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Structuring Your Quality by Design Framework

The impact of establishing clear objectives, dosing strategies, quality attributes, and critical process parameters early on.

The implementation of quality-by-design (QbD) principles remains a cornerstone approach to process development for cell therapies. This strategic, systematic methodology begins with clearly defined objectives, followed by building a comprehensive understanding of your product, processes, and controls through scientific rigor and quality risk management. Having well-developed drafts of your quality target product profile (QTPP) and critical quality attributes (CQAs), alongside a thorough understanding of how process parameters and material attributes impact them, creates the foundation for successful development. The following insights offer practical guidance on navigating the challenges unique to cell therapies while establishing an effective QbD framework that evolves alongside your product development journey.

Translating these principles into practice requires thoughtful preparation before entering clinical manufacturing. Defining your product profile and corresponding specifications becomes achievable when you begin with clear end goals and thoroughly understand your process capabilities. As David Smith, VP & Head of Development, notes,

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Define your goals early and refine them often. In an industry where innovation moves fast, breakthroughs come from coupling deep scientific expertise with the mindset of challenging conventions and progressing with bold determination.

- David Smith, VP and Head of Development

This approach creates a solid foundation for managing the complexities of development while maintaining scientific rigor and strategic flexibility.

While establishing QTPP and CQA will help you start to develop your process, it is not as cut and dry as it is for typical biologics. CQAs are not as well established for cell therapy. This is attributed to starting material variability, a relative lack of understanding of the mechanism of action, and reliance on surrogate measurements. Often, the link between the CQA and the clinical outcome is unknown.

The nature of cell therapies means that QTPP and CQA are inherently designed to evolve

throughout the development rather than being finalized early. Creating initial drafts of these frameworks provides essential structure by defining the design space and adequate control strategies for your process. These working documents, intended to be refined over the clinical lifecycle, enable you and your manufacturing partners to establish parameters that deliver process consistency and reliability while identifying opportunities for improvement. Throughout the clinical lifecycle, these frameworks should be adjusted to optimize process performance and outcomes. This iterative approach to QTPP and CQA development is fundamental to the quality-by-design philosophy, enabling continuous process optimization while maintaining appropriate controls at each stage of your product's journey.

Defining CQAs is an ongoing process of compounding data across the product lifecycle. The best data will always come from the most representative experiments. However, the earlier the phase of development the product is in, the more reliant on surrogate measures the experiments will be. That might mean using healthy donor tissue as a starting material as opposed to more relevant disease state tissue, or using small scale in-vitro studies versus human trials. It is important to remember that product development is a process, and your target product profile and quality attributes should evolve as more relevant data is obtained.

Aiming for a well understood and characterized process and initiating your potency assay development from the outset will also help you establish your CQAs as best as possible — with the understanding that you will continue to refine both your process, its parameters, and better define your critical quality attributes as you continue through the lifecycle of maturing your product.

Moving past the difficulties of QTPP and CQA specifications through collaboration

The regulatory pathway for many cell therapies is still being fully defined, and agency expectations continue to evolve. They are typically unique products with profiles that require a custom quality control strategy. That is why, as opposed to having your QTPP and CQAs perfectly defined from the very beginning (which, as we noted earlier, is a near impossibility), the best approach is to create a dialogue with your chemistry, manufacturing, and controls (CMC) team and the regulatory body governing your location.

This framework translates into a collaborative CMC relationship between the therapy sponsor and manufacturer. Questions, such as which traits one can know and must know going into your current phase of production and how it fits into the quality-by-design strategy, are brought to light to help drive a deeper understanding of process control, product consistency, and regulatory expectations – ultimately paving the way for a more reliable and repeatable manufacturing strategy.

Quality by Design is not about managing product development with rigid expectations, it's about structured flexibility, applying a risk-based approach (QRM), and progressing with recognition and understanding of the dynamic between your product and process. In early-

phase development, the full picture of your QTPP and CQAs may not be clear, but through targeted experimentation, ongoing analysis and characterization, we can hone our approach over time. The key is ongoing dialogue between innovators, manufacturers, and regulatory bodies to align on what is possible today and what must evolve as we go forward.

- Chithkala (Ck) Harinarayan, VP & Head of Quality & Compliance

Quality-by-design is a data-driven approach, but because there is a limited data set during the early-phase of clinical trials, you may develop your current product profile without knowing how it will translate into robust CQAs. The key to navigating these uncertainties is fostering an understanding that you will not know everything from the moment you start. It is important that you have an open dialogue between your regulatory experts and manufacturing sites, so that both parties are aligned on what you can analyze, what you are looking for, and what the governing regulatory bodies' input into your approach will be.

The quality-by-design process can be enhanced by implementing process control strategies early on and defining potential critical process parameters (CPPs). Critical process parameters indicate if the final product will meet all quality attributes. Some examples include the cell number at the beginning of the expansion step and pre-formulation cell viability. For many, CPPs are likely beyond what can be defined as you enter GMP manufacturing, but the goal should be to continuously add further definition as you progress to ensure a smooth transition into higher volume production.

At **Made Scientific**, we work alongside your team to optimize your current process to a scalable, future-ready state. Following knowledge transfer of the existing process, our team applies a QbD product strategy that is robust, phase-appropriate, and in support of commercial viability. With proven expertise in process and analytical development for cell therapies, we are laser-focused on optimizing yield and cost efficiency while maintaining sound science, engineering principles, and cGMP standards.

About Made Scientific

Made Scientific is a leading cell therapy contract development and manufacturing organization (CDMO) dedicated to advancing the field of cell therapy. Since 2019, the company has specialized in developing, manufacturing, and releasing autologous and allogeneic cell therapy products for early- to mid-stage clinical trials, and has evolved into an end-to-end clinical-to-commercial service provider. Operating from two U.S.-based manufacturing facilities, Made Scientific combines the flexibility and entrepreneurial spirit of a specialist CDMO with the global expertise and resources of GC Corporation of South Korea, a global leader in the pharmaceutical and biotechnology sectors.

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