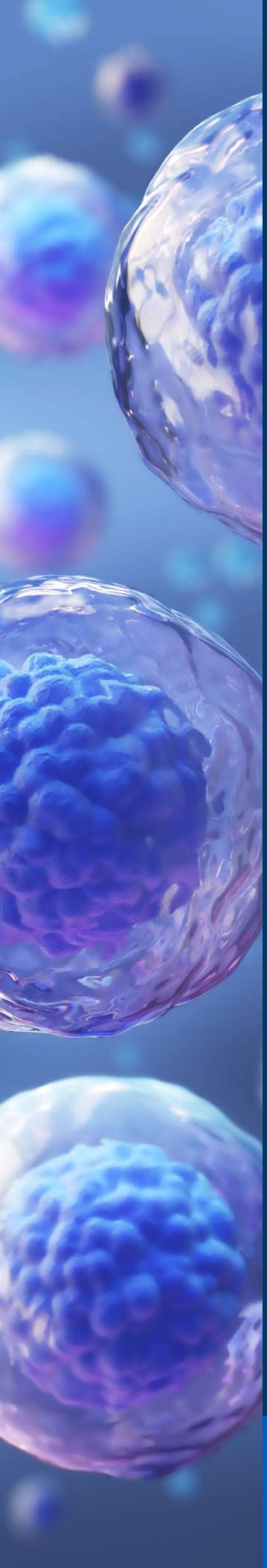

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RISK MANAGEMENT ACROSS THE CELL THERAPY LIFECYCLE

Guiding Principles for Process Development and IND Readiness

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INTRODUCTION

Cell therapy development is uniquely challenging. Sponsors must deliver high-quality therapies quickly and cost-effectively while navigating critical early decisions. Choices like prioritizing a "quick-to-clinic" approach versus investing in a scalable, commercial-ready process often leave teams at a standstill. These decisions lay the foundation for success—or create roadblocks—across the entire development lifecycle.

Commercializing a cell therapy introduces even more complexity. Regulatory demands, accelerated clinical timelines, and limited opportunities for late-stage optimization increase the stakes. Early-stage decisions directly impact the feasibility of scaling to commercial production. An overly narrow, science-driven focus can unintentionally complicate downstream development, regulatory submissions, and commercialization.

This white paper outlines a structured roadmap for managing risk throughout the drug development lifecycle. By leveraging stage gates and guiding principles, innovators can simplify decision-making, proactively address risks, and align early development with long-term commercialization goals. This approach transforms drug development into prioritized milestones that balance innovation with practical risk management.

By partnering with experienced contract drug manufacturing organizations (CDMOs), innovators gain access to expertise and proven frameworks for managing these challenges. Risk-based stage gates enable teams to mitigate uncertainties early, optimize processes for scalability, and maintain regulatory compliance—all while keeping commercialization in focus.

This white paper also provides actionable process and analytical optimization strategies, from candidate selection to a successful Phase 1 Investigational New Drug (IND) application. It highlights key principles for minimizing execution risks, improving process scalability, and positioning products for commercial success. For cell therapy innovators, a risk-managed, milestone-driven approach is essential for building stronger partnerships and achieving better outcomes.

CRITICAL ELEMENTS OF PROCESS AND CONTROL STRATEGY

Risk management begins in early-stage development, from candidate selection to Phase 1 IND application. Decisions can be prioritized by approaching development as a series of milestones and stage gates, and mitigation strategies can be defined a priori as part of the product development lifecycle. Navigating this transition effectively requires careful planning.

Four key components drive this phase:

1

A well-designed DoE program minimizes risks and streamlines development by leveraging the client's product expertise and the CDMO's historical knowledge. This collaboration saves time and cost while ensuring the process supports the target product profile (TPP).

2

The process evaluation phase significantly influences the final process. Choosing between a parallel or sequential process evaluation is critical in developing an IND-enabling package that efficiently balances quality and time.

3

A phase-appropriate analytical control strategy allows developers to ensure product quality, begin understanding inevitable patient variability within the trial's overall scheme, and establish an early path into the clinical trial setting.

4

Process establishment and final pilot runs are an opportunity for a final process shakedown and a chance to begin assessing donor-to-donor variability and its potential effect on the final target product profile before process lock and transfer to manufacturing.

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DESIGN OF EXPERIMENT STUDIES

At a cell therapy program's inception, the critical question is what is needed to enable clinical efficacy in a given indication and what factors (e.g., media, cytokines, growth factors, genetic modifications, etc.) can be modulated to ensure cells differentiate in needed directions. As such, nearly all cell therapy products are a “population” of cells defined by analytical measurements of purity and identity (often via flow cytometric measurements of cell surface markers). Traditional one-factor-at-a-time testing is expensive and often does not fully provide all the data needed to evaluate a process parameter change's impact. To ensure a parameter selection supports the TPP, a client's deep product knowledge can be leveraged with a CDMO's breadth of historical information to generate efficient Design of Experiments (DoEs).

DoEs and process evaluations with material isolated from an initial donor before moving on to full-scale runs (with additional donors) balance client needs while minimizing experimentation, testing, time, and cost. Focus on critical analytics and robust manufacturing unit operations blunts the impact of starting material variability while providing the necessary means to measure and understand it. Efficient DoE studies are a powerful tool. They allow the assessment of multiple variables across a wide range of values relative to each other without having to test every permutation of the parameters in question.

Statistical DoEs can thus shorten development time and decrease costs by facilitating analysis of multiple factors over a wide range of values (e.g., Multiplicity of Infection (MOI), a given set of cytokines over a range of concentrations, expansion duration, etc.) without having to test every combination possible. These results rely on DoE design expertise (from a CDMO partner) and expert knowledge of the product (from the client/partner). With each manipulation, a knowledgeable development partner will also understand the potential for downstream impacts.

For example, longer manufacturing processes (e.g., >7-10 days) or activation conditions early in the process can dramatically impact the composition of cell populations several days later. An analytical control strategy (e.g., release and characterization tests) that considers an assessment of these potential changes is key to creating a robust

IND-enabling package. In this scenario, measuring purity or identity alone may not be sufficient to identify changes in cell properties (e.g., differentiation of T cells).

PROCESS EVALUATIONS

Process evaluations are a critical stage gate in risk management and IND preparation. Designing process evaluation runs marks the next key stage gate in mitigating risks and ensuring readiness for an IND application. Data from DoE assessments narrow the parameter selection (often to 3 or 4 sets) to be tested in a series of process evaluation runs. These may be conducted in parallel (saving time) or in sequence (maximizing quality). The choice between the two is critical in streamlining the path to the clinic and should be dictated by confidence in the DoE work, existing product understanding, and client needs.

Sequential evaluation runs allow for course corrections in response to additional data, enabling parameter optimization to fine-tune outcomes. In this approach, the first evaluation run is defined, but later runs are informed by the previous run. Understanding the most critical parameters (e.g., viability, phenotype, function, etc.) is vital to inform the next experiment. Analytical methods must be established and agreed upon upfront to be able to test and interpret results from each evaluation run.

While sequential evaluation runs minimize quality risks by allowing analysis and adjustment, this approach is necessarily slower. If there is high confidence in the results of the initial DoE, sequential fine-tuning may not be necessary, and the evaluation runs can be conducted in parallel. In parallel evaluation runs, parameters are chosen based on the DoE work alone and tested at full or intermediate scale. This approach saves time but at the expense of the ability to redirect in response to incoming data. Again, a solid understanding of the critical parameters (and intact analytical methods) is required to aid in interpreting the results obtained from the study. By conducting parallel runs, sufficient data to support an IND-enabling package can be generated at an accelerated pace.

In choosing between parallel and sequential evaluation runs, innovators may also consider other factors, such as analytical method readiness, raw material availability, and regulatory requirements, all of which may factor into this decision. Regardless of the product evaluation strategy, the results of the process evaluation phase will dictate the final parameters to use for full-scale runs in the process establishment and pilot runs leading up to process lock.

ROBUST ANALYTICAL CONTROL STRATEGY

Developing a phase-appropriate analytical control strategy is essential for mitigating quality and compliance risks as cell therapy programs move toward early clinical validation. To understand manufacturing and clinical outcomes, a developer must understand the product well enough to interpret patient-to-patient variability within the trial's overall design. Health authority regulations ensure the product meets specified quality measurements, such as identity, purity, potency, and safety. However, these required tests are often insufficient in the early stages of development to ensure complete product understanding. In partnership with their CDMO, innovators are well-served by investing in characterization assays designed to interrogate additional aspects of the product.

Health authority regulations establish several assays required to release the product for clinical administration (e.g., release tests). Specific testing patterns are dependent on the actual product being developed. For a common modality, such as a CAR-T or TCR-T, assays include identity and purity by flow cytometer, viability by

dye-exclusion or automated cell counting (also used to calculate dose), depending on the cell product potency is often assessed by cytokine secretion following stimulation or cell killing if there is a targeting mechanism. Safety is often evaluated using compendial sterility, mycoplasma, and endotoxin detection methods. Molecular methods also examine genomic modifications (e.g., vector copy number (VCN), on/off-target editing, etc.). These assays are developed and qualified to ensure a level of performance fit for quality control testing. Specifications determined during the development and qualification process, in turn, determine a minimum set of performance criteria required for future batches produced with the same manufacturing process and tested with the same release methods.

While release tests ensure the product's quality, safety, and potency through the established specifications, characterization assays are used to understand other product attributes better early in development. These assays include assessments of phenotype, metabolomics, transcriptomics, additional potency assays, and other product-specific assays.

These assays do not have specifications and are used for a number of reasons: to increase the knowledge of the product or specific attributes, introduce new technology or testing techniques, confirm observations via parallel routes of testing, or address stability concerns or other product-specific questions. These tests may replace release tests as they are developed over time and elevated from characterization to release tests once data are compiled and specifications can be determined. Product knowledge is a combination of the release and characterization testing pattern.

PROCESS ESTABLISHMENT AND FINAL PILOT RUN

Process establishment and final pilot runs are the final stage gates before manufacturing. These runs validate the process, assess donor variability, and ensure readiness for technology transfer. Collaborating with a CDMO during this phase strengthens process documentation and supports a seamless transition to manufacturing.

Establishment runs present excellent opportunities to begin to establish donor variability data in the context of a given process. Assuming an initial establishment run with a new donor material conforms to expectations, further establishment runs expand process knowledge and build supporting documentation. Intentionally using new donor material in these runs reduces the gap in donor variability data left from the DoE and process evaluation runs. Innovators can get additional cost-effective mileage out of these runs by engaging a biostatistician early in the process—statistical analysis can provide additional insights needed to design an appropriately powered study.

Following the establishment runs, a pilot run locks the process and begins technology transfer to manufacturing. Pilot documentation should be written by process development personnel in conjunction with the cognate manufacturing lead and performed by manufacturing personnel who observe and assist. An effective technology transfer process entails collaborative process documentation generation and hands-on training.

The process establishment and pilot runs confirm the efficacy of a parameter set derived in the DoE and evaluation phases and expand process knowledge to include donor-to-donor variability influences (an unavoidable challenge in cell therapy manufacture). These final steps lock the process and serve as the final checkpoint before declaring development program completion and moving on to the next phase of the program lifecycle. A successful pilot run is an active tool for successful technology transfer.

THE PATH TO IND

The transition from research-focused exploration to commercially-driven product development presents significant risks during the path to IND and later development stages and commercialization. Often, this transition involves a handoff to a different organization tasked with scaling and preparing for a commercial launch. These groups may have competing priorities: early-phase research teams prioritize rapid clinical entry to address scientific questions (e.g., targeting, safety, trafficking), while development and commercial operations emphasize scalable, cost-efficient, high-throughput manufacturing processes. Careful alignment is essential to balance these priorities and avoid costly pitfalls.

The disconnect between early clinical processes and commercial requirements can jeopardize promising therapies without early alignment. Alterations to early clinical processes for commercialization may require clinical comparability studies or, in severe cases, result in a new IND filing and program restart. Early planning, including integrating manufacturing strategies into the initial Target Product Profile (TPP), facilitates proactive development conversations and minimizes risks.

Key Considerations for Early Planning

1. ***Assessment of Key Factors***
   Evaluate the patient population, dosing requirements, product attributes, and market differentiation factors (e.g., safety, efficacy). This assessment informs the design of scalable manufacturing processes.

2. ***Process Optimization Strategy***
   Develop strategies to enhance control, reduce complexity, and lower costs. Early risk assessments can identify streamlined development options and guide decisions on process or analytical method changes.

3. ***Process Characterization***
   Refine analytical control strategies by tightening specifications and elevating critical characterization assays to release tests as data accumulates. This refinement ensures consistent product quality.

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DESIGN OF AN EARLY TARGET PRODUCT PROFILE

An early TPP should assess key attributes such as patient population, dose, product characteristics, and differentiation elements. As development progresses, this evolves into a quality TPP (qTPP), defining attributes, manufacturing components, and a control strategy for consistent production.

Early risk assessments are critical to identifying components that must be established during initial development, including:

- *Critical attributes like cell population and engineering technology (e.g., viral or non-viral).*
- *Raw materials (e.g., serum, activation reagents) that may be challenging to change later.*
- *Product formulation and cryopreservation steps to streamline logistics.*

Understanding which elements can be refined and which need to be set in stone at this point is critical. Factors such as cost, timing, and complexity often compete for the attention of the research teams as the milestone of an IND filing drives their activities.

A risk assessment should be conducted early in development to identify these components that must be well established early in the development cycle. Items to consider here include critical attributes of the product, such as selection of cell population, engineering technology (e.g., viral or non-viral), critical raw materials that may be difficult to change in the future (e.g., serum, activation reagents, selection/purification strategy) and product formulation.

Additional considerations that often create a comparability challenge later in development include adding a cryopreservation step. This can be done either post-leukapheresis, post-selection, or at the end of the manufacturing process (or at multiple points across the process) to better support supply chain and manufacturing logistics. Making changes in development may require more extensive comparability (e.g., analytical and potentially clinical).

Raw material manufacturing presents another challenge. Many early-phase research teams use an adherent viral vector production system to move quickly to the clinic or save or defer costs. Once clinical proof of concept is achieved, new considerations around the ability to supply ample raw materials, cost of goods (CoGs), and reducing supply chain complexity result in the transition to larger-scale, suspension-based production processes.

This shift can impact the quality and potency of the viral vector based on changes in production systems, biomass, purification requirements, etc. Early consideration of commercial viability mitigates these risks.

Important Note

Another risk assessment will need to be done as part of late-stage readiness to prepare for a Biological License Application (BLA) or Marketing Authorization Application (MAA), depending on the target region (US or EU, respectively), to identify criticalities of the manufacturing process and analytical control strategy for the product.

DEFINE A PROCESS OPTIMIZATION STRATEGY

Early-phase manufacturing processes are often insufficient for later stages. Innovators must invest additional chemistry, manufacturing, and control (CMC) resources. Specifically, they must often optimize the manufacturing processes to enable better control or higher throughput, which may be required as an understanding of the commercial patient population clarifies in clinical development.

Here, innovators may be frustrated by early research decisions to develop scientifically valid but complex processes that inadvertently increase time, cost, and risk when these operations are performed in a GMP (Good Manufacturing Practices) environment. The problem is that researchers make early-stage decisions on media, serum, cytokines and growth factors, transduction aids, and final formulation excipients. Each of these decisions impacts pre-clinical safety, efficacy, and IND-readiness, but they also collectively inform the overall robustness and cost of goods to produce the therapeutic at larger commercial scales. For these reasons, early consideration of short-term and downstream impacts is critical to an asset's scientific and industrial success.

Process length, manual 'touch time,' and operator interventions drive up facility overhead costs and increase operational risks. Unsurprisingly, the nature of the therapy (autologous or allogeneic) will impact the extent and type of optimization required and may introduce the need for large-scale unit operations or automation to scale out.

Earlier consideration of these downstream impacts can streamline this review process and minimize the risk that updated unit operations could impact regulatory filings (e.g., are these minor or significant changes?), resulting in the need to perform costly and time-consuming comparability studies.

PROCESS CHARACTERIZATION

Process characterization is foundational to regulatory and safety requirements for commercialization. While an in-depth discussion of process characterization is out of scope for this whitepaper, understanding the concept is critical to sequencing the events and understanding the commitment of resources required to accomplish this precursor to process validation. In other words, timely and robust process characterization is a critical foundation for commercialization's regulatory and safety requirements.

Here, research-focused innovators make two understandable manufacturing missteps. First, many invest too late in analytical development, meaning they cannot generate meaningful data to enable process characterization. Second, innovators may try repurposing their research teams to execute analytical and process development work.

While this strategy may make sense from a short-term business perspective, it usually results in significant (and avoidable) costs in time and money needed to fix deficiencies in the future. The fundamental differences between research (e.g., depth of knowledge on a specific attribute) and development (e.g., breadth of knowledge across the attributes leading to robustness) result in the potential to develop and mature methods and processes that are difficult to translate into the commercial environment.

Scaling programs for commercial production introduce downstream risks that must be anticipated and proactively managed. First, production volumes will increase exponentially, and the cost(s) to staff the facilities with highly trained scientists to perform complex processes and analytical tests will create a particularly challenging environment to maintain.

Late-stage validation should explicitly aim to simplify the manufacturing processes and testing elements. Second, complex processes and testing strategies inherently increase the number of potential failure points, either due to operator errors or variability that cannot be correctly identified and controlled.

With the right team and focus, innovators can continuously improve analytical method performance while manufacturing and releasing clinical batches. This improvement involves release tests (tied to product specifications) and characterization tests (used to enhance product understanding).

As development progresses, sponsors should link tests to critical quality attributes (CQAs) and critical process parameters (CPPs), refining the analytical control strategy.

Key steps include:

- *Tightening test specifications as data on method performance and manufacturing history grows.*
- *Elevating informative characterization tests to release tests.*
- *Establishing reference standards for commercial production.*
- *Optimizing methods for the long-term analytical control strategy.*
- *Developing a coherent potency assurance strategy in line with FDA guidance.*
- *Preparing for method validation, conducted per ICH guidelines (e.g., ICH Q2R2).*

Neglecting these actions can lead to regulatory setbacks, inadequate quality control, and potential product delays.

OPPORTUNITY IN EVERY BATCH

Innovators must optimize analytical methods with every clinical batch to enhance understanding and product quality. This analysis involves refining tests, aligning with CQAs and CPPs, and preparing for method validation under ICH guidelines. Failure to focus on these steps risks an inadequate analytical control strategy, which could delay product approval or compromise its safety and efficacy.

FROM RISK TO REWARD: SMARTER DECISIONS IN CELL THERAPY

Cell therapy development is uniquely challenging because it demands a balance of scientific innovation, regulatory foresight, and scalability. Early decisions—such as selecting raw materials, designing robust processes, and prioritizing analytical development—can shape the success of a product's journey from research to commercialization. Proactively managing risks at each stage is critical to achieving long-term success.

Stage gates provide an effective framework for navigating these risks. These checkpoints allow teams to evaluate cost, time, and quality tradeoffs, ensuring thoughtful decisions as development progresses. Tools such as well-designed DoEs,

phase-appropriate analytical control strategies, and careful evaluations of sequential versus parallel processes streamline early development and ensure smoother transitions through each stage.

Addressing challenges like donor variability and material shifts requires iterative strategies. Early investments in robust analytical methods and a clear CMC roadmap enable teams to anticipate and mitigate risks while allowing for flexibility as knowledge deepens. This approach minimizes uncertainty and builds a foundation for scalability and product consistency.

A trusted CDMO can support these efforts by offering expertise and resources to address critical development needs. For example, CDMOs can assist with validating donor variability data, optimizing analytical methods, and facilitating technology transfer to manufacturing. By working collaboratively, innovators and their CDMO can align clear priorities, reduce risks, and create a smoother path to commercialization.

Risk management in cell therapy development is about avoiding setbacks and creating the best possible foundation for success. By leveraging stage gates, thoughtful strategies, and expert resources, innovators can confidently navigate the complexities of development. These efforts deliver high-quality, transformative therapies that improve patient outcomes globally.

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ABOUT KINCELL BIO

Kincell Bio supports innovative companies developing immune cell therapies, including autologous and allogeneic CAR-T, TCR, and Treg programs, as well as developing expertise in stem cell products and iPSCs. With manufacturing facilities located in Research Triangle Park, NC, and Gainesville, FL, Kincell Bio is a contract development and manufacturing organization (CDMO) with the mission to streamline CMC development, apply expertise in analytical and process development, and GMP manufacturing, testing, and release from early clinical to pivotal studies and product launch.

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