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WHITE PAPER

CMC Considerations in Development of Cell Therapies

Cells as living entities have unique properties and are being leveraged as potent therapies to treat diseases in a way that conventional therapies cannot, like CAR-T therapy for B-cell malignancies. There are currently twenty cell therapies (ten autologous and ten allogeneic) approved by the US Food and Drug Administration (FDA)[1]. Many cell therapies have been approved by the European Medicines Agency (EMA), and other regulatory agencies around the world as well. Cell therapies are either autologous, allogeneic, or xenogeneic and involve manipulation or *ex vivo* processing of living cells. Manufacturers should ensure adequate quality, safety, purity, and potency of the cell therapy product while maintaining compliance with global and local health authority policies and regulations[2]. Critical Chemistry, Manufacturing, and Controls (CMC) considerations are required to be considered in the development of cell therapies and their respective application (investigational or marketing) submissions[3]. In this article, we will take a closer look at the various components involved in the production of a cell therapy product and how you can minimize the regulatory compliance risk for your firm.

Cells

In the case of autologous cells, donor eligibility determination is not required, although precautions should be in place and manufacturing procedures need to be controlled to prevent the spread of adventitious agents to persons other than the autologous recipient. While for allogenic cells, donor screening and testing should be performed for adventitious agents such as human immunodeficiency virus, hepatitis B virus, syphilis, human T-lymphotropic virus etc[4]. using health authority cleared testing kits. Master or working cell banks need to be characterized enough against set specifications to adequately establish the safety, identity, purity, and stability of the cells.

Excipients & Ancillary Materials

Components present in the final product other than cells are called excipients (such as 0.9% sodium chloride injection, human serum albumin, dimethyl sulfoxide). Reagents used in the manufacturing of cell therapy products (such as cell growth media, media components, fetal bovine serum, trypsin, digestion enzymes, antibiotics, cell washing/purification buffer) and processing devices such as vessels and transfer tubing sets are called ancillary materials. The quality of excipients and ancillary materials is critical as they have a direct impact on the quality, purity, and potency of the final product[5]. For instance, a poor-quality animal/human origin material can add adventitious bacterial and/or viral agents to your final product.

It is strongly recommended to use health authority cleared or licensed materials as excipients or ancillary materials. At a minimum, these materials need to be of GMP/ISO grade and sufficiently qualified for safety, purity, (free of adventitious agents, endotoxins, mycoplasma) and functionality. Proper relevant certifications (i.e.: TSE/BSE, CoA, GMP/ISO compliance certificate) need to be provided in regulatory applications. The sourcing of Phase 3 clinical supplies is very critical, and the facility should be prepared for commercial supply as well. Considering risk of patient hypersensitivity, the use of beta-lactam antibiotics in manufacturing of cell products is discouraged. Manufacturers should ensure they are not present in the final product. Performing a risk-based impact evaluation of critical material attributes on critical quality attributes of the final cell therapy product is recommended.

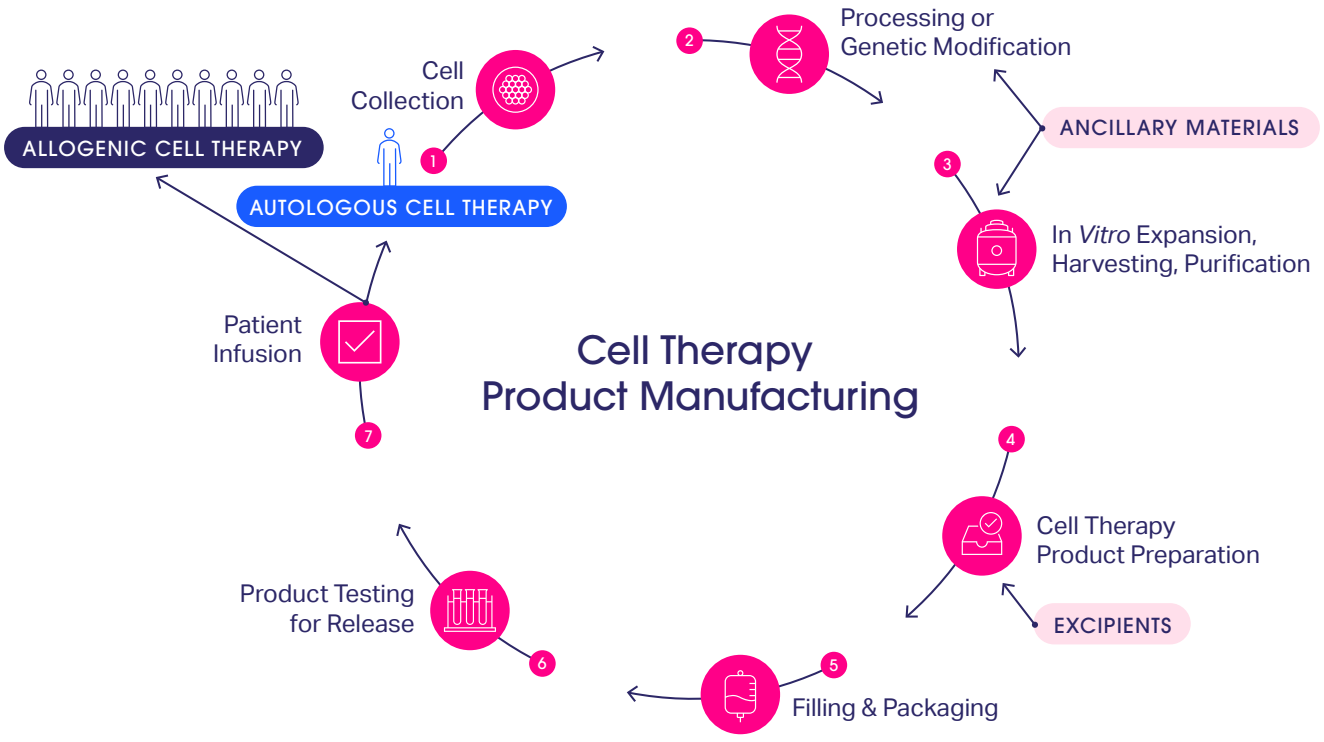
Product Manufacturing and Controls

Cell therapy products are not usually amenable to extensive purification, filtration, and terminal sterilization procedures; therefore, manufacturers need to adopt strict aseptic manufacturing procedures during cell collection, processing, production/in *vitro* expansion in bioreactors, harvesting, purification and storage of the cellular therapy products. Critical process controls need to be established and adopted considering the critical quality attributes of the final cell product. Standard operating procedures (SOPs) covering manufacturing procedures and controls in manufacturing facilities need to be established and compliant with current good practices (cGxP)[6].

Product Testing

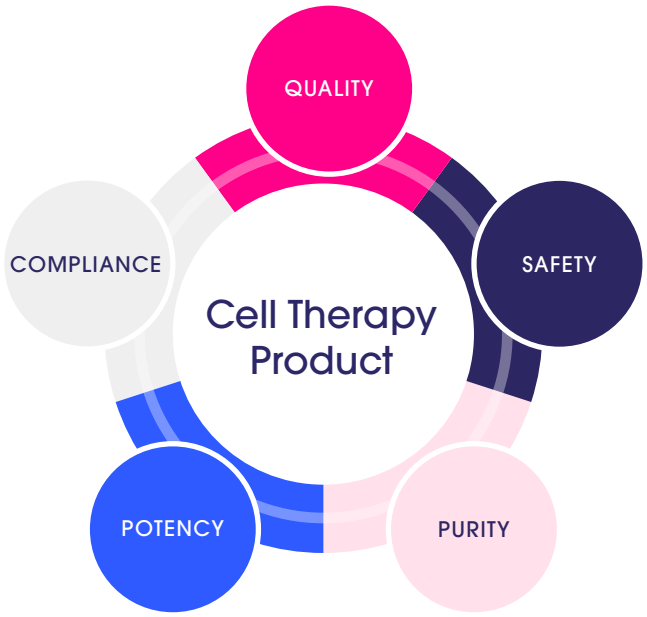
Manufacturers need to establish in-process and final product specifications and relevant testing methods or assays to ensure quality, purity, and potency of the product and lot-to-lot consistency. Cell products are tested for identity, clonality (if applicable), viability, cell number per dose, potency, microbial content (sterility, endotoxin, mycoplasma, and adventitious viral agent), and residual reagents that may be present in the final product[7]. Testing method qualification and validation requirements, product or process specifications, and the level of data required to support the application depends on the clinical development stage. A CMC expert can provide guidance on global requirements for various cell therapy applications.

Final product release testing results should be available prior to human administration. Due to the short shelf life of many cellular products, it is not feasible to complete compendial release tests such as USP <71> Sterility, USP<85> Bacterial Endotoxin, and USP<63> Mycoplasma. Alternative sampling before final harvest or alternative rapid microbial test needs to be employed on such cell therapies. Manufacturers need to select GMP compliant, sensitive, specific, and reliable testing instruments and methods. It is recommended to work with a CMC expert who has experience in guiding development of short-lived cell therapy products which need to be administered as quickly as within 6 hours of harvesting.



Delivery Device & Container Closure System

Manufacturers need to demonstrate compatibility of the cell therapy products with container closure system[8]. Biocompatibility and dose accuracy data for the intended device delivering the final product should also be performed. The device and system will also need supporting documentation demonstrating adequate sterilization, among other requirements. Data demonstrating the suitability of the delivery device for its intended use by evaluating how passage of the cells through the delivery device affects the final cellular product is also required.



Stability

Manufacturers should demonstrate that the stability of a formulated cell therapy product in its final container closure system remains stable and meets specification through the intended shelf-life[9]. Critical quality attributes (CQAs) should remain within the acceptable limits for quality during storage and transport to the clinical site and until human administration. A stability protocol is developed based on the type of cell therapy and covers the duration of the clinical study and/or intended shelf-life. Depending on the stage of development, the data required in the submission package will vary for each application. A qualified CMC expert can advise on how to navigate this process with regulators.

Conclusion

While presenting unique challenges and regulatory requirements, cell therapies have exciting possibilities in treating several unmet medical conditions, and the cell therapy industry is continuously growing. A successful regulatory CMC strategy and its implementation is critical to the overall success of the project while saving a significant amount of time and money for your organization. Working with a qualified CMC expert can aid in accomplishing your goal of bringing cell therapies to patients quicker by providing strategic guidance through all stages of product development and enabling a successful health authority application.

References

[1] US FDA website: Approved Cellular and Gene therapy Products

[2] Guidance for Human Somatic Cell Therapy and Gene Therapy. US FDA guidance for Industry.

[3] Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs). US FDA guidance for Industry

[4] ICH Q5A (R1): Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin.

[5] USP 1043: Ancillary Materials for Cell, Gene, and Tissue Engineered Products

[6] ICH Q10: Pharmaceutical Quality Systems

[7] ICH Q6B: Specifications: Test Procedures and Acceptance Criteria for Biotechnology/Biological Products.

[8] Container Closure Systems for Packaging Human Drugs and Biologics. US FDA guidance for Industry

[9] ICH Q5C: Quality of Biotechnology Products: Stability Testing of Biotechnological/ Biological Products.

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