MADE SCIENTIFIC

Structuring Your Quality by Design Framework

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

A prevalent dialogue in the biotech industry today is the urgency to implement a quality-by-design approach to process development work. Quality by design is a strategic, systematic approach to development and manufacturing. It begins with predefined objectives. From there, you build an understanding of your product, processes, and controls through application of sound science and quality risk management. Having a draft of both your quality target product profile (QTPP) and critical quality attributes (CQA) in place — and having a firm handle on how your process parameters and material attributes impact them — is a must.

While that is easier said than done, the work that needs to be completed before you move into clinical manufacturing, in terms of defining your product profile and corresponding specifications, can be achieved by beginning with an end goal in mind and understanding your process capabilities as much as possible.

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

While establishing QTPP and CQA will help as 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 and a lack of understanding mechanism of action, as well as reliance on surrogate measurements. Often, the link between the CQA to the clinical outcome is unknown.

These challenges make it extremely difficult to have a QTPP and CQA finalized early on, but you can create drafts of QTPP and CQAs with the understanding that they will be modified as you learn more about your product and process. These drafts provide the framework you and your manufacturing partners need to evaluate and better understand whether the process is consistently and reliably delivering the anticipated outcomes — and if not — why they are not doing so. Without these drafts, it is difficult to perform that analysis and work on continuous process improvements.

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.

Convenient shortcuts — and why you shouldn't take them

Most people take shortcuts when trying to minimize their timelines. While this is a misstep, it is understandable given the pressures placed on early-stage biotech companies from their stakeholders and investors to advance their pipeline and move from development to clinical proof of concept quickly, with often constrained capital investment.

Unfortunately, process characterization is the area in which most companies try to save time on — a dangerous shortcut. Put simply, companies are set up with surprises down the line, when shortcuts or abbreviated development, pilot and engineering runs are not conducted robustly to fully understand potential variability in the manufacturing process and its sources.

The reality is that variables in patient-starting material and raw material have a major influence on your product characteristics. As a result, these variables also influence how well-defined your process parameters, critical quality attributes, and even release specifications are when you start. If you do not allow yourself enough time and budget to fully explore that potential variability in the beginning, you put yourself at risk of incurring far more costly delays, rework, and scrapped batches during GMP or clinical manufacturing.

Another common point of variability is using research-use only material to reduce timelines or avoid upfront costs for GMP-grade materials. While acceptable for early-phase products, the red flag here is a failure to spend enough time doing a proper comprehensive risk assessment to demonstrate the quality and safety of your raw materials, which can later lead to process variability or potential clinical disruption. Research-grade materials should be established as like-for-like with potential GMP alternatives, and critical material attributes (CMAs) must be established. Otherwise, costly comparability studies will be required.

A third shortcut to resist is trying to save time by delaying development of your potency assays. If you can afford to invest enough time in developing a matrix of potency assays, your program will greatly benefit, and when you reach the stage of your program where true potency is required, you will find the initial investment of time pays off in spades.

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 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

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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 critical process parameters (CPPs). Critical process parameters are the in-process results that indicate if the final product will meet all quality attributes. Some examples include the cell number at the beginning of the expansion step, pre-formulation cell viability, and post-transduction engineering efficiency. 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 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 commercially 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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