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FROM SOURCE TO PRODUCT: STARTING MATERIAL CHALLENGES IN ATMP DEVELOPMENT

Cellular starting material in ATMP manufacturing

A challenge that many developers of ATMP products are faced with is the selection and qualification of starting material. The large diversity of ATMP products requires a tailored strategy for each product, whether you are working on an autologous or allogeneic cell product, a gene engineered product or expanded and differentiated cells. Cell based ATMP manufacturing starts with human cells, that inherently vary. High quality starting material is key for the quality of the final drug product and one of the challenges is to develop a strategy to manage donor variability and its impact on the manufacturing process. In this blog we will dive into the regulatory framework around starting material for ATMPs and how to approach the development of an appropriate control strategy.

Defining your starting material

A large diversity of Advanced Therapy Medicinal Products (ATMP) exists, including cell-based products manufactured from primary cells or expanded and differentiated cells to gene therapy products like naked plasmid DNA, viral vectors and genetically modified cells. Starting material for ATMP is defined as all materials from which the active substance is manufactured or extracted. For viruses or viral vectors, the starting materials are the components from which the viral vector is obtained, e.g. master virus seeds or the plasmids used to transfer packaging cells. For products that consist of plasmids, non-viral vectors and genetically modified microorganisms other than viruses or viral vectors, the starting materials are defined as the components used to generate the producing cell, thus the plasmid, the host bacteria and the master cell bank of recombinant microbial cells. For genetically modified cells, starting materials comprise the vector, the material to produce the vector and the cells themselves. The manufacturing of cell based ATMP often begins with human tissues or cells, which inherently vary. This variability must be managed during the development process to ensure a consistent final product.

In this blog, we will focus on the challenges with human tissues and cells as starting material for ATMP manufacturing. Different strategies will apply for autologous versus allogeneic products, since differences in risks for safety, efficacy, manufacturing and quality control could be identified, e.g. in batch size (one or multiple patients treated with one batch), immunogenic potential, testing possibilities (testing of actual batch or surrogate) and starting material consistency (patient donor versus healthy donors). Good insight in these risks and aids with the selection of the best vendor matching your needs and assuring safety for donors and patients.

Regulations and GMP

Global regulations and guidelines

Regulatory guidance for cellular starting material differs around the world. In the US, the FDA Code of Federal Regulations requires collections sites to establish procedures to control all documents required for the entire cellular process, including processing and storage. In collaboration between the US and Europe, the Foundation for the Accreditation of Cellular Therapy (US based) and the Joint Accreditation Committee of ISCT and EBMT (EU

based) set evidence-based standards (FACT-JACIE standards) for cellular therapy product collection, processing and administration. Those institutions have attempted to generate the standards conform the existing US federal regulations and the requirements of the EU directives, and are accepted in many countries across the world.

EU legislation regarding primary cell starting material is outlined in Directive 2004/23/EC[1] and Directive 2006/17/EC (tissues and cells, excluding blood and blood products) or Directive 2002/98/EC[2] (blood and blood products). These directives cover donation, procurement and testing of the tissues or cells and the tissue establishment responsible for these activities should be authorized under this legislation. It is to be noted that these activities thus fall outside of the GMP guidelines as described in EudraLex volume 4[3].

Selecting your supplier

Tissue establishments are responsible for donor selection, procurement and testing of the starting material and should ensure traceability at every step, from donation until distribution or disposal. This is important to ensure donor and patient safety throughout the process, ensuring quality and compliance with the requirement of voluntary and unpaid donation (in EU). Donor screening and testing is required in most instances. In case of allogeneic products this is crucial for product safety. Also, the manufacturer often require testing to minimize the risk of bringing in pathogens into their facilities.

While a GMP certificate is not required for the procurement of starting materials, compliance with GMP principles is essential. In the case of ex-vivo genetically engineered cells, where cell procurement falls outside GMP guidelines, plasmid and vector manufacturing must follow GMP principles, and the final cell product must comply with GMP.

As sponsor, you are responsible for vendor selection and qualification. In agreement with the selected supplier, you work on the establishment of quality requirements (specifications) for the cellular starting material.

Control Strategy

The quality of starting material is key in the production of ATMP and early planning with a Quality Target Product Profile (QTPP) is recommended.

With a focus on controlling parameters affecting Critical Quality Attributes (CQAs), the use of a QTPP helps identifying process outcomes. To perform a meaningful risk assessment, a thorough understanding of the process is essential, supported by reliable analytical methods. Donor qualification, especially for allogeneic materials, can improve the quality of starting material and therefore enhance the robustness of the manufacturing process.

Depending on the product characteristics, additional testing might be needed compared to what is described in the applicable directive. Starting material qualification should include safety testing like sterility, infectious diseases, and other relevant criteria, e.g. mycoplasma, viability and additional characterization e.g. cellular composition.

Drug products should be free of adventitious agents and the cellular starting material is a possible source for contamination. Therefore, appropriate testing (compliant with ICH Q2 (R2)[4] throughout the process must be performed to maximize the chance of detecting contaminants. This should all be reflected in your control strategy. When results of a test required to release the starting material take a long time, e.g. a sterility test, it is allowed to start manufacturing before the results of required test are available. In this way it is possible to start manufacturing with fresh leukapheresis material. In that case, a risk assessment should be performed and the final drug product can only be released when results of these tests are available and within the pre-set acceptance criteria.

A well designed control strategy considering the quality of the cellular starting material and appropriate testing throughout the process, supports the quality and robustness of your process and will result in a lower risk for batch failure.

What can we do for you?

3D-PharmXchange can provide valuable support in this area. We have broad experience with a variety of ATMP products. We can support you in the development of autologous and allogeneic (engineered) cell therapy products and work out a strategy to source and qualify high quality starting material for each phase of your program. With our network of suppliers in the US and Europe, we can offer customized strategies to meet the specific needs of your project.

Conclusion

Successfully navigating the complexities of drug development requires a thorough understanding of the key aspects involved in each stage. With the right knowledge, strategies, and support, you can overcome challenges and achieve your goals. We can support you in navigating the landscape of suppliers and use our network to help you with vendor selection and qualification. At 3D-PharmXchange, we are committed to guiding you through every step of this journey. Contact us today to learn how we can assist you in your drug development projects.

Stay updated with the latest insights and developments by subscribing to our blog and following us on LinkedIn. Let's work together to bring innovative therapies to the market.

References

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