A perspective on GMPS for cellular therapy commercialization

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Introduction

Many current therapeutic treatments are not able to address the underlying cause of a disease, alter its course, or reverse damage that has already occurred. Cellular therapies offer the potential of the human body to heal and regenerate itself. Regulatory precedents for cellular therapy products continue to evolve for a widening array of product of types. This article will review the new frontier of cellular therapies from cell source to commercial manufacturing requirements.

Cellular therapies can be classified by their therapeutic indication, by whether they contain cells taken from and administered to the same individual (autologous), or derived from a donor (allogeneic), and by their cell types. The regulatory classification of cellular therapies differentiates between minimally manipulated cells for homologous use, transplants or transfusions, and those more than minimally manipulated which are regulated as medicines. Medical cellular therapies are required to demonstrate quality, safety, and efficacy standards to obtain a marketing authorization (1-8). These medical therapies can be subdivided into somatic cell, gene therapy, and tissue engineered products. They can be manufactured from autologous or allogeneic donors and can also contain non-cellular components for example chemical or biological compounds and matrices.

Off-the-shelf allogeneic products are based on cells obtained from healthy donors that are modified with gene editing to knock out functions, such as immune rejection responses. These modified cells are then expanded to produce large quantities of product that can be frozen and stored for use when needed by many different patients. Patient-specific cell therapies are most often autologous, but can also be allogeneic, from a donor matched to the patient to avoid immune rejection. The key difference for patient-specific cell therapy from off-the-shelf products is the need for patient-specific cell therapies to use a separate manufacturing batch for each patient. Gene editing has been

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proven successful for commercial patient-specific cell therapies, such as in adoptive cell transfer with Chimeric Antigen Receptor T Cells (CAR-T)

Regulatory requirements

Regulations for minimally manipulated cellular therapy products are already in place. These regulations focus on the prevention of the introduction, transmission, or spread of communicable diseases. There is a requirement for establishment registration, donor eligibility standards, and that cellular products are processed with current good tissue practices (1-8). Medicinal cellular therapy products are regulated as drugs, medical devices, and biological products which adds the regulatory requirement of manufacturing under current good manufacturing practice (cGMP) conditions (9-11). As medicinal cellular therapies move from clinical to commercial manufacturing, regulatory agencies are evolving regulations using a risk-based approach. Regulations are in the process of being established that will permit the manufacturing of safe and effective cellular therapy products. Scientific and technical developments are still needed to aid companies in applying processes for cGMP manufacturing and quality control of these products.

Cell source

Source cell variability must be addressed to assure product consistency. Some manufacturers of patient-specific products provide both detailed training and specialized collection kits to address source cell variability. With the high value of source cell material, having ample amount for process-development and validation of the manufacturing processes is an industry challenge. Furthermore, limited shelf life and quantity of cells can complicate quality control testing and stability determinations. Banked cells must be extensively characterized for potential contamination with microbial or viral agents and for tumorigenicity. Determining Critical Quality Attributes (CQAs) for products and developing assays for their potency are essential to the commercialization of cellular therapy products. Characterization of both the starting source cells

and final cellular product is important for both autologous and allogeneic therapies. Source cells are characterized based on the presence of surface markers, size, and combinations of attributes associated with cell source and mode of action. Optimal cellular characterization is essential to increase accuracy of cellular specific population selection for the production of cell therapies.

Autologous or allogeneic cellular therapies

In general, medicinal cell therapies are categorized as either autologous or allogeneic. Autologous and allogeneic products exhibit different features and represent different challenges in the manufacturing of safe and efficacious products. Autologous product challenges include patient variability and the need for small scale manufacturing lots. Benefits exist for immunogenicity because of the patient-specific nature of these cells. Allogeneic products are considered to be less complex, often having banks of cells that can be characterized for safety and scaled-up for mass-produced universal product-s for a large number of recipients. Complications for such allogeneic products include potential immunogenicity (either from the recipient in which case the cells only survive for a short time after administration or graft versus host reaction) or tumor formation and the development of appropriate manufacturing platforms.

For autologous cellular therapy, the patient is both the raw material source and the recipient, so the focus is on the collection, processing, and re-administration of the cells from and to an individual patient. Autologous therapies are advantageous for patient safety in that there is no concern about graft-versus-host disease. For these therapies a closed manufacturing system should be used to reduce the risk of product contamination. Individualized batch records for processing documentation should be accessible at the collection point and trace the material via the entire life cycle including during the shipment, manufacturing, and through to patient administration. Because many of these therapies are time sensitive, it may be feasible to process the cells using an automated system used by a health care professional at the site of the collection. This could include cell collection, characterization, processing for example with viral transfection, and re-administration.

Allogeneic cell therapies have common donor cells as the source of treatment for many patients. Donation logistics can be complex if the number of cell expansions is limited, and thus additional collections from the same donor maybe required. Allogeneic product manufacturing is more feasible for automation cell processing because the cells are obtained from a universal donor. Scaling-up production from development scale to manufacturing scale can be challenging because of the involvement of different processing systems for cell expansion, volume reduction, and harvest. Manufacturing equipment used in the scaled-up manufacturing paradigm such as single-use bioreactors with microcarriers may not yield the same product potency as flasks and trays used for research and development.

Collection and processing

Raw materials and components used in manufacturing cell therapies must be carefully evaluated. These include media components, matrices for cell attachment, culture vessels, tubing sets, bags and other disposables. Testing culture vessels, tubing sets, and bags for extractables and leachables is required because such materials can potentially affect cell growth and viability as well as patient safety. Recombinant serum proteins should be used in replacement of animal and human derived serums to avoid the risk of bacterial and viral contamination. Vendor qualification procedures should be well established. These procedures include vendor screening, a site audit, a Quality Agreement and vendor monitoring. Each new lot of component materials should be tested and have an accompanying certificate of analysis, generated by the vendor, to ensure that they meet specifications.

The health care professional who perform the collection procedures are typically not trained in cGMP regulations. Collection documentation should become part of the cGMP record including any electronic data generated from the collection equipment and any on-site testing. The cell manufacturing location depends on the type of cell product and the product's application. Whether a bedside point-of-care or a centralized manufacturing model is most appropriate should be based on indication and the stability of the product.

Cell therapy manufacturing performed offsite from the collection location requires strict control in cGMP facilities. This includes the manufacturing space, the storage warehouse for raw and finished product and laboratory areas (12). Cellular therapy manufacturing facilities must be designed for aseptic processing. Development of fully enclosed manufacturing equipment and built-in controls for in-process testing is optimal for cellular processing.

For the manufacturing facilities, the prevention of contamination microbiological or cross-product contamination due to raw material, environmental conditions, or handlers is essential. The establishment of robust methods for container sterilization and the control of raw materials and reagents is important. The use of high efficiency particular absorbing filters and manufacturing in a clean room aids in the prevention of airborne cross-contamination of materials from environmental contaminants or other products. Parameters such as temperature, humidity, and pressure should be monitored because of their impact on particle generation and microorganism proliferation. Materials and staff flows should be separated and be unidirectional to minimize cross-contamination. The operators should be trained in aseptic processing technique for clean rooms (13).

Feedback automation processing is optimal for the manufacturing of cellular therapies. The variability of source cell properties would be best addressed with a manufacturing process that is flexible and adaptable to ensure that the end products are of the same quality and consistency. The feedback can control culture conditions in-process based on real-time measurements of CQAs (14). The integration of in-line assays and measurements for CQAs, as

well as, rapid measurements of potency, efficacy, and safety parameters are important elements for automation of the cell manufacturing process and will enable the establishment of robust CQAs. Each batch of a cellular therapy product should pass very specific tests unique to the characteristics of the product. Additionally, tumorigenicity, and biocompatibility testing should be performed where appropriate (15, 16). Furthermore, extensive characterization of the product is essential for proper process validation and the development of in-process and release testing specifications.

The manufacturing of therapeutic cells does not allow for terminal sterilization of the product or removal of microbial contaminants via filtration. Therefore, testing of starting materials and validated aseptic manufacturing processes are important to ensure that the products are free of contamination. Sterility testing for the absence of the bacteria, mycoplasma, and fungi should be conducted at product release whenever possible. Some cellular products require release and administration to patients prior to the completion of all required compendial testing. Rapid test methods may be used. For example, mycoplasma detection based on polymerase chain reaction and rapid microbial detection methods have been used in release testing of cell therapies as these methods enable earlier read-outs on potential microbial contamination. A fourteen day sterility test is still required to be completed even after the administration to the patient.

Living cells are dynamic, can continue to grow, differentiate, migrate, and interact within the body. Characterization of the cell population prior to administration does not fully describe the phenotypes and genotypes of cells in the patient after cellular treatment. Characterization and CQAs should be redefined based on feedback from patient data and improved understanding of mechanisms of action as patients are monitored post-treatment.

Using post-treatment patient data to understand the most effective therapeutic cells may lead to decreased numbers of cells necessary for treatment and manufacturing timelines.

Distribution procedures

Most cell therapies will not remain viable at ambient temperature over an extended period of time. This applies to both allogeneic and autologous cell therapies. Autologous cellular therapies are additionally challenging when patient cells need to be transported to a processing facility and processed cells are then sent back to the patient for treatment. Allogeneic products that are stable enough to be shipped globally could be supplied from a single central manufacturing site, thus providing efficiency and consistency. However, products with limited stability, both autologous and allogeneic, may require a distributed model in which manufacturing occurs in multiple regional centers or are even at the site of treatment. The shipment of cellular therapy products needs to be validated and temperature-monitored. Chain of custody and cellular environmental condition records should continue from collection through to administration.

Conclusion

Cellular therapies may offer the potential to move beyond conventional disease treatment by addressing the underlying cause of disease, altering its course, or reversing damage that has already occurred. The transitions from discovery, to research and development, to commercially manufactured products brings the challenge of the regulatory requirements for incorporating cGMP regulations into the collection, production, and delivery of these products. The cGMP regulations for this new frontier in regenerative medicine will be defined with a collaboration of clinicians, manufacturers and regulatory agencies. These developments will allow for cellular therapy treatments to become increasingly available to patients and will offer new treatments and the hope to cure many diseases.

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