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Regulatory and Manufacturing Pathways to Expand Access to Genetically Modified Cell-Based Therapies

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The views expressed in this white paper do not necessarily reflect the views of all individuals or organizations listed. Participation in the development process does not imply endorsement of specific recommendations or conclusions.

Executive Summary

Genetically modified cell-based therapies, including chimeric antigen receptor (CAR) T-cell and T-cell receptor (TCR)-based approaches, are reshaping possibilities in the treatment of cancers and other complex diseases. Despite their potential, these therapies sometimes struggle to advance beyond early clinical trials—particularly for rare diseases or small patient populations, where traditional models for development, manufacturing, and reimbursement may not be conducive. Further compounding these challenges, fewer than one-quarter of relapsed or refractory hematologic malignancy patients eligible for these therapies receive them, often due to the real or perceived complexity of their use.

This white paper outlines potential regulatory, manufacturing, and cost recovery strategies to address the barriers that prevent promising therapies from reaching patients. The proposals are intended to inform future policy discussions, highlight areas for regulatory clarity, and identify operational solutions to support sustained therapy development. While exploratory in nature, the concepts aim at synergies between scientific rigor, operational feasibility, and patient need.

Key Focus Areas

1. Regulatory Engagement and Flexibility: The paper proposes clarifying and structuring the application of existing regulatory flexibilities—particularly in small populations, where traditional evidentiary expectations from large numbers of patients may not be practical. This includes aligning Chemistry, Manufacturing, and Controls (CMC) expectations with phase-appropriate standards and using early regulatory engagement to support risk-based development. These flexibilities could build on existing programs like the Regenerative Medicine Advanced Therapy (RMAT) and Breakthrough Therapy Designation (BTD) without reducing FDA's statutory approval standards.
2. Manufacturing Adaptability: Scalable access to genetically modified cell-based therapies will depend on flexible manufacturing ecosystems. The paper explores frameworks to support comparability, quality oversight, and site certification, along with mechanisms for implementing iterative process improvements without triggering full regulatory reassessment.
3. Sustainable Pre-Market Access: For therapies that show early clinical promise but face financial and commercial barriers due to the exceptionally small size of the relevant patient population, structured cost recovery and pre-approval access mechanisms could support continued development. Potential strategies include public-private partnerships, supplier collaboration, and grant-based funding. These concepts are not intended to replace traditional reimbursement pathways but may serve as transitional tools in select high-need settings.

The goal of this white paper is to identify actionable solutions that can help promising genetically modified cell-based therapies move from early development to clinical use—especially in areas of high unmet need. Continued dialogue with regulators, payors,

developers, and patient advocates will be essential to refining these ideas and ensuring that future pathways remain responsive, responsible, and focused on improving patient outcomes.

Introduction

Genetically modified cell-based therapies, including chimeric antigen receptor (CAR) T-cell and T-cell receptor (TCR)-based approaches, are beginning to transform treatment paradigms for complex diseases such as cancer. These therapies hold great potential for personalized medicine by targeting underlying genetic or cellular causes of disease. However, despite their promise, several barriers remain that prevent some of these therapies from transitioning from clinical trials to sustained patient access. These challenges are particularly acute for rare cancers and other small populations, where uncertainties in regulatory flexibilities and high costs associated with current manufacturing requirements create hurdles to sustainable development, often limiting commercial interest. At the same time, the specialized infrastructure required for production may be difficult to scale efficiently under traditional manufacturing models, underscoring the need for more adaptable solutions.

As a result, many promising therapies stall after early clinical development, leaving patients with few or no treatment options. Without clear regulatory pathways and cost-effective manufacturing solutions, these therapies may remain in limbo, lacking a viable pathway for continued development and access. This challenge is becoming more common as advances in cancer biology and therapeutic technology make it increasingly feasible to develop highly targeted cell-based therapies for narrowly defined patient populations—including rare adult and pediatric cancers—where traditional development and commercialization models may not be viable.

To address these challenges, a structured approach is needed that balances regulatory oversight and development of evidence to demonstrate safety and effectiveness with operational feasibility and sustainable reimbursement and/or cost recovery. This white paper explores solutions addressing several barriers that hinder genetically modified cell-based therapies from advancing beyond early-phase development, focusing on three critical areas:

1. Regulatory Uncertainty: While existing regulatory pathways offer some flexibility in demonstrating safety and efficacy, particularly for small patient populations with high unmet medical needs, there is no structured framework that defines when and how these flexibilities should—and should not—be applied to Chemistry, Manufacturing, and Controls (CMC) and manufacturing requirements. Tailored evidentiary requirements, including stage- and context-specific (e.g., fit-for-purpose) Good Manufacturing Practice (GMP) requirements, may be accepted on a case-by-case basis depending on the development program. Without transparency around how flexibilities have been applied in past scenarios, developers face uncertainty when

trying to align their development plans with regulatory expectations.[1] Establishing a more predictable framework for development-stage appropriate regulatory flexibilities, without compromising demonstrated product safety, efficacy, and quality, could enhance clarity, reduce inefficiencies, and foster greater alignment between developers and regulators.

2. Manufacturing Feasibility: Current regulatory requirements for product quality, safety, and site GMP compliance are often designed for large-scale commercial manufacturing, which can pose challenges for low-throughput production models. These challenges are especially true when therapies are developed or produced outside of traditional commercial settings. Iterative updates to manufacturing processes, such as adopting new technologies or refining production platforms, can also introduce regulatory complexity, increasing uncertainty for developers. These challenges are particularly relevant for decentralized manufacturing models, where maintaining product consistency and regulatory compliance across multiple sites adds another layer of complexity. While existing tools like pre-approved comparability protocols can help facilitate process changes, further clarity or guidelines on the application of this framework to distributed manufacturing for genetically modified cell-based therapies would be valuable. Without clearer pathways to support implementation of different manufacturing models and manufacturing improvements, developers may struggle to enhance turnaround times, reduce manufacturing costs, and expand patient access.
3. Reimbursement Barriers: A predictable reimbursement pathway is essential to ensuring long-term patient access to approved engineered cell-based therapies. However, even before approval, investigational genetically modified cell-based therapies, particularly those targeting rare diseases with limited commercial viability, often face financial barriers during development, as they typically fall outside the scope of traditional payor coverage. While the FDA approval process enables entry into standard reimbursement systems, clearer pathways to support development-stage access may be needed. Exploring pre-approval cost recovery strategies, such as limited, regulated mechanisms or public-private support models, may help sustain access in select, high-need cases while additional evidence is generated.

This white paper explores policy solutions across these three interdependent areas to support broader access to genetically modified cell-based therapies. While particularly relevant for manufacturing CAR T-cell treatments for rare cancers and small patient populations, many of the proposed manufacturing strategies could have broader applications across the landscape of genetically modified cell-based therapies, such as TCR-based approaches and cell and gene therapies for rare, non-malignant diseases. These solutions also aim to strengthen

national biomanufacturing infrastructure by promoting more resilient and distributed models that enhance domestic and local preparedness.

By aligning regulatory flexibility, adaptable manufacturing approaches, and predictable reimbursement models, the goal is to support access to therapies that might otherwise remain out of reach. This effort seeks to balance scientific rigor with operational feasibility, ensuring timely access to innovative, safe, and effective treatments while maintaining appropriate regulatory oversight. Importantly, this white paper does not propose lowering regulatory standards. Rather, it emphasizes applying existing standards in a structured, risk-based, and context-appropriate way. Patient safety, product quality, and regulatory integrity remain central to all proposals outlined herein. These proposals would apply exclusively to genetically modified cell-based therapies regulated under Section 351 of the *Public Health Service Act* and developed under active Investigational New Drug (IND) applications. The aim is to thoughtfully apply existing regulatory tools to improve access in high-need settings without compromising safety or efficacy.

Scope of Application: Illustrative Development Scenarios

Representative scenarios can help illustrate where the proposed solutions might have the greatest impact. While the overarching goal is to expand patient access to promising genetically modified cell-based therapies for rare diseases, the path to achieving this can vary widely depending on the nature of the sponsor, maturity of the clinical program, and anticipated commercial potential.

This white paper focuses on scenarios in which a therapy has demonstrated preliminary evidence of both safety and efficacy in early-phase studies but faces obstacles to initiating or completing a registrational trial due to limited commercial incentives, insufficient funding, or regulatory uncertainty. The proposals are intended to enable continued development by establishing regulatory and financial frameworks that support pivotal trial execution and approval.

While many of these challenges are particularly acute for programs led by research institutions or public-sector developers, the intent is not to create a framework limited to any one type of organization, but rather to address scenarios in which therapies with demonstrated potential face barriers due to scale, feasibility, or financial constraints. By shifting the economic and regulatory calculus, these models could create viable opportunities to advance these therapies. Several illustrative development scenarios are outlined below:

- Therapy with early-phase data in a rare disease: A genetically modified cell-based therapy developed and tested in a single-center, Phase 1 study in a rare disease population with no existing therapies. The therapy has demonstrated acceptable safety and preliminary efficacy, has a selected dose or dose range, and has received

a designation such as Breakthrough Therapy (BTD) or Regenerative Medicine Advanced Therapy (RMAT), acknowledging its potential clinical value. However, the pathway to a multi-center, registrational trial is unclear due to limited commercial interest and financial or regulatory constraints.

- Development of a therapy for a niche indication: A developer identifies a therapeutic opportunity in a small patient population that may not be commercially viable under current models. Regulatory flexibility and cost-sharing mechanisms—such as limited pre-approval coverage or shared public-private funding—could make development more feasible and support long-term access.
- Optimization of manufacturing for an approved therapy: An approved therapy could benefit from more efficient manufacturing processes. Regulatory processes that allow streamlined comparability between manufacturing processes without requiring a full new clinical development program could enable greater scalability and cost-effectiveness, ultimately improving patient access.

These scenarios are not exhaustive but are intended to reflect the range of programs that could benefit from targeted regulatory and financial innovation. The recommendations that follow aim to be broadly applicable across these settings while remaining grounded in operational feasibility and regulatory rigor.

Regulatory Pathways to FDA Approval for Genetically Modified Cell-Based Therapies in Small Patient Populations

Regulatory frameworks currently allow for flexibility in the development and approval of genetically modified cell-based therapies, particularly when supported by strong biological rationale and early clinical evidence. These flexibilities, such as use of surrogate endpoints, acceptance of single-arm trial data, and tailored post-approval commitments, are available through existing mechanisms like accelerated approval, INTERACT meetings, the CMC Development and Readiness Pilot (CDRP) Program, and the RMAT or Breakthrough designation.[2] They are especially relevant when traditional development models are infeasible due to factors such as small patient populations, disease severity, or lack of alternative therapies.

However, the how and when regulatory flexibility could extend to CMC requirements remains less well defined. While FDA has tools to support modified manufacturing approaches, such as risk-based GMP implementation or comparability protocols, these are often applied on a case-by-case basis, with limited transparency or precedent.[3–6] This lack of clarity can hinder planning, particularly for therapies developed in low-throughput, decentralized, or academic settings. A more structured and predictable fit-for-purpose approach to CMC flexibility could

reduce inefficiencies, support risk-based oversight, and ultimately improve patient access without compromising quality or safety.

To ensure such approaches remain appropriately scoped, it is important to outline circumstances where flexibility may be warranted. The following illustrative factors, when considered in combination, could help define appropriate use of regulatory flexibilities:

- A rare disease or narrowly defined patient subset, potentially affecting a very small number of patients annually.
- Lack of existing approved therapies and a serious or life-threatening condition.
- Preliminary clinical evidence suggesting meaningful clinical benefit or potential to address an unmet medical need.
- A therapy that has received a designation such as RMAT or BTD, reflecting compelling biological rationale and early data.

Likewise, clear boundaries should be defined for when flexibility would not be appropriate. Providing examples of acceptable evidence and fit-for-purpose manufacturing strategies would enable developers and regulators to align on a fit-for-purpose, risk-based framework that maintains rigorous standards while accounting for practical constraints.

Under this framework, core quality and safety principles would remain intact. Developers and regulators could collaboratively define fit-for-purpose GMP expectations tailored to low-throughput or site-specific manufacturing models. To support this approach, FDA could consider issuing guidance to clarify fit-for-purpose, adaptable CMC requirements that may be acceptable for genetically modified cell-based therapies in rare or underserved populations. This would build on existing programs such as RMAT and BTD, while specifically addressing manufacturing and feasibility constraints that may prevent promising therapies from advancing.

For example, similar to how the accelerated approval framework accepts surrogate endpoints, a complementary approach could define when fit-for-purpose manufacturing standards may be used. This might include cases where therapies are developed in autologous or low-volume settings, or where delays in production or distribution prevent timely access for patients.

By providing clearer expectations, such a framework could improve predictability for developers and payors while maintaining rigorous oversight. It would not be a prerequisite for regulatory flexibility but could serve as a tool to streamline engagement, align stakeholders, and support development and access in high-need settings.

Together, these strategies can support a more predictable, risk-based regulatory pathway for genetically modified cell-based therapies in small patient populations, helping to bridge the gap between early clinical promise and sustained patient access while allowing CMC

requirements to be more appropriately tailored to benefit-risk considerations that support timely availability. .

Manufacturing Models to Support Scalable and Sustainable Genetically Modified Cell-Based Therapy Production

A major barrier to sustained patient access is the absence of a flexible manufacturing ecosystem that can support a range of production models—particularly those tailored for small patient populations. Making genetically modified cell-based therapies available for patients requires manufacturing models that balance regulatory oversight and quality standards with operational feasibility.[7,8] Traditional large-scale commercial manufacturing requirements present challenges for autologous cell-based therapies, especially when production may occur at low-throughput or in decentralized, and point-of-care (POC) settings.[9–13] A more structured framework that supports risk-based, fit-for-purpose manufacturing approaches could help ensure product consistency, compliance with regulatory expectations, and scalability while allowing for process efficiencies. For example, fewer GMP requirements may be appropriate in early-stage development taking place in very limited populations than when a product advances further in clinical development toward more widespread use and full licensure, at which time somewhat more rigorous GMP might be required.[4,14] In addition to the above, strengthening manufacturing capacity for genetically modified cell-based therapies may also support national health security and align with broader efforts to bolster the national and local biomanufacturing infrastructure.

This section explores strategies for comparability and quality oversight, decentralized and mobile manufacturing solutions, and regulatory flexibility that could enable adaptive, scalable manufacturing.

Comparability and Quality Oversight

An operational consideration for decentralized, POC, and academic-based manufacturing is ensuring product consistency across multiple sites. To address this, standardized definitions and frameworks for comparability and quality oversight could be established, tailored to the therapeutic context and specific stage of therapy development.[15] This approach could help maintain product quality and consistency while allowing the flexibility necessary for feasibility, particularly in early-phase development and low-throughput production settings.

Early-Phase Development (e.g., Phase 1 multi-center academic trials):

- Comparability assessments may focus on foundational analytical measures (e.g., cell viability, sterility, and potency assays) to ensure product consistency across sites while providing predictability for developers and maintaining feasibility for small-scale production.

- A risk-based approach to identifying critical quality attributes (CQAs) could guide validation strategies, minimizing unnecessary data generation while still supporting regulatory expectations for investigational studies.
- Flexibility in demonstrating comparability—for example, allowing smaller, fit-for-purpose datasets in lieu of extensive at-scale comparability runs—would maintain quality standards while ensuring early-phase development remains feasible.

Late-Phase Considerations (e.g., submission package for rare disease genetically modified cell-based therapy):

- As therapies advance toward regulatory submission, the CMC package would need to evolve beyond early-phase expectations to include more structured data demonstrating batch-to-batch and site-to-site consistency.
- Validated analytical assays (e.g., flow cytometry for purity and identity, PCR for vector copy number) could serve as the basis for comparability assessments aligned with regulatory expectations.
- While split-batch comparability studies are a well-established standard, particularly for technology transfer, regulators could consider allowing alternative data sources in specific contexts. For example, small-scale representative runs or non-donor-matched material may be acceptable to support comparability, provided they are scientifically justified, validated, and supported by a risk-based assessment.

Post-Approval Modifications (e.g., process improvements that do not trigger classification as a new product):

- Regulatory flexibility could enable iterative manufacturing refinements without requiring extensive new clinical data, when supported by a risk-based assessment. This could include updates to automation, manufacturing platforms, or site-specific optimizations, provided quality parameters remain within pre-specified and validated bounds.
- A centralized Pharmaceutical Quality System (PQS) could serve as a mechanism for remotely governing multiple decentralized manufacturing sites, ensuring adherence to GMP while allowing for site-specific adjustments.

Decentralized Manufacturing Models for Genetically Modified Cell-based Therapies

A hub-and-spoke manufacturing model offers a structured approach to decentralization, enabling multiple sites ("spokes") to operate under the oversight of a lead-site ("hub"). This approach can help promote consistency, regulatory alignment, and quality control (QC) across multiple locations. Key components may include:

- New sites could undergo gap assessments, regulatory audits, and compliance agreements (e.g., MOUs or contractual frameworks) to ensure alignment with lead-site standards.
- A comprehensive tech transfer program could help ensure that standard operating procedures (SOP), batch records, personnel training, and equipment align with standardized expectations.
- Product release and QC testing could be centralized at the hub or designated testing facilities to promote consistency in release criteria, support regulatory compliance, and reduce variability across manufacturing locations.
- Virtual and in-person site reviews and third-party quality audits could support new site onboarding, compliance verification, and troubleshooting of manufacturing challenges.
- A comprehensive CMC package, potentially incorporating split-batch comparability studies, could help demonstrate consistency and support regulatory submissions.

This model has the potential to enhance scalability and regulatory predictability while supporting a more distributed domestic manufacturing infrastructure. However, it places significant operational responsibility on the hub, particularly for sustaining training and oversight at sites with intermittent production, which can be resource-intensive in low-volume settings.

Mobile Point-of-Care (POC) Manufacturing as an Emerging Solution

In addition to fixed decentralized sites, mobile point-of-care (POC) manufacturing units offer a promising solution for flexible, localized production of genetically modified cell-based therapies.[16] To be viable, these units would require clear regulatory pathways and alignment with GMP expectations. Key considerations include:

- Predefined GMP compliance standards, including sterility, product consistency, and quality control.
- Integration within an existing quality oversight framework, ensuring that mobile POC units align with lead-site regulatory governance.
- Defined regulatory expectations for including mobile POC units as part of the product license, ensuring they meet the same quality and safety standards as fixed GMP sites.

Mobile manufacturing or cell collection may be especially valuable in geographically dispersed regions or in settings requiring immediate cell collection and on-site processing. As these models continue to evolve, regulatory clarity and operational feasibility will be essential for broadening patient access safely.

Pre-Certification and Accreditation Models for Manufacturing Scalability

A potential mechanism to support decentralized manufacturing scalability is the pre-certification of manufacturing sites through an accreditation-based model. Pre-certification could:

- Establish clear regulatory expectations for non-commercial GMP facilities. For example, additional clarity on how phase-appropriate CGMPs apply in low-throughput or resource-constrained settings—such as appropriate documentation, environmental monitoring, or quality oversight expectations—could support more consistent implementation and reduce uncertainty.
- Enable pre-certified sites to function under centralized regulatory oversight within a hub-and-spoke manufacturing structure.
- Leverage existing accreditation frameworks, such as those from Foundation for the Accreditation of Cellular Therapies (FACT) or Association for the Advancement of Blood & Biotherapies (AABB), to ensure minimum infrastructure standards, validated analytical assays, and appropriate personnel training. These accreditation frameworks can help support elements of infrastructure readiness and could inform context-appropriate GMP expectations.

This approach could help build a distributed, domestically anchored manufacturing ecosystem, enhancing both scalability and national manufacturing readiness. By addressing gaps before product onboarding, pre-certified sites may be better positioned to support multi-site manufacturing efforts efficiently and compliantly while ensuring product quality and regulatory alignment.

Regulatory Flexibility for Manufacturing Process Evolution for Approved Products

To support scalable and sustainable manufacturing of genetically modified cell-based therapies, a regulatory approach could enable certain pre-defined, risk-based process modifications without requiring extensive additional regulatory reassessment. Through pre-defined process modifications plans, updates such as changes to automation technologies, site-specific optimizations, or adoption of new production platforms could be pre-defined, provided that CQAs and other relevant process controls remain within scientifically justified and pre-established parameters. Flexibility in process evolution should be accompanied by careful risk assessment and, when appropriate, additional supporting data or staged clinical evaluation to ensure that modifications do not introduce unintended variability or impact clinical outcomes.

Uncertainty around regulatory expectations and inconsistency of those expectations can delay or prevent critical refinements, such as optimizing production efficiency or reducing vein-to-vein time. Addressing these challenges through risk-based manufacturing flexibility could lower costs and broaden access without compromising product quality or safety.

Such a model could facilitate:

- Regulatory recognition of iterative improvements, allowing agreed-upon modifications across sites and product versions without triggering new clinical studies for each change.
- Structured comparability assessments, leveraging prior product knowledge to refine validation strategies for process changes, particularly in decentralized settings.
- Flexibility in oversight, enabling decentralized manufacturing sites to implement process refinements while maintaining product consistency and regulatory compliance.

Integrating predefined modification plans with comparability assessment strategies could allow developers to refine processes in real time. This approach aligns with broader risk-based strategies used in other regulatory contexts to streamline data requirements.[17,18]

Exploring Cost Recovery and Pre-Market Access Strategies for Genetically Modified Cell-Based Therapies

Enabling continued development of promising investigational genetically modified cell-based therapies—particularly for rare diseases with limited commercial viability—remains a critical challenge. While regulatory approval typically enables traditional reimbursement mechanisms, therapies in early stages often face financial barriers that limit evidence generation. In some cases, structured funding approaches may be needed to support participation in pre-approval studies where commercial investment or trial infrastructure is lacking. These strategies are not intended to replace the clinical trial process, but rather to supplement it in settings where resource limitations may otherwise halt development.

This section explores potential approaches to support financial sustainability during the investigational phases of development, particularly in cases where promising therapies for rare or underserved populations might otherwise stall due to limited commercial incentives. These proposals are intended to enable continued development and evidence generation in select, high-need cases. Structured access mechanisms, such as cost recovery, may offer a bridge where traditional funding models fall short. These ideas are exploratory and would require engagement with regulators, payors, patients, and other stakeholders to evaluate feasibility and ethical implementation.

Considerations for Pre-Market Cost Recovery and Access

In select cases where a therapy demonstrates strong early evidence of safety and potential clinical benefit—but lacks a clear commercial path—cost recovery approaches could help support continued development and patient access.

Options for exploration may include:

- Structured cost recovery mechanisms, consistent with existing FDA regulations, that allow limited reimbursement to offset manufacturing and delivery costs under defined conditions, such as through expanded access protocols with FDA authorization.
- Public-private partnerships or grant-based funding models to sustain access and continued evidence generation, especially for ultra-rare conditions or small populations with no alternative options.
- Supplier collaboration models, such as at-cost provision of critical materials, or academic-CMO partnerships or cost-sharing agreements to reduce the financial burden of continued production and delivery.

Any such mechanisms would need to be limited in scope, carefully defined, and clearly distinguished from traditional reimbursement for approved products. Congressional action would likely be needed to enable such mechanisms under fee for service Medicare and could be explored in the context of a targeted pilot program.

Transitioning to Traditional Coverage Pathways

Once a therapy receives regulatory approval, it qualifies traditional coverage frameworks under Centers for Medicare and Medicaid Services (CMS) and other insurers. Existing mechanisms—such as coverage determinations or clinical guidelines—would govern reimbursement and inform access decisions.

If a therapy is made available during the investigational phase through a structured cost recovery model, the developer could be expected to generate ongoing evidence to support regulatory approval and future coverage decisions. The evidence collected during this period could be critical in informing long-term coverage policies and ensuring a smooth transition to traditional reimbursement pathways following regulatory approval.

Opportunities for Future Dialogue

Meaningful discussion with CMS, private payors, and regulatory agencies will be critical to exploring these concepts further. Key questions include:

- Under what conditions—if any—might early access models be appropriate for therapies with limited commercial viability but high potential impact?

- How could such models be structured to ensure ethical safeguards, scientific rigor, and fiscal accountability?
- What mechanisms could support a transition from investigational access to traditional reimbursement without disrupting patient care?

Conclusion

Advancing the development and availability of genetically modified cell-based therapies, particularly for rare diseases, requires a coordinated approach that integrates regulatory flexibility, adaptable manufacturing models, and mechanisms to support evidence generation and associated access prior to approval. The proposals outlined in this white paper aim to address persistent barriers to development, helping ensure that promising therapies for patients do not stall.

Key considerations include:

1. Regulatory Engagement and Flexibility: Establishing a more structured regulatory pathway, within existing statutory approval standards, that aligns fit-for-purpose evidentiary requirements with the distinct challenges of developing therapies for small patient populations. This may include leveraging accelerated approval frameworks not only for clinical evidence, but also for fit-for-purpose manufacturing and CMC requirements, supported by early engagement with regulators.
2. Manufacturing Adaptability: Supporting decentralized and scalable production through comparability frameworks, pre-certification of GMP sites, and clearly defined mechanisms for implementing manufacturing improvements. Strengthening domestic and local infrastructure, particularly through distributed manufacturing and POC models, could also enhance national readiness.
3. Sustainable Pre-Market Access: Exploring structured cost recovery and early access strategies to support investigational therapies with compelling clinical promise but limited commercial viability. While exploratory in nature, these approaches may help facilitate continued development and evidence generation in high-need areas and inform future policy dialogue.

By aligning innovations across development, manufacturing, and access, the proposals in this white paper aim to create viable processes for delivering transformative genetically modified cell-based therapies to patients with limited treatment options. Continued dialogue with regulators, developers, payors, and patient advocates will be essential to refining these proposals and ensuring they remain grounded in both scientific rigor and patient need.

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