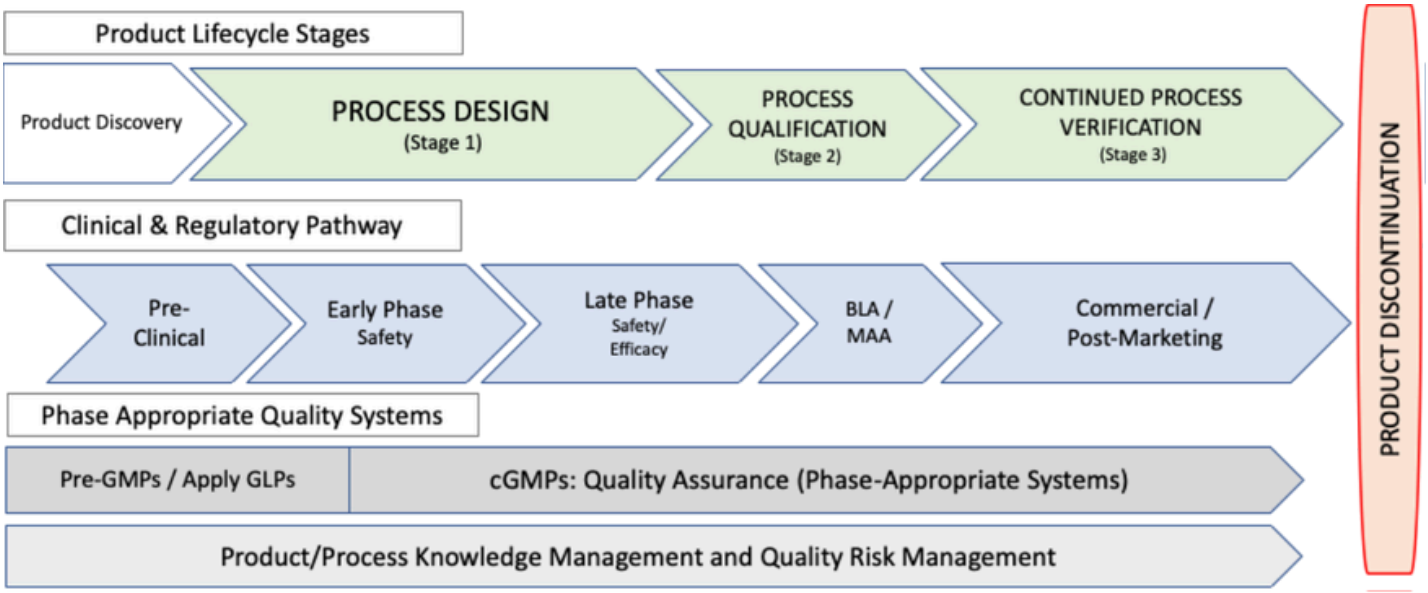
The Only Constant in Life is Change: Science-Driven and Risk-Based Approach to Managing Manufacturing Process Changes for ATMPs

"The only constant in life is change". This adage, attributed to the ancient Greek philosopher Heraclitus, feels especially relevant today as the field of Advanced Therapy Medicinal Products (ATMPs) inclusive of cellular-based, tissue-engineered, and gene therapies continues to accelerate. Managing process changes effectively is essential for organizations developing ATMPs, particularly as these therapies move rapidly through development toward commercialization. A structured, science-driven and risk-based approach ensures that these products remain consistently safe and efficacious for patients with diseases that currently have no treatment options.

Many organizations that are developing novel therapies like ATMPs can be reluctant to implement changes to a manufacturing process. This apprehension may be due to many reasons, namely, an immature or ineffective change management program and the pressures associated with a compressed CMC (Chemistry, Manufacturing, and Controls) development timeline due to accelerated clinical regulatory pathways. When performing a change to a manufacturing process throughout the stages of the product lifecycle, as shown in Figure 1, an organization needs to do so in a formal and controlled manner that is compliant with expectations of regulatory health authorities. A science-driven and risk-based approach should be employed to manage these changes. Poor management of a manufacturing change can potentially lead to deleterious impact to product quality (e.g., product batches failing to meet specifications) and unintended consequences elsewhere in the process, which in turn can lead to costly delays and failures in the progress of a clinical program, and even in some extreme cases, a regulatory hold.

Figure 1. Main Stages of the Product Lifecycle Aligned with Regulatory and Quality Pathways



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Processes for the manufacture of ATMPs are typically initially transferred directly from research to the cGMP clinical manufacturing environment. These processes tend to be based on a limited development history that may not be readily compliant with requirements for cGMP manufacturing. As product knowledge and process understanding is continually and rapidly gained based on learnings from process development and product characterization studies, as well as from manufacturing experience, there exists a need to modify and optimize the process in the pursuit of ultimately establishing a comprehensive and robust control strategy (which FDA has referred to as the "Cookbook" (1)) for commercial manufacturing. A high-level view of a holistic control strategy, which is a key output of the process design stage of the product lifecycle, is shown in Figure 2. The manufacture of ATMPs presents unique challenges due to the limitations in product knowledge and process understanding, limited product quantities, and complexity of the manufacturing processes, which can pose higher risk to product quality than for conventional biological products.

Figure 2. Elements of the Overall Control Strategy for the Manufacture of ATMPs



There may be many reasons for why changes to a process may be required through the product lifecycle. These changes reflect the natural maturation of a CMC program for an ATMP, as it progresses toward commercialization, including (but not limited to):

- Modification of process controls and equipment used in manufacturing unit operations including a change from manual to automated operations for more consistent process control.
- Reduction in process times to reduce turnaround times for timely delivery of personalized autologous therapies.
- Conversion of "open" operations to "closed" systems to mitigate aseptic processing risks.
- Expansion of production capacity to support late-stage clinical trials or commercial demand, including additional production suites or new manufacturing sites.

The expectations of global health authorities continue to rapidly evolve for the regulation of ATMPs. For significant process changes, where there is a high potential risk to product quality and process performance, global health authorities request the manufacturer provide a risk assessment

based on the specific changes proposed. The supporting activities may include an analytical product Comparability Study where the goal of the study is to show that the change does not adversely impact product quality (product CQAs) as well as potential impact to the performance of the manufacturing process (e.g., Critical Process Parameter, In-Process Controls, product yields).

The amount of knowledge required to support a process change is commensurate with:

- The type of change in terms of the potential impact of the change to product quality and process performance, where greater risk can be mitigated through more extensive development and validation studies.
- The stage of the product lifecycle as the organization progresses through development and into commercialization, where the bar becomes higher (i.e., regulatory expectations increase) to demonstrate that the change can be successfully implemented.

ICH Q5E (2004) (2) for many years has set the guiding principles for performing an analytical-based product comparability study to support major process changes. Additionally, the FDA guidance on manufacturing changes and comparability specific to human cellular and gene therapy products (2023) (3) identifies “using a risk-based approach to comparability studies” to support a major process change where “the extent of the analytical evaluation needed to adequately evaluate a manufacturing change in comparability studies generally increases with the stage of clinical development and product development and should be supported by knowledge of CQAs, accumulated manufacturing experience, and further understanding of the mechanism of action (MOA).”

Recently, the FDA published a guidance specific to human cellular and gene therapies (2026) (4) that highlights “using a risk-based approach to comparability studies” including where “the FDA recommends performing a risk assessment for all manufacturing changes to determine the impact on product quality” and “leveraging prior knowledge and experience to facilitate CMC development” in an effort to provide flexibilities in the manufacture of human cellular and gene therapy products.

Successful change management relies on two key enablers:

1. Knowledge Management (KM): the greater the amount of product knowledge and process understanding, the more objective and data-driven the assessment.
2. Quality Risk Management (QRM): potential risks to product quality and process performance need to be understood for the implementation of any change to a manufacturing process. The concepts and principles detailed in ICH Q9(R1) (5) thus must be employed.

Use of the principles and key elements of KM and QRM support a structured, science-driven and risk-based approach to effective change implementation.

Change in life is unavoidable. When managed properly, change can be a strategic advantage, not a source of risk, enabling efficient development and successful commercialization of ATMPs. In a future article, we will continue to explore the application of this science-driven and risk-based approach to the design of a product comparability study to support the evaluation of process changes with some examples unique to ATMPs.

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Documents referenced in this article:

1. "FDA's Efforts to Facilitate the Development of Cell and Gene Therapies" (CASSS Meeting on Cell and Gene Therapy Products) https://www.casss.org/docs/default-source/cgtp/2022-cgtp-speaker-presentations/marks-peter-cber-fda-2022.pdf?sfvrsn=386e1982_6
2. ICH Q5E Comparability of Biotechnology/Biological Products Subject to Changes In Their Manufacturing Process (November 2004)
3. FDA Guidance for Industry: Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products (July 2023)
4. FDA Guidance for Industry: Chemistry, Manufacturing, and Controls Flexibilities for Developing Human Cellular and Gene Therapy Products for a Biologics License Application (May 2026)
5. ICH Q9(R1) Quality Risk Management (January 2023)

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