Project-Based Regulatory Strategy & Submission Services

GENE AND CELL THERAPY PROGRAMS

Mainly based on starting materials of human origin and often produced with sophisticated manufacturing processes, these advanced therapy medicinal products involve complex procurement, testing, processing, preservation, storage, and distribution. They require sequential testing and release from raw and starting materials to the drug product, as well as an adapted control strategy.

Overcome complicated and unique challenges in the development and commercialization of your New Active Substances (Gene and Cell Therapy) program. We supply sponsors with regulatory recommendations on how to provide enough CMC information to assure the safety, identity, quality, purity, and strength/potency of investigational gene therapy products.

In addition, we aid in gene therapy investigation of new drug application submissions. These regulatory submissions apply to human gene therapies and to combination products that contain a human gene therapy in combination with a drug or device.

With enthusiasm continuing to grow around these novel therapies, it is imperative to understand and assess the Chemistry, Manufacturing, and Controls (CMC) factors required for the manufacturing and development of commercially viable CGT products.

Characterization of the Manufacturing New Active Substance Materials

The IND should include specifications and testing of all materials and components using in the manufacturing process of gene and cell therapies.

Vectors - The vehicle used to transfer genes into cells is termed vector or vector construct. The FDA requires that the IND contain a description of the vector, including the changes made to the vector and the history of the vector. A gene map should be made available detailing relevant restriction sites, the gene that was inserted, and important regulatory elements such as the promoter, promoter enhancers, and selection markers.

A diagram of the vector showing the gene insert, regulatory regions, and other relevant elements should also be included within the IND. Vectors that are less than 40 kilobases should have the entire vectors sequenced. Vectors larger than 40 kilobases should at least have the gene insert, flanking regions, and any regions of the vector that have been modified sequenced. The IND should include a summary of the sequence analysis and the extend of sequencing.

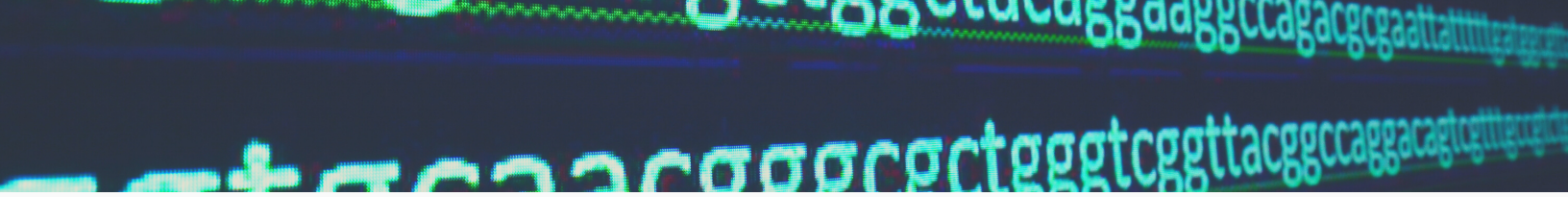
Cells - Cells used for gene therapy or cell therapy can be Allogeneic (from other individuals) or Autologous (from the patients themselves). All Allogeneic cells must be screened for HIV, HBV, HCV, Syphilis, and CJD. Leukocytes have additional screening requirements. The cell type and tissue type should be described in the IND as would be the method used for activating and mobilization of the cells. Cell mobilization is the process of getting stem cells out of the bone marrow so that they can be collected. Cell collection and the recovery methods should be determined and described. Donors should be screened.

DSI provides expert insight on:

- The basics of Cell and Gene Therapy including definitions and differences between the two therapies, Ex Vivo and In Vivo methodologies, and FAQs about the CMC development of CGT products
- Details and descriptions of vector and cell production methods, as well as quality and characterization strategies
- The latest FDA thinking and Industry standards for mapping a successful development plan for your CGT products
- The most common pitfalls and challenges in Cell and Gene Therapy, and important things to consider throughout the CMC and development processes

Gene and Cell Therapy CMC Testing at DSI

DSI does not perform DNA or RNA work, however, we can help with sterility testing, endotoxin testing by LAL, pyrogenicity using the rabbit pyrogen test, residual testing, potency assays, purity and identity testing. If you are interested about learning more about DSI and our capabilities, please contact us.



Cell bank systems are of particular importance to the FDA. The history, source, derivation, and characterization of the master cell bank (MCB) and working cell bank (WCB) should be described in the IND. The frequency of testing should also be included. The master cell bank and packaging cell line should be tested for identity, purity, stability, and safety. The master viral bank (MVB) should have the safety, purity, and identity of the viral vectors tested. For both the working cell bank and working viral bank, testing should include adventitious viral testing, testing for replication-competent viruses, sterility tests for bacterial, fungus, and mycoplasma as well as identity testing.

Reagents - Reagents used in gene therapy or cell therapy manufacturing can include fetal bovine serum, trypsin, digestion enzymes, growth factors, and media. Concentrations of the reagent, the manufacturing steps in which the reagents are used and the vendor and species source (if applicable) should be included in the IND. Residual reagents should be tested in the final product.

Excipients - All components that are intended to be part of the final product should be listed on the IND. This should include the concentration of the excipient, source, and qualification of the excipient.

Product Testing

The gene or cell therapy product must be tested during production and in its final stage. These tests consist of microbiological testing, identity, purity, potency, viability, and cell numbers (dose).

Microbial Testing - Sterility testing following USP <71> should be performed at critical time points during the manufacturing such as during the purification steps or during extended culturing periods. If the product is frozen before use the sterility testing should be performed before cryopreservation so that the results are available before the product is administered to the patient. If the product requires manipulation after thawing, sterility testing may need to be repeated. Because of stability constraints after thawing, the product may not be stable during the 14 days required for sterility testing, so in these cases, alternative approaches such as rapid microbial testing can be used. The recommended mycoplasma testing 28 days culture method per USP should be done on the product during the manufacturing stage when the test is most likely to detect contamination such as after pooling cultures prior to cell washing. Because of the time required for the culture method, the product release testing could be done using rapid methods such as PCR.

Adventitious agent testing also needs to be performed on the final product. These tests should include in vitro viral testing and in vivo viral testing. Specific viruses such as CMV, HIV, HTLV, EBV, HBV, HCV, and B18 can be tested by the murine antibody production (MAP) tests or other antibody production tests. PCR may also be used. Testing for retroviruses can be performed using reverse transcriptase assays and electron microscope analysis. If retroviral vectors are being produced, the FDA recommends testing for replication-competent retroviruses at multiple time points in production.

Identity - If the product is an ex vivo genetically modified cell product, the FDA recommends that the final cell product be tested for identity. Testing should include an assay to measure the presence of a vector (such as an expression assay or restriction digest) and an assay specific for the cellular component of the final product such as cell surface markers.

Purity - Purity testing should consist of assays for pyrogenicity, endotoxin, and residual contaminants. Residual proteins, DNA, RNA, cytokines, growth factors, serum, antibodies and solvents should be tested. For cell therapy products, purity testing should include contaminating cell types or cellular debris. The preferred method for testing pyrogenicity is the rabbit pyrogen test, however, if the product has a short shelf-life, LAL endotoxin testing can be performed instead.

Potency - For phase three clinical trials, potency assays should consist of an in vivo or in vitro method that measures the appropriate biological activity. Potency assays are typically done as part of a lot release assay and should be validated. For clinical trials previous to phase three, the potency assay can be less stringent and can consist of an assay that quantifies the expression of a gene therapy vector product.

Viability - The viability of the cell used for genetically modified cellular therapies should have a minimum specification of 70%. If 70% viability cannot be achieved, justification should be presented to the FDA.

Cell Number/Dose - If the final product is a genetically modified cell therapy, a specification for the minimum number of viable cells as part of the product testing and release should be documented. If the product is a gene vector, the dose should be described as the concentration of plasmid DNA, viral particle number, or titer.