

## Integrating Analytical Method Development and Quality Control A Roadmap for Successful Advanced Therapy Development

In the rapidly advancing field of cell and gene therapies the complexity of the therapeutic products combined with the evolving regulatory landscape presents unique challenges. Analytical methods are critical tools in the development and manufacturing of these advanced therapies. Often designed for research and development, these methods must evolve to meet the demands of clinical testing, aligning with current Good Manufacturing Practices (GMP) to assess critical attributes like identity, dose, potency, purity, and safety. These assays are vital for confirming the product's quality at various stages—whether in-process, as drug substances, or as final drug products—while supporting product characterization, manufacturing investigations, and product release. Critical to the drug product life cycle is to have aligned and integrated Analytical Method Development (AMD) and Quality Control (QC) activities, helping to ensure a seamless method transfer. This alignment provides numerous benefits which may contribute to the successful development and commercialization of the drug product. Failure to appropriately align these activities could result in significant setbacks, potentially compromise product quality, and may ultimately delay time to market.

### The Challenges of Analytical Method Development in Cell and Gene Therapies

Cell and gene therapies are distinct from traditional small-molecule drugs in that they involve living cells, genetic material, and dynamic biological systems. As such, analytical methods for these advanced therapies must be sophisticated and adaptable to accommodate the complex nature of the therapeutic products. Some of the key challenges faced in analytical method development for advanced therapies include:

#### Complexity of Therapeutic Products

Cell-based therapies often involve a heterogeneous population of cells with varying degrees of differentiation, functional activity, and viability. Characterizing these cell populations to ensure consistency between batches is a significant challenge. Similarly, gene therapies involve the delivery of genetic material (such as DNA or RNA) to patient cells, which introduces complexities in tracking integration, expression, and stability of the genetic material over time.

#### Product Heterogeneity

The biological nature of both cell and gene therapies leads to variability between batches, which can affect product consistency. Factors such as the culture conditions, starting materials, or the vector production process can all introduce variations that need to be assessed using robust and reproducible methods.

#### Lack of Standardized Assays

Unlike small-molecule drugs or biologics, where platform assays may exist, there is often a lack of established or validated assays for many cell and gene therapies. This requires the development of new, tailored methods for each specific therapeutic candidate, further complicating the method development process.

## Safety Concerns

For gene therapies, there are several potential safety risks, including off-target effects, immunogenicity, and clonal expansion, which could lead to malignant transformation. Similarly, cell therapies that involve stem cells or modified cells may also pose risks related to tumorigenicity or unintended differentiation. Developing assays to assess potential safety risks is a critical challenge that requires continued development.

## Regulatory and Quality Control Requirements

Similar to all therapeutics, regulatory agencies such as the FDA and EMA have stringent requirements for cell and gene therapies, and the analytical methods used must be validated to meet these standards. However, the regulatory guidelines for advanced therapies are still evolving, which adds an extra layer of complexity to the development process.

## The Benefits of Integrating AMD and QC in Drug Development

Given the unique challenges posed by cell and gene therapies, integrating AMD and QC functions offers several compelling advantages. By aligning these two crucial areas, developers can streamline processes, ensure higher quality, and reduce risks throughout the development lifecycle. This integration is particularly valuable in the context of complex biologics, where precision, safety, and consistency are critical. The seamless coordination between AMD and QC not only optimizes the efficiency of drug development but also strengthens the foundation for regulatory compliance and long-term product success. Below are some of the key benefits to this integrated approach:

### Streamlined and More Efficient Development

When QC and AMD are integrated, the entire method development process becomes more efficient and can expedite assay development in a non-GMP state and move the assay through qualification and into a GMP state for routine QC testing. Both functions can work simultaneously, ensuring that analytical methods are fine-tuned and validated while real-time quality control checks are in place. This collaboration leads to proactive identification and mitigation of potential quality risk helping to facilitate a smoother transition from method development to routine quality control testing.

### Improved Robustness of Analytical Methods

QC teams play a vital role in providing feedback on the practicality of newly developed analytical methods. They can offer insights into the reliability, reproducibility, and sensitivity of methods under real-world quality control testing conditions. By integrating their input during AMD, analytical methods can be refined to ensure they are both scientifically robust and practically implementable in routine QC testing.

### Regulatory Compliance and Alignment

An integrated approach ensures that both AMD and QC teams are aligned with regulatory expectations from the start. Regulatory bodies such as the FDA and EMA require that analytical methods are thoroughly qualified and/or validated to ensure consistency and product quality. By working together early in the development lifecycle, the AMD and QC teams can ensure that methods meet Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP) standards, facilitating smoother regulatory submissions and approvals.

### Improved Data Integrity and Traceability

The early integration of AMD and QC creates a unified data ecosystem, improving the ability to track trends and maintain comprehensive documentation. This cohesive approach facilitates a smoother transfer to QC, easier audits, ensures data integrity, and supports regulatory compliance by providing a clear, traceable record of all testing and development processes.

### Faster Time to Market

With a streamlined development, and a more efficient process, integrated AMD and QC can reduce the time required to move from development to clinical production. This is particularly important in the rapidly evolving field of cell and gene therapies, where early access to therapies can have significant benefits for patients.

### Better Adaptation to New Technologies

Cell and gene therapies often involve cutting-edge technologies, such as novel gene editing techniques or advanced cell culture systems. An integrated AMD and QC approach provides the flexibility to incorporate new technologies quickly and effectively. Both teams can work together to develop new assays and testing strategies that are tailored to the specific needs of emerging therapeutic technologies, ensuring that the therapies remain at the forefront of innovation.

### The Pitfalls of Misaligned and AMD and QC

The integration of AMD and QC offers significant advantages, but misalignment between these functions can create several challenges that threaten the success of therapeutic programs. When AMD and QC operate in silos, critical gaps can emerge in method development and quality assurance, undermining the overall reliability, safety, and compliance of therapies. This is particularly problematic in the development of complex advanced therapeutics, such as cell and gene therapies, where consistency is crucial. Without alignment, the risks of increased costs, delays, and regulatory issues escalate. To mitigate these risks, it is essential to establish clear roles and responsibilities, especially for analysts who may have overlapping responsibilities. Effective communication, robust GMP training, and careful resource allocation are key strategies to ensure smooth coordination and compliance with industry standards. Early planning and prioritizing workloads can help address resource constraints and streamline the development process, preventing unnecessary delays or inefficiencies. Below are the key pitfalls of misaligned and non-integrated AMD and QC functions:

#### Inconsistent and Unreliable Analytical Methods

Without regular input from QC, analytical methods developed during AMD may not be optimized for practical, long-term use in QC testing. This can result in methods that are unreliable, inconsistent, or unsuitable for high-throughput testing, which ultimately affects product quality.

#### Regulatory Non-compliance

Disconnected AMD and QC functions can lead to incomplete documentation or gaps in validation and qualification. This can result in regulatory delays or even rejection of the product due to non-compliance with FDA, EMA, or other regulatory bodies' requirements.



### Longer Time to Market

When AMD and QC functions are not aligned, the process of method development, validation, and transfer to QC testing can become more time-consuming. The time required to reconcile the two functions can delay the overall timeline for product development, reducing the competitive advantage of the therapy.

### Increased Costs

Non-integration can lead to inefficiencies, duplication of efforts, and costly rework. If AMD methods do not align with QC requirements, additional rounds of method development and validation may be necessary, increasing costs and lengthening timelines.

### Compromised Patient Safety

Failing to address potential safety risks early in the development process can lead to compromised patient safety, especially in gene and cell therapies, where unintended genetic modifications or cell behaviors could cause severe adverse effects.

### Case Study and Conclusions

By integrating AMD and QC functions, Landmark Bio has created a collaborative, holistic problem-solving approach to analytical method development and quality control. This integration has streamlined method transfers, helped to facilitate a smooth transition from non-GMP to GMP unit operations, and has incorporated GMP standards earlier in method development. Additionally, the integrated approach has minimized the need for parallel teams, preserving subject matter expertise throughout the product lifecycle, and reduced training requirements by eliminating the need for arduous method transfers between teams.

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### About Landmark Bio

Landmark Bio is a cell and gene therapy manufacturing company committed to developing innovative technologies, products, and services that bridge the gap from bench to patient. <https://landmarkbio.com/>