Roundtable Session 2 - Table 8 - QbD Tools for MAbs Don`t Quite Work for CGT Products

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Abstract

Recent product approvals & positive clinical outcomes has resulted in the increased investment in CGTs which has in turn led to an accelerated pace of activity and aggressive milestones. CBER estimated there are presently well over 1700 active clinical trials; there are 32 currently approved (were 17 in March 2021) CGT products on the market. CMC continues to be the major reason CGT products are held back from regulatory approvals. Several companies have publicly acknowledged CMC-related challenges for e.g. BMS-RTF for ide-cel BLA and Kymriah that has approximately 10% failure rate of products not shipping to patients due to manufacturing failures. Manufacturing solutions for CGT products are non-standard and are still emerging. They typically evolve with industry offering as well as clinical stages. To complement the maturation of CGT manufacturing, the approach to development must also mature. We would like to possibly consider discussing a QbD based framework for ongoing phase-appropriate innovation in both product & process development as well as manufacturing. With this proposed discussion we hope to be able to identify critical attributes, plan characterization studies and focus development efforts that will eventually help us to demonstrate product and process understanding.

Discussion Questions:

1. Can a QbD approach be applied for the development of CGT products?
2. What are the challenges when applying an enhanced development approach for CGT product development?
3. What elements from the ICH Q8 guideline can be used for a systematic development of CGT products?
4. What primary tools have you developed for the application of an enhanced development approach?
5. What are the key factors to consider when establishing an enhanced development approach for CGT products?

Round Notes:

Enhanced development

Quality by design (QbD) approaches, which have been established for biologics and synthetic products, may not directly apply to cell and gene therapy (CGT) products. This is due to the fact that within CGT, a majority of the products are not well characterized, and in many cases, the quality attributes are unknown until more information unfolds during clinical development.

However, there was an overall consensus among the participants that the application of QbD concepts would still be beneficial for CGT products. It was agreed that while a design space may not be within the scope of the QbD approach, an enhanced development using tools that enable systematic assessment and development is necessary. One sponsor shared their experience regarding the use of Design Space claims, which ultimately resulted in a significant increase in regulatory documentation. Unfortunately, this approach did not effectively substantiate the goal of reducing regulatory burden throughout the product life cycle. For CGT products, even though product knowledge is currently lacking, the use of tools and a systematic approach are beneficial as at a certain point, a control system needs to be established.

One such tool used within the QbD approach is the Target Product Profile (TPP) / Quality-TPP (QTPP), which guides development in a prospective fashion, in accordance with ICH Q8. However, only a small number of participants at the table reported using a QTPP to guide CGT product development. If a QTPP is in place, it is considered a document with a life cycle, and some companies perform an annual review of the QTPP. It was agreed that the QTPP should not be part of the regulatory submission at early stages.

Currently, there is limited understanding of the structure/function relationship, and a systematic thought process will help facilitate the acquisition of more knowledge. Additional characterization of the product and enhanced understanding will also enable successful comparability approaches.

The participants at the table reached a consensus that the publication and sharing of data at conferences should be encouraged and supported by sponsors.

In summary, an enhanced development and thorough characterization of CGT products are critical to elevate process and product knowledge, which in turn will contribute to the maturity of manufacturing process and control system development.