational predictability:

1. Early-phase clinical development and strategy
2. CMC expectations and lifecycle flexibility
3. Clinical trial design and evidentiary expectations

These issues have recently drawn broader policy attention,[3] including through guidance and other documents focused on early-phase trial competitiveness, flexible CMC requirements for small-population therapies, and

[a] While this brief draws primarily on experience with CAR-T and other genetically modified cell-based therapies where the evidence base and regulatory precedent are most developed, many of the challenges and opportunities described are likely applicable across a broader range of cell and gene therapy modalities.

regulatory predictability as priorities,[2,4] underscoring their relevance to U.S. leadership in cell-based therapy development.

Improving Operational Predictability in Early-Phase Clinical Development Programs

Early-phase clinical development, including first-in-human (FIH) and additional Phase 1 studies, represents a critical inflection point for innovative cell-based therapies. These studies generate the initial safety, dosing, activity, and feasibility data needed to determine whether potentially promising therapies should advance into later-stage development and ultimately reach patients. They also serve as the foundation for the evidentiary pathways that support regulatory decision-making, particularly in settings where early-phase studies may become registrational. Ensuring that sponsors initiate and conduct early-phase trials efficiently and predictably is therefore central to advancing innovation in cell-based therapy development.

Policymakers, the FDA, and the broader clinical development community have raised concerns about the increasing conduct of early-phase clinical trials outside the U.S.[5] This trend carries implications beyond competitiveness, limits U.S. patient access to early-stage therapies, and reduces domestic research experience in a rapidly evolving field. Importantly, regional differences in regulatory requirements and ethical standards may limit the applicability of data generated outside the U.S. to FDA expectations, narrowing the evidentiary foundation that informs future trial design and potentially complicating later-stage development. Sponsors cite a combination of factors when deciding where to initiate early development programs, including access to specific patient populations, speed of trial initiation and completion, trial costs, institutional infrastructure, and real or perceived complexity or unpredictability of regulatory processes. While the U.S. still retains important structural and scientific advantages, uncertainty around evidentiary thresholds and expectations during investigational new drug (IND) application preparation and early development is a frequently raised concern among sponsors and investigators.

Certain structural elements of early-phase trial design are sometimes revisited during formal IND review (e.g., cytokine release syndrome (CRS) grading thresholds or observation windows between cohorts that were addressed at pre-IND may be re-opened for discussion), which can result in repeated protocol amendments. Inconsistency in how sponsors and regulators interpret and operationalize these elements, particularly across products with similar mechanisms or risk profiles, can result in repeated redesign of common protocol elements. Additionally, sponsors may generate additional preclinical or manufacturing data to mitigate regulatory uncertainty rather than focusing on evaluating product-specific scientific and clinical considerations, ultimately contributing to delays in trial initiation.

A recent report noted that trial start-up is up to three times faster in other countries, and China has surpassed the U.S. as the global leader in clinical trials.[6] China and other countries offer accelerated pathways for Investigator-Initiated Trials (IITs) in academic settings to generate initial human data more quickly, often with reduced CMC requirements compared to what is expected in a full IND submission.[7] The U.S. does not currently have comparable accelerated pathways for IITs, which may discourage sponsors from selecting the U.S. for FIH trial initiation. Exploring opportunities to improve operational clarity and reduce barriers to early-phase trial initiation, including whether lessons from accelerated pathways in other countries could inform future approaches, represents an area for further dialogue between sponsors, academic institutions, and the FDA.

Cell-based therapies have unique product characteristics that influence trial design and regulatory expectations. Protocols for these therapies often incorporate product-specific approaches to enrollment staggering, eligibility

criteria, dose escalation, bridging therapy guidelines, dose-limiting toxicity (DLT) criteria, reporting practices, and study stopping rules. Additionally, factors such as autologous manufacturing timelines, supply chain logistics, and the need for trial sites with specialized capabilities introduce operational complexity that can compound protocol design challenges. Together, the uniqueness of these characteristics highlights the need for clearer best practices around protocol components where precedent exists and greater consistency in how the FDA reviews those elements across similar programs.

Protocol components where greater consistency in review may reduce iterative burden include:

Eligibility and enrollment

- Eligibility criteria, including prior therapy exposure, patient population inclusion, and requirements for companion diagnostics or laboratory-developed tests
- Eligibility to proceed to lymphodepleting chemotherapy and cell infusion
- Bridging therapy allowances and exclusions
- Considerations unique to pediatric enrollment, including age of enrollment and the potential necessity, feasibility, and applicability of treating adults before children

Dose escalation and trial design

- Starting dose justification and dose-escalation methodology (e.g., rule-based vs. model-based)
- Cohort structure, enrollment staggering rules, and observation periods between dose cohorts
- Requirements for pharmacodynamic sampling (e.g., tumor biopsies or other biomarker assessments)

Safety monitoring and toxicity assessment

- DLT definitions and assessment windows
- CRS, immune effector cell-associated HLH-like syndrome (IEC-HS), and immune-cell-associated neurotoxicity syndrome (ICANS) grading and management approaches
- Study stopping criteria and escalation or de-escalation triggers

Operational and site considerations

- Monitoring requirements and trial site considerations (e.g., inpatient vs. outpatient)
- Long-term follow-up requirements

These components are central to trial design and necessary to ensure patient safety and scientifically interpretable outcomes. Many early-phase trials share common structural features, and when expectations are not well established, development teams and reviewers alike may spend additional cycles on protocol elements that already have precedent.

A Common Framework for Early-Phase Development

A common framework for early-phase development could provide a starting point for protocol design and regulatory interaction by helping to distinguish elements of trial design that may benefit from greater consistency across programs from those that may require product-specific tailoring based on mechanism of action, risk profile, or target population. The intent would be to create a framework that serves as an initial reference point, focusing regulatory discussions on the unique scientific and safety considerations of individual products, rather than creating rigid requirements, introducing unnecessary variability across similar programs, or repeating negotiation of elements with established precedent.

Overly rigid toxicity definitions or stopping rules could inadvertently halt programs despite manageable or reversible toxicities. Consensus-based approaches to toxicity grading and management, such as those developed for CRS and ICANS in immune-based therapies,[8] have improved consistency in how programs are designed and reviewed. Developing analogous frameworks for early-phase cell therapy development could meaningfully reduce the iterative burden on sponsors and reviewers.

The distinction between structural and tailored approaches plays out differently across protocol elements. Table 1 proposes which components of early-phase cell-based therapy trials could benefit from greater alignment across programs as well as those that are inherently product-specific and warrant more individualized regulatory discussion.

Table 1. Structural Starting Points and Tailored Considerations in Early-Phase Cell-Based Therapy Development

Clinical Trial Protocol Component	Structural Starting Points (Potential Areas for Alignment Across Programs)	Situations Where Tailored Approaches May Be Appropriate
Preclinical evidence generation and IND-enabling studies	Phase-appropriate GLP toxicology studies and use of validated NAMs or advanced in vitro systems when scientifically justified to support early-phase clinical entry	Novel biological mechanisms or products with uncertain safety profiles that may require expanded toxicology packages or additional mechanistic studies
Use of prior knowledge or product experience	Leveraging prior knowledge, including cross-referencing their own data from approved BLAs and late-stage IND programs, as well as clinical or preclinical experience from related constructs, vectors, or manufacturing platforms to inform safety monitoring, escalation strategies, and toxicity management approaches	First-in-class platforms, novel targets, or products with no closely related prior experience, where established safety monitoring frameworks or escalation strategies from similar programs cannot be readily applied
Eligibility criteria	Eligibility definitions informed by precedent from similar trials, including commonly used disease stage, prior therapy exposure, and age thresholds	Highly refractory populations, biomarker-defined subgroups, or pediatric populations where enrollment in earlier line settings or modified age thresholds may be scientifically justified[8]
Enrollment staggering and cohort progression rules	Standard staggered dosing approaches commonly used in similar cell-based therapy trials	Products with unprecedented biology, novel manufacturing approaches, or theoretical safety concerns
Dose-escalation strategy	Established escalation models and cohort structures used in prior early-phase trials	Therapies with uncertain therapeutic windows or limited preclinical dose-response data
Safety monitoring and toxicity assessment (including DLT definitions, CRS/ICANS grading, and stopping rules)	Use of previously established toxicity definitions and monitoring windows for known class effects or well-characterized platforms; use of established consensus grading systems and management algorithms for immune-cell therapies; use of predefined	Novel mechanisms of action, first-in-class targets, or limited prior human safety data where targeted tailoring may be justified; products where immune activation mechanisms or toxicity risks may not be adequately captured by existing grading or

Clinical Trial Protocol Component	Structural Starting Points (Potential Areas for Alignment Across Programs)	Situations Where Tailored Approaches May Be Appropriate
	safety monitoring frameworks, including protocol-specified pause rules, cohort review procedures, and escalation stopping criteria commonly used in early-phase cell-based therapy trials[8]; leveraging operational/logistical approaches (e.g., outpatient vs. inpatient design, requirements for hospital-level of care) from similar cell-based therapy trials	management frameworks; products with complex or poorly characterized toxicity profiles that may require tailored safety monitoring thresholds or review processes
CMC readiness expectations for early trials	Phase-appropriate manufacturing expectations and product characterization requirements for early clinical material, leveraging prior platform knowledge	Products involving novel manufacturing technologies or novel product attributes
Translational and pharmacodynamic data collection	Use of established assay platforms and sampling approaches with prior analytical validation; incorporation of translational endpoints (e.g., PK, pharmacodynamic assessments, biomarker sampling) that build on experience from related programs or platforms to inform safety monitoring, dose selection, and early activity signals	Novel mechanisms of action or first-in-class targets where established assay platforms may not adequately capture relevant biological activity; programs where the translational biology is sufficiently distinct to require development of new assays or sampling strategies without prior precedent

Abbreviations: GLP, Good Laboratory Practice; DLT, dose-limiting toxicity; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; NAM, new approach methods; IND, Investigational New Drug Application; BLA, Biologics License Application; CMC, Chemistry, Manufacturing, and Controls; PK, Pharmacokinetic

Additional Operational Considerations

Operational considerations, including patient access, trial infrastructure, and oversight costs, also significantly affect feasibility, particularly for biomarker-defined subsets, rare diseases, and pediatric indications where patient populations are limited and multi-center coordination adds complexity. Cell-based therapy-specific approaches, such as leveraging centralized institutional review boards and institutional biosafety committees with relevant expertise, could further reduce operational burden.

Potential Pathways for Implementation

Several mechanisms may support the development and implementation of a common early-phase framework. These could include:

- Develop guidance describing common structural considerations for early-phase cell-based therapy trials and provide clarity of their application
- Create a publicly available protocol template or reference framework for early-phase trial design to standardize shared components, allowing sponsors to focus more on product-specific considerations; greater consistency in submission structure may also improve the efficiency of FDA review, particularly as

artificial intelligence (AI)-assisted tools are increasingly incorporated. Existing efforts, such as the Foundation for the National Institutes of Health (FNIH) Accelerating Medicines Partnership Bespoke Gene Therapy Consortium (AMP BGTC) playbook, provide a useful precedent.[9]

- Establish ad hoc or rapid feedback mechanisms to facilitate earlier dialogue with FDA review teams during IND preparation, reducing uncertainty before formal submission; for example, the FDA's Support for Clinical Trials Advancing Rare Disease Therapeutics (START) Pilot Program provides a model that could be extended beyond rare disease applications
- Collaborate with cross-sector groups to identify areas where greater alignment may be appropriate
- Pilot efforts to evaluate whether common early-phase frameworks improve development efficiency

Collectively, these approaches are intended to provide more structured and transparent starting points for early-phase development, while preserving the flexibility needed to address product-specific scientific considerations.

Questions for Further Dialogue

1. Which elements of early-phase cell-based therapy trial design have sufficient precedent to support a common framework, and what process could be used to identify and validate those elements across stakeholders?
2. How should a common early-phase framework be structured to preserve the FDA's ability to exercise scientific judgment while reducing iterative negotiation of protocol elements with established precedent?
3. What mechanisms, such as rapid feedback pathways, protocol templates, or expanded pre-IND engagement, would most meaningfully reduce barriers to early-phase trial initiation in the U.S., and how could their impact be evaluated?

Advancing Predictable and Flexible CMC Expectations Across the Development Lifecycle

Manufacturing evolution is inherent to cell-based therapy development. Processes established for early-phase studies are rarely identical to those used in later development or commercial stages, and growing process knowledge over time often requires refinement of the manufacturing process, product specifications, analytical methods, and release testing matrices. The challenge is not that regulatory flexibility in this area is unavailable, but that the framework for predictably applying it across development stages is not always clear. As a result, sponsors may establish detailed specifications before there are data to support them or encounter uncertainty about how and when CMC packages are expected to evolve.

Early in development, drug substances such as viral vectors and gene editing tools can be prohibitively expensive and time-consuming to produce at Good Manufacturing Practices (GMP) scale, making it difficult to justify the cost of producing multiple batches prior to generating any clinical data. While the FDA has recognized these challenges and acknowledged that phase-appropriate CMC expectations may apply, sponsors frequently encounter uncertainty in how that flexibility translates to specific submissions and development decisions. Greater clarity on how CMC expectations should evolve predictably across the development lifecycle, and on the conditions under which risk-based flexibility is appropriate, could reduce this friction without compromising standards for safety, purity, and potency.

The FDA announced that flexibility in CMC requirements is allowed for cell and gene therapies to help accelerate product development.[4] To better support sponsor development plans and ensure that more sponsors have a comprehensive understanding of regulatory expectations, the FDA should define the conditions under which CMC

flexibilities could be applied. Additionally, creation of a public-facing resource for sponsors, akin to the Complex Innovative Trial Design Meeting,[10] with anonymized, real-world examples of contexts where CMC flexibilities were applied, would improve alignment between FDA expectations and sponsor development strategies.[4]

Current Application of CMC Flexibilities

Below we outline key challenges and considerations related to CMC development including specification lifecycle management, comparability, and lot release testing and analytical validation.

Specification Lifecycle Management

Specifications established during clinical development are often based on limited datasets that may not reflect the full range of future process variability, creating challenges as programs progress. Key challenges for specification lifecycle management include:

- At IND filing, manufacturing history is typically limited to a small number of lots, making it difficult to establish statistically meaningful numerical limits, even though numerical acceptance criteria are often expected.
- As manufacturing processes mature and additional data are generated, there may be pressure to tighten specifications, which can paradoxically reduce long-term operational flexibility. Once established, narrow specifications are difficult to revise, even when scientifically justified.
- Specifications based on limited clinical experience may not reflect the full variability of the process, potentially excluding a product that fails one or more product specifications but could still be safe and effective.
- Specifications may need to be further refined based on real-world evidence obtained from commercial use.

For some attributes, clear specifications are appropriate at IND submission. For safety-critical attributes such as sterility, mycoplasma, and endotoxin, established numerical limits are expected at initial IND submission. However, for other attributes, a more staged approach may be warranted. Setting meaningful product specifications is often more challenging for viral vectors, gene-editing tools, and other ancillary materials, where manufacturing history may be particularly limited. To address this, a staged approach for product-specific attributes could distinguish the types of specifications appropriate at each phase of development. For example, for quality attributes and other characteristics that require sufficient data to establish meaningful ranges, "report results" approaches could be appropriate at early phases, particularly for attributes that do not impact safety, such as potency and process impurities. Additionally, where manufacturing history may be limited to fewer than three lots, numerical limits may not be warranted until sufficient data are available to understand process variability.

A defined set of stage gates across IND filing, pivotal study initiation, pre-commercial, and post-approval stages could clarify when and how specifications are expected to be refined, allowing development programs to plan CMC evolution more predictably and reducing repeated negotiation of expectations that could be established prospectively. Additionally, allowing sponsors to leverage data from similar or platform products, drawing from both IND submissions and other regulatory filings, would provide a larger dataset for establishing specifications and could result in more robust acceptance criteria.

A related friction point involves refining specifications post-approval. For example, when variability in starting materials, patient health, and prescribing patterns become better understood. As manufacturing processes mature and run more consistently, there may be pressure to tighten specifications to reflect improved process performance. Similarly, sponsors may establish commercial specifications based on product lots that generated

clinical responses at the time of approval rather than from a broader dataset, which restricts available information to the relatively small number of batches used in clinical settings. This approach can lead to overly tight specifications that do not reflect the full variability of the process,[11] may exclude a product lot that fails one or more product specifications but could still be safe and effective, and are difficult to revise post-approval, thereby limiting patient access and future flexibility. Manufacturing consistency may be more appropriately managed through continued process verification as part of the Pharmaceutical Quality System rather than through increasingly narrow release specifications. Conflating the two can reduce long-term operational flexibility and may contribute to divergent global specifications when expectations are applied inconsistently across regulatory authorities.

Comparability

Comparability expectations present a distinct but related set of challenges, particularly in the context of process changes and evolving manufacturing models. The 2023 FDA draft guidance on comparability for cell and gene therapy products provides a general framework,[12] and sponsors retain latitude to design risk-based strategies consistent with it. In practice, however, formal equivalence testing, which requires sufficient batches to achieve adequate statistical power, can be costly and logistically complex in ways specific to cell-based therapy manufacturing. For allogeneic products, side-by-side split-donor comparability studies may be impractical when the number of required runs substantially exceeds clinical need. For site changes, donor-matched comparisons may be impossible if the original site is no longer operational. These constraints can create a dynamic where the cost of a comparability exercise exceeds the benefit of the underlying change, leading programs to defer or bundle process improvements rather than implement them when scientifically appropriate.

Clearer articulation of when risk-based or descriptive approaches are appropriate could help address this, with particular relevance for well-characterized processes on established platforms and site changes where process, equipment, and procedures are held constant. An emerging area warranting attention is decentralized manufacturing. Point-of-care and distributed manufacturing models offer potential advantages for access and scalability,[13] but demonstrating comparability across multiple sites raises questions the current guidance framework was not specifically designed to address. Furthermore, articulation of what types of manufacturing changes are considered minimal enough to not require formal equivalence testing would be helpful. In such cases, approaches based on demonstrating process expectation rather than formal statistical equivalence may be sufficient. For example, comparison of analytical data from pre- and post-change groups, in conjunction with supporting development data from a scale-down model system, may represent a sufficient alternative approach.

Lot Release Testing and Analytical Validation

Lot release testing and analytical validation are closely related areas where similar lifecycle principles apply. Recent FDA communications acknowledge flexibility in lot release, including the ability to use material before full internal release in appropriate circumstances, and reflect the kind of risk-based accommodation that can support development efficiency.[4] For analytical methods, fit-for-purpose qualification is expected during clinical stages, and clarification is needed on what parameters from validation would be sufficient to demonstrate that methods are qualified. For products on established manufacturing platforms, leveraging platform-level analytical data across programs differing primarily in target or sequence could also reduce redundant validation work.

Potential Pathways for Implementation

Several areas warrant further discussion as potential approaches to improving CMC predictability across the development lifecycle:

- Exploration of a staged specification framework defining expectations across IND filing, pivotal study initiation, pre-commercial, and post-approval stages, with clarity on when "report results" approaches are appropriate versus numerical limits, and how specification ranges can be refined as data accumulate, independently of manufacturing performance improvements
- A cell-based therapy-specific lifecycle mechanism analogous to the Predetermined Change Control Plan (PCCP), enabling prospective alignment with the FDA on a defined roadmap for how specifications and testing approaches evolve as process knowledge grows, reducing repeated regulatory interactions and providing greater planning certainty for both sponsors and the FDA
- Greater clarity on when risk-based or descriptive comparability approaches are appropriate, with attention to allogeneic products, site changes on established platforms, and decentralized manufacturing models
- Consideration of updated or consolidated guidance on phase-appropriate GMP and analytical validation, reflecting current practices and risk-based approaches that may not be fully captured in existing documents
- Exploration of lower-barrier dialogue mechanisms with the FDA during CMC development, including informal consultation pathways for questions that do not warrant formal meeting requests

Questions for Further Dialogue

1. What conditions should define when "report results" approaches are appropriate versus numerical acceptance criteria, and how should those thresholds evolve as manufacturing history accumulates across development stages?
2. How can comparability expectations be adapted for cell-based therapies where conventional study designs, such as split-donor comparisons or matched site changes, are operationally infeasible, and what alternative approaches would the FDA consider sufficient?
3. What would a cell-based therapy-specific lifecycle mechanism analogous to the PCCP look like in practice, and what level of prospective alignment with the FDA would be needed to make it workable?

Aligning Clinical Trial Design with Evidentiary Expectations for Registrational-Stage Trials

Chimeric antigen receptor (CAR) T-cell therapies in hematologic malignancies were initially developed and approved based on single-arm trials in multiple relapsed or refractory settings, where dramatic and durable responses far exceeded effects observed with available standard of care therapies at the time. Subsequent randomized clinical trials supporting earlier-line approvals in large B-cell lymphoma and multiple myeloma further validated the magnitude of benefit and overall survival advantages for these products.

As CAR-T and other cell-based gene therapy development programs advance into earlier lines of treatment, they are entering settings where regulators traditionally expect randomized clinical trials. Randomized clinical trials are typically required in settings where effective alternative therapies exist, curative intent is established, or when the magnitude of benefit from an investigational product cannot be reasonably inferred from uncontrolled data. However, the novel aspect is the transition of a therapeutic class defined by novel and distinct complex biology and manufacturing into these settings, bringing operational complexities that pose trial design challenges that have not been fully addressed in regulatory guidance. Recent FDA communications have made this expectation more explicit, noting that randomized evidence is preferred for traditional approval, while single-arm trials are generally more appropriate to support accelerated approval.[14]

Single-arm development is appropriate in some contexts, including settings where no effective standard of care exists, where the magnitude of response is so pronounced that randomization raises ethical or feasibility concerns, or where morbidity associated with available alternatives makes enrollment to a control arm difficult to justify. These determinations are context-specific based on the combination of clinical need, available alternatives, and expected magnitude of benefit. Several factors may inform whether a single-arm or randomized design is most appropriate for a given program:

- Available treatment alternatives, line of therapy and the availability of meaningful comparators, and the degree of unmet need in the intended patient population
- Expected magnitude and durability of response based on mechanism of action and prior clinical experience
- Operational feasibility, including manufacturing timelines, surgical procedures, out-of-specification rates for autologous products, bridging therapy logistics, and lymphodepletion requirements
- Ethical considerations in heavily pre-treated populations where access to promising therapies may itself be a relevant factor
- Global development considerations that may complicate comparability, including regional differences in standard of care, access to approved therapies, and site compliance burden

As the likelihood that cell-based therapies may be evaluated in combination with other treatments increases, there is a need to consider evidentiary standards for demonstrating contribution of effect in these combination settings. The introduction of novel endpoints as the regulatory landscape evolves also introduces additional complexity, making it important to prespecify approaches (e.g., leveraging prior knowledge from similar products) for determining contribution of effect.

Comparator Selection in Randomized Trials

When sponsors conduct randomized trials, comparator selection presents distinct operational challenges for the current advanced products (i.e., autologous CAR-T and T cell receptor-engineered T cell (TCR-T) products). If an approved cell-based therapy is to be the comparator, manufacturing timelines and out-of-specification rates can tangibly affect whether patients in the control arm receive the assigned treatment and with what delay. Limited commercial accessibility of approved products outside major academic centers can introduce further heterogeneity, while the high cost of manufacturing the comparator product imposes significant cost constraints on the clinical program. Bridging therapy and lymphodepletion logistics add complexity with no clear analog in conventional oncology development.

If investigator's choice serves as the comparator, heterogeneity across eligible treatments can complicate interpretation of results and limit the generalizability of conclusions. Clearer regulatory guidance on how sponsors should approach comparator selection, including the factors the FDA weighs and the threshold at which operational barriers justify alternative design strategies, would reduce uncertainty for programs entering registration-stage development. In settings where a concurrent control arm is infeasible, natural history and real-world evidence datasets, including those that incorporate projection algorithms, have been used with some regulators to construct external comparators.[15,16] As commercial experience with approved cell-based therapy products accumulates, the feasibility and reliability of such approaches may improve.

As cell-based therapy development matures, questions are also emerging about whether dimensions of benefit beyond response rates and survival, including speed of treatment delivery and tolerability, should factor into benefit-risk assessment and comparator selection. Faster access to therapy may be meaningful to patients even when comparative efficacy is similar, and improved safety relative to existing options may be relevant. How these

tradeoffs should be weighed in trial design and approval decisions has not been clearly established, but the questions are increasingly relevant as allogeneic and off-the-shelf products advance and head-to-head comparisons between cell-based therapy options become more common.

Endpoint Considerations

The drug development ecosystem has shifted towards an increased reliance on early endpoints and the use of expedited approval programs (i.e., Accelerated Approval); however, the regulatory acceptance of these early endpoints in cell-based therapy trials is less clear. The FDA's draft guidance on use of minimal residual disease (MRD) as an endpoint in multiple myeloma establishes a framework for use of MRD negativity to support accelerated approval in multiple myeloma, though the underlying meta-analyses did not include CAR T-cell therapy trials, leading to the FDA noting that applicability to this therapeutic class is unknown.[17] While sponsors incorporate MRD into cell-based therapy trials, its use as a primary endpoint to support regulatory approval for these therapies has not yet been accepted. A question for further dialogue is what types of data and level of evidence would be needed to extrapolate this use case to cell-based therapy and other therapeutic contexts. Similarly, ctDNA assessments have been increasingly incorporated into advanced solid tumor trials, where on-treatment reductions are associated with improved survival outcomes and can serve as an early readout of treatment response. While the evidence base in hematologic malignancies is less mature, emerging data suggest that ctDNA dynamics may provide meaningful clinical information in these settings as well.[18,19] Whether ctDNA could serve as a regulatory endpoint for cell-based therapies either in solid tumors or hematologic malignancies remains an open question and represents an area where further evidence generation and regulatory dialogue could inform future development.

Potential Pathways for Implementation

- Identify and articulate the factors that inform when single-arm trials provide sufficient evidence versus when randomization is needed to support more predictable development planning
- Clarify how operational challenges specific to cell-based therapy trial design, particularly when an approved CAR-T product is the comparator, are weighed in setting evidentiary expectations, and what approaches may be available when those challenges are substantial
- Explore how novel early endpoints, building on frameworks like the January 2026 draft guidance on MRD in multiple myeloma,[17] could improve clinical trial feasibility across cell-based therapy indications

Questions for Further Dialogue

1. What factors should inform whether a single-arm trial provides sufficient evidence for traditional approval in cell-based therapy settings, and how should operational challenges specific to these therapies, such as manufacturing timelines and out-of-specification rates, factor into that determination?
2. When an approved cell-based therapy product is the designated comparator, what alternative design strategies are available to sponsors when conventional randomized approaches are operationally infeasible, and what evidentiary standard applies?
3. What data and level of evidence would be needed to support extrapolation of novel endpoint frameworks, such as MRD negativity in multiple myeloma, to cell-based therapy indications where these endpoints have not yet been accepted?

Forward-Looking Regulatory and Policy Considerations

While many opportunities identified in this brief may be addressed through greater clarity, alignment, and use of existing regulatory tools, some barriers to efficient development may require more structural approaches. In parallel with near-term efforts to improve how existing flexibility is operationalized, there is an opportunity to explore targeted policy initiatives, pilot programs, and systemic changes that could enable more consistent and efficient development of cell-based therapies, particularly in areas where operational complexity, limited patient populations, and evolving manufacturing processes create challenges that extend beyond what current frameworks were designed to address.

Potential Areas for Further Exploration Include:

- Targeted pilot programs for high-risk early-phase development: Explore pilot programs to evaluate streamlined, notification-based oversight for FIH trials for serious, life-threatening diseases. Such pilots could evaluate more structured approaches to IND readiness, including expectations for preclinical data, CMC readiness, and early dose-escalation strategies. These efforts may help address key drivers contributing to the conduct of early-phase studies outside the U. S. by improving predictability and reducing time to trial initiation.
- Development of case-based or modality-specific guidance for early-phase studies: Providing more detailed, example-driven guidance reflecting accumulated regulatory and clinical experience with cell-based therapies. This could include illustrative approaches to common areas of uncertainty, such as starting dose selection, escalation design, and toxicity management for early clinical material.
- Centralized or specialized IRB models for complex therapies: Exploring the establishment of therapy-specific or centralized institutional review boards with expertise in cell-based therapies. Such models could improve consistency and efficiency in ethical and safety review, reduce duplicative review across institutions, and accelerate trial activation timelines while maintaining rigorous patient protections. These centralized approaches would focus on ethical oversight and safety considerations, while preserving investigator and sponsor responsibility for scientific design.
- Accreditation or pre-certification pathways for experienced clinical centers: Establishing mechanisms to recognize and pre-certify institutions with demonstrated expertise in the manufacturing, delivery, and clinical management of advanced therapies. Analogous to a master file for manufacturing processes, such a pathway could establish a standing institutional record covering core elements unlikely to change across products, including infrastructure, qualified personnel, standard assays, and facility capabilities, that could be referenced across individual INDs rather than re-evaluated each time. This could shift aspects of regulatory review from a product-specific to a system-level assessment of institutional capability, reducing the need to repeatedly evaluate similar infrastructure and processes across individual INDs and enabling more efficient activation of early-phase trials.
- Frameworks to support platform-based development and use of prior knowledge: Developing policy approaches that more explicitly enable the use of data from related products, shared manufacturing platforms, or common vectors to inform development decisions. Such frameworks could support more efficient evidence generation while maintaining appropriate scientific justification and product-specific considerations.
- Exploration of lifecycle-based regulatory models for complex therapies: Evaluating approaches that more explicitly recognize development as a continuous lifecycle, rather than a series of discrete regulatory

checkpoints. This could include structured mechanisms to prospectively align on how manufacturing processes, analytical methods, and evidentiary expectations are expected to evolve over time.

- Endpoint validation pathways for novel therapeutic contexts: As novel endpoints validated in one therapeutic setting are considered for use in others, clearer frameworks for how extrapolation is evaluated, including what data are needed and what standard of evidence applies, would reduce uncertainty for sponsors designing trials in areas where endpoint acceptance has not yet been established.

These forward-looking approaches are not intended to replace existing regulatory pathways, but rather to complement them by addressing areas where current frameworks may not fully account for the complexity and rapid evolution of cell-based therapies. In many cases, pilot programs may provide an appropriate mechanism to evaluate these concepts in a controlled and evidence-generating manner before broader implementation.

Conclusion

Cell-based therapies represent a rapidly advancing and highly promising class of therapeutics. As the field continues to evolve, ensuring that regulatory and operational frameworks keep pace will be essential to translating scientific innovation into timely and reliable patient access.

This issue brief highlights a central challenge across the development lifecycle: while regulatory flexibility for these therapies is increasingly being recognized, the application of that flexibility is not always clear or consistent in practice. Variability in how risk-based principles are interpreted and operationalized can introduce uncertainty, contribute to inefficiencies, and, in some cases, influence how and where development programs are initiated.

Across early-phase clinical development, CMC lifecycle management, and clinical trial design, there is an opportunity to improve development efficiency by establishing more structured and transparent approaches that clarify how flexibility is applied while preserving the ability to tailor decisions to individual products. Doing so may help reduce unnecessary iteration, support more efficient regulatory interactions, and enable sponsors and regulators to focus more directly on addressing meaningful scientific and clinical questions.

Importantly, improving clarity in this context is not intended to create uniform or deterministic outcomes, but rather to provide a more structured and transparent framework for decision-making that preserves appropriate scientific flexibility.

Many of the opportunities described in this brief can be advanced within existing regulatory frameworks through enhanced alignment and more lifecycle-oriented approaches to development. Others may benefit from targeted pilots or longer-term policy development. Continued collaboration among regulators, developers, clinicians, and patients will be essential to refine these approaches and ensure they are both scientifically grounded and operationally feasible. Ultimately, improving clarity around how flexibility is applied in practice will support more efficient and scientifically rigorous development pathways for cell-based therapies and expand timely access to transformative treatments for the patients who need them.

References

1. U.S. Food and Drug Administration. Considerations for the use of the Plausible Mechanism Framework to Develop Individualized Therapies that Target Specific Genetic Conditions with Known Biological Cause (Draft Guidance, February 2026). Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-use-plausible-mechanism-framework-develop-individualized-therapies-target-specific
2. U.S. Food and Drug Administration. Innovative Designs for Clinical Trials of Cellular and Gene Therapy Products in Small Populations (Draft Guidance, September 2025). Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/innovative-designs-clinical-trials-cellular-and-gene-therapy-products-small-populations
3. Senate Health, Education, Labor, and Pensions Committee. Patients and Families First: Building the FDA of the Future (February 2026). Available from: https://www.help.senate.gov/imo/media/doc/fda_report.pdf
4. U.S. Food and Drug Administration. Flexible Requirements for Cell and Gene Therapies to Advance Innovation. Available from: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/flexible-requirements-cell-and-gene-therapies-advance-innovation
5. Alliance for Regenerative Medicine. Q4 2025 Sector Snapshot. Available from: https://alliancerm.org/wp-content/uploads/2026/02/Sector-Snapshot-Q4-2025.pdf
6. Beaney, A. OCT West Coast 2025: China surpasses US for annual number of clinical trials. Feb 12, 2025. Available from: https://www.clinicaltrialsarena.com/news/china-surpasses-us-for-annual-trials/
7. Yang Y, et al. The Role and Challenges of Investigator-Initiated Trials in the Cell and Gene Therapy Products Boom in Mainland China. Clinical and Translational Science. 2025 Feb 12;18(2):e70148. DOI: 10.1111/cts.70148
8. Naik S, et al. International consensus guidelines for the conduct and reporting of CAR T-cell clinical trials in AML. Blood Advances. 2025 Dec 9;9(23):6047-6058. DOI: 10.1182/bloodadvances.2025017011
9. Foundation for the National Institutes of Health. AMP® Bespoke Gene Therapy Consortium (BGTC) Regulatory Playbook. 2025 May. Available from: https://bgtcplaybook.document360.io/
10. U.S. Food and Drug Administration. Complex Innovative Trial Design Meeting Program. Available from: https://www.fda.gov/drugs/development-resources/complex-innovative-trial-design-meeting-program
11. Borogovac A, et al. Safety and efficacy of out-of-specification ciltacabtagene autoleucel (cilta-cel) in Relapsed/Refractory multiple myeloma (RRMM) (Abstract). American Society of Hematology Annual Meeting. December 6, 2025. Available from: https://meetings-api.hematology.org/api/abstract/vmpreview/300695
12. U.S. Food and Drug Administration. Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products (Draft Guidance, July 2023). Available from:

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/manufacturing-changes-and-comparability-human-cellular-and-gene-therapy-products

13. Stewart M, et al. Enabling access to genetically modified cell therapies through flexible approaches to manufacturing and cost recovery. Journal for ImmunoTherapy of Cancer. 2025 Dec 2;13(12):e013518. DOI: 10.1136/jitc-2025-013518
14. Mahat U, Das A, Kumar V. Evidence-Based Trial for Chimeric Antigen Receptor T-Cell Therapy in Oncology. JAMA. 2026 Jan 6;335(1):21-24. DOI: 10.1001/jama.2025.21721
15. Merz M, et al. Adjusted Comparison of Outcomes between Patients from CARTITUDE-1 versus Multiple Myeloma Patients with Prior Exposure to PI, Imid and Anti-CD-38 from a German Registry. Cancers. 2021 Nov 29;13(23):5996. DOI: 10.3390/cancers13235996
16. Jahanshahi M, et al. The Use of External Controls in FDA Regulatory Decision Making. Therapeutic Innovation & Regulatory Science. 2021 Sep;55(5):1019-1035. DOI: 10.1007/s43441-021-00302-y
17. U.S. Food and Drug Administration. Minimal Residual Disease and Complete Response in Multiple Myeloma: Use as Endpoints to Support Accelerated Approval (Draft Guidance, January 2026). Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/minimal-residual-disease-and-complete-response-multiple-myeloma-use-endpoints-support-accelerated
18. Kim WS, et al. Odronextamab monotherapy in patients with relapsed/refractory diffuse large B cell lymphoma: primary efficacy and safety analysis in phase 2 ELM-2 trial. Nature Cancer. 2025 Mar;6(3):528-539. DOI: 10.1038/s43018-025-00921-6
19. Kurtz DM, et al. Circulating Tumor DNA Measurements As Early Outcome Predictors in Diffuse Large B-Cell Lymphoma. Journal of Clinical Oncology. 2018 Oct 1;36(28):2845-2853. DOI: 10.1200/JCO.2018.78.5246