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Regulatory Knowledge Guide for Cell and Gene Therapies

NIH SEED Innovator Support Team

Introduction

Cell and gene therapies (CGT), a subset of regenerative medicine therapies, are **biological products** and include plasmid DNA and RNA, viral vectors, bacterial vectors, products incorporating human gene-editing technology, and patient-derived cellular gene therapy products. CGTs are transformative therapies that are being used to treat a variety of cancer, genetic, and infectious diseases. However, there are relatively few CGTs that have been approved for patient use globally, reflecting the infancy of this modality.

As an innovator of CGT products, you will have to adhere to additional regulation (beyond that of traditional biologics and traditional small molecule therapeutics) due to CGT products' unique **mode of action** (MOA), and the subsequent novel risks associated with these products. This guide presents information on specific aspects of CGT products in the context of non-clinical product development, process development and manufacturing considerations, clinical strategy, **product development lifecycle**, and the U.S. **Food and Drug Administration's** (FDA) regulatory framework. FDA's Center for Biologics Evaluation and Research (CBER) Office of Therapeutic Products oversees the development, testing, and review of CGT products. Throughout this guide, you will be referred to sections of the Regulatory Knowledge Guide for Biological Products and the Regulatory Knowledge Guide for Small Molecules as appropriate, to learn about regulatory information shared between these drug types and CGT products.

Please use the Word navigation panel to jump to relevant sections for your specific needs. Bolded terms within the text are defined in the Glossary.

If you have questions about the CGT development process, contact the SEED Innovator Support Team or FDA.

After reading this Regulatory Knowledge Guide, you will have a better understanding of CGT development and regulatory lifecycle. Specific topics that will be described are listed below:

- Key differences between manipulated versus minimally manipulated products, and how the level of manipulation impacts FDA's regulatory requirements.
- What orphan drug designation and exclusivity entails.
- Clinical objectives, endpoints, long-term follow-up of patients, and multiple versions of a CGT product in a single clinical trial.
- Why manufacturing of CGT products to support IND studies and submissions involves so many materials, procedures, and challenges and how to document them.
- What safety measures are required for viral vector-based gene therapy products.

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1 Regulatory Considerations and Product Classification

An essential first step in developing a cell and gene therapy (CGT) product is to determine the appropriate regulatory pathway to bring it to market. FDA's Center for Biologics Evaluation and Research (CBER) Office of Therapeutic Products oversees the development, testing, and review of CGT products.

CGT products require submission of an **Investigational New Drug** (IND) application before initiating clinical studies. In addition, an approved **Biologics License Application** (BLA) is required to market the product in the U.S. For CGT combination products, a formal determination of product jurisdiction can be made through the Request for Designation process, administered by the Office of Combination Products, which uses an assignment algorithm that considers the medical product's primary mode of action. The regulatory pathway that is applicable to a specific CGT product may have necessary implications for its product development and approval processes; for example, reporting requirements, sponsor responsibilities, type of marketing application, and other regulatory requirements may be dependent on the applicable regulatory pathway.

Certain regulatory pathways have been designed to expedite the development process and submission review timelines. These additional regulatory pathways include more frequent interactions between **innovators** and regulators to expedite the exchange of recent scientific and technological advances. In addition, increased communication between innovators and regulators has proven to be extremely valuable for product development in the rapidly evolving field of regenerative medicine therapies. The expedited pathways available for CGT products intended to treat serious medical conditions are:

- Fast Track
- Breakthrough Therapy
- Regenerative Medicine Advanced Therapy Designation
- Accelerated Approval
- Priority Review

CGTs are often approved using expedited review programs to help ensure therapies for serious conditions are available to patients as soon as FDA determines that the benefits justify the risks.

FDA recognizes the uniqueness and complexity of CGT development and has published several guidelines on specific expectations on manufacturing quality, non-clinical, and clinical considerations of CGTs. Consult these guidelines when identifying and assessing the regulatory risks linked to your product.

Of particular note, FDA has issued draft guidance focused on **chimeric antigen receptor (CAR) T-cell** therapies. (See the specific CAR T-cell resources listed below.) If your product is a CAR T-cell, it's important to know the FDA framework for biological products regulates CAR-T cells as human gene therapy products. FDA guidance provides CAR T cell-specific recommendations regarding **chemistry, manufacturing, and controls** (CMC), pharmacology, toxicology, and clinical study design. This guidance applies not only to CAR T-cell products but also to other genetically modified lymphocyte products such as CAR natural killer (NK) cells or receptor-modified T-cells.

Resources:
FDA: Expedited Programs for Serious Conditions—Drugs and Biologics
FDA: Regenerative Medicine Advanced Therapy Designation
FDA: Cellular & Gene Therapy Guidances
FDA: Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Product
FDA: Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational
New Drug Applications (INDs)
Article: Key Points from the FDA's Guidance for CAR T-Cell Products

See Appendix A for a checklist of points to consider for CGT product expedited pathways.

1.1 Orphan Drug Designation and Exclusivity

CGT products are a diverse group of biotherapeutics developed to treat specific conditions for which there are limited or no effective treatments. The complexity and novelty of this product class require a data-driven, regulatory, risk-based approach to define a sound development plan for clinical development and registration. This risk-based approach is beneficial when no detailed product-specific regulatory guidelines are available.

Orphan drug designation (ODD) may be granted to a drug or biological product to prevent, diagnose, or treat a rare disease or condition. Orphan status is granted to most CGT drugs in development. To receive the ODD, the product needs to treat a rare condition: this is defined by a prevalence criterion of fewer than 200,000 individuals in the U.S. population. Its use also needs to be supported with evidence of non-clinical or clinical efficacy. ODD qualifies sponsors for incentives including tax credits for qualified clinical trials, exemption from user fees, and potentially seven years of market exclusivity after approval.

If you are seeking an ODD, you must submit a request for designation to FDA, which is distinct and separate from the marketing approval request. Drugs for rare diseases go through the same rigorous scientific review process as any other drug for approval or licensing. When seeking an ODD, be sure to contact FDA early in the development process. FDA feedback will help refine the product strategy for orphan drug exclusivity.

Most CGT products target rare diseases or unmet medical needs, they frequently qualify for expedited programs and may receive orphan drug designation.

To qualify as an orphan product and be considered for regulatory incentives, you must clearly specify what differentiates your new product in comparison to an existing similar product for the same use or disease. For gene therapy products and other large molecule drugs, FDA regulations define "same drug" as a drug that contains the same principal molecular structural features (but not necessarily all the same structural features). FDA considers certain key compositional features of CGT therapy products, such as transgenes and vectors, to be principal determinants of molecular structural features. FDA evaluates the differences or sameness in CGT products on a case-by-case basis.

You can apply for other regulatory designations if the drug fails to meet the ODD criteria but treats a severe condition. Regenerative medicine advanced therapy **(RMAT) designation** can be requested during the IND submission or as an amendment. A drug is eligible for RMAT designation if it meets the following criteria:

- Meets the definition of regenerative medicine.
- Aims to treat, modify, reverse, or cure a serious condition.
- Preliminary clinical data shows the potential to address an unmet medical need.

RMAT designation shares the same features as breakthrough therapies, such as expedited development and a rolling review process. However, it also requires early discussions with FDA on potential surrogate or intermediate endpoints as ways to support accelerated approval.

Resources:

FDA: Designating an Orphan Product: Drugs and Biological Products
FDA: Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations
FDA: Clarification of Orphan Designation of Drugs and Biologics for Pediatric Subpopulations of Common Diseases
FDA: Orphan Drug Act (ODA) – Relevant Excerpts

1.2 Manipulated (351) Versus Minimally Manipulated (361) Products

Regenerative medicine technologies—including CGT products—are overseen by CBER through Sections 351 and 361 of the Public Health Service Act (PHSA). The PHSA gives CBER the authority to establish requirements for marketing traditional biologics and human cells, tissues, and cellular and tissue-based products. It establishes two regulatory pathways, which differ markedly in terms of the time, effort, and expense required to bring a product to market in the U.S.

There are different regulatory pathways for manipulated and minimally manipulated products, they differ markedly in terms of the time, effort, and expense required to request market authorization.

Human cell, tissue, and cellular and tissue-based products (HCT/P) are regulated as a drug, device, and/or biological product via Section 351 (termed a 351 product) if they *do not* meet all the criteria below for a minimally manipulated 361 products. 351 products are subject to the same standards of safety and effectiveness as drugs and medical devices that are approved by FDA under a BLA. Most CGT products are blood-derived cell or tissue-based products and fall under the category of 351 products because they are more than minimally manipulated, and they are used for non-homologous work.

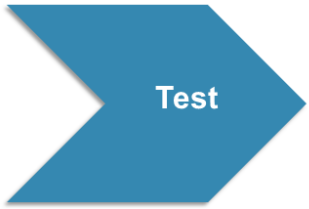
361 products are minimally manipulated/altered HCT/P that are only minimally unregulated. 361 products are differentiated from 351 products based on the following criteria:

- A 361 product is minimally manipulated. Minimal manipulation is defined in two ways in this context:
    a. For structural tissue, processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement.
    b. For cells or nonstructural tissues, processing that does not alter the relevant biological characteristics of cells or tissues.
- The product is intended for homologous use only: the tissue/cells have the same function for the recipient as for the donor.
- The product is not combined with another article/product/cell/tissue except for water, crystalloids, or a sterilizing, preserving, or storage agent.
- The product does not have a systemic effect; does not depend upon the metabolic activity of living cells for its primary function; and is for autologous use, reproductive use, or allogenic use in a first or second-degree blood relative.

Minimally manipulated 361 products are not subject to any FDA pre-approval process and are not required to have any clinical data before marketing. They are rarely subject to FDA requirements concerning manufacturing and clinical programs. The 361 HCT/Ps are considered a subset of CGT products (see 21 CFR 1271 Parts A–D) and may be eligible for designation as regenerative medicine advanced therapy (**RMAT**).

Note that some 361 products may be reclassified as 351 products by FDA due to stricter regulations and interpretation of cell and tissue products. See Appendix B for a flow chart that illustrates FDA's decision-making process for whether HCT/Ps are regulated as 351 versus 361 products.

Resources:
FDA: Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use
FDA: FDA Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products Product List
FDA: Tissue Reference Group (TRG)
FDA: TRG Rapid Inquiry Program (TRIP)
Article: FDA's Framework for Regulating Regenerative Medicine Will Improve Oversight



2 Non-Clinical Study Considerations

During non-clinical development of CGTs, consider what experiments should be conducted to address safety concerns specific to your investigational product. These studies are especially important when there are no relevant animal models in which to conduct a toxicology assessment. For additional information, see Section 4 in the Regulatory Knowledge Guide for Biological Products.

A set of non-clinical studies and testing parameters uniformly applicable to all types of CGT products does not exist. Instead, you should address a set of general objectives to guide product-specific non-clinical testing. These should be evidence-based, data-driven, and tailored to the specific product and clinical indication. The objectives of these studies are listed below:

- Establish and confirm the mechanism of action.
- Confirm biological performance, therapeutic benefit/efficacy, and reproducibility in the appropriate animal model.
- Demonstrate or uncover the CGT product's potential safety risks (e.g., off-target effects, immune response to the product/vector, vector integration).
- Evaluate the long-term persistence/gene expression in suitable animal models.
- Establish the feasibility of the animal model for the target indication.
- Determine optimal/active dose selection and range, dosing schedule, and effect of route of administration (ROA) on the product performance.
- Identify physiologic parameters that can guide clinical monitoring and support of patient eligibility criteria.

While the selection of a first human dose may be based on these *in vivo* animal studies, you should also consider dose selection of similar CGT products that have been tested clinically. You can seek regulatory feedback at an INTERACT meeting (i.e., an **IN**itial **T**argeted **E**ngagement for **R**egulatory **A**dvice on **C**BER Produc**T**s meeting, an informal, non-binding meeting held early in product development) after you have identified the preclinical models best suited to address your CGT product's efficacy and safety attributes.

This meeting can also help identify if pilot studies are needed to confirm the suitability of your proposed preclinical models. In some cases, FDA may recommend that the non-clinical studies include a comparison of different CGT product batches (especially after **scale-up**), interaction with concomitant drugs, and additional tumorigenicity studies.

Resources:

FDA: Preclinical Assessment of Investigational Cellular and Gene Therapy Products
FDA: Presentation: Preclinical Considerations for Gene Therapy Products
FDA: Presentation: Preclinical Studies for Cell-Based Immunotherapies
FDA: Briefing (2021): Toxicity Risks of Adeno-Associated Virus (AAV) Vectors for Gene Therapy

2.1 Devices for Delivery of the CGT Product

CGT products sometimes require specialized devices or novel procedures for administration, customized preparation, special handling (e.g., rapid expiry), or adjunctive therapy. For this reason, you should perform non-clinical studies using the intended clinical delivery device. These studies should evaluate the usability of the device and assess potential risks associated with how the product is administered. The ROA used to deliver the investigational CGT product in the non-clinical studies should mimic the ROA to be employed in the clinical setting to the greatest degree possible.

If it is not possible to replicate the clinical ROA in the animal model, then alternative routes/methods should be proposed and scientifically justified as a part of the preclinical development plan. In addition, the formulated product compatibility with the device at the storage conditions and its product performance (potency, stability, and *in vivo* efficacy and safety) will have to be tested. It is critical to evaluate these aspects as early as possible to set an adequate control strategy for the CGT product and to avoid surprises later during product development.

You can seek regulatory feedback from the Office of Therapeutic Products after you have identified all the key elements of the non-clinical studies (including animal models, dosing and delivery device considerations, pharmacology and toxicology endpoints, etc.) that are best suited to meet the **target product profile** (TPP) requirements of the investigational CGT candidate. Regulatory guidance through a meeting with FDA can help identify gaps and confirm the suitability of the preclinical development path (including delivery device use and selection) and ensures that the product's overall preclinical strategy is well-aligned with regulatory expectations.

Resources:

NIH SEED: Regulatory Knowledge Guide for Combination Products
NIH SEED: Creating a Target Product Profile for New Drug Products
NIH SEED: Target Product Profile Questionnaire
NIH SEED: Example TPP for a Cell and Gene Therapy
FDA: Evaluation of Devices Used with Regenerative Medicine Advanced Therapies

FDA: Combination Products
FDA: CBER-CDRH Cross-Center Guidance Documents
FDA: Preclinical Assessment of Investigational Cellular and Gene Therapy Products

2.2 Biomarkers for Surrogate Endpoints

Surrogate endpoints are biomarkers or intermediate endpoints intended to substitute for and predict a clinical outcome. They may be validated or non-validated. Finding an established or validated biomarker for use as a surrogate/intermediate endpoint to predict/estimate clinical efficacy enables determination of product safety and can accelerate the regulatory approval process. For additional information, see Section 9.3 in the Regulatory Knowledge Guide for Biological Products.

Investigational CGT products often have a high degree of subjectivity in determining the surrogate endpoint and validating that surrogate endpoint's ability to predict clinical benefit.

You should be prepared to prioritize, identify, and integrate product-specific biomarkers in the non-clinical development plans. For investigational CGT products, there is a high degree of subjectivity in determining the surrogate endpoint and validating that surrogate endpoint's ability to predict clinical benefit. FDA typically has not defined the type of data needed for a CGT product to demonstrate a projected durable effect before approval through the accelerated approval pathway or the data needed to assess durability after product approval. This landscape is evolving rapidly in the context of CGT products.

Resources:

FDA: Biomarker Qualification: Evidentiary Framework
FDA: Considerations for Use of Histopathology and Its Associated Methodologies to Support Biomarker Qualification
FDA: Facts: Biomarkers and Surrogate Endpoints
FDA: FDA Facilitates the Use of Surrogate Endpoints in Drug Development
FDA: Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure

3 Clinical Considerations

The clinical development of CGT products usually follows the conventional process for biologics. Depending on the phase of clinical development, you can request feedback on the clinical development strategy and endpoints from appropriate regulators, **key opinion leaders,** and clinicians on a case-by-case basis. This CGT-specific information will help align your strategy with your TPP. You should also review the relevant FDA guidance documents, available literature/reports, and FDA product assessment reports on approved/marketed CGT products. For additional information on TPPs

and clinical considerations, see Sections 1, 3, and 4 of the Regulatory Knowledge Guide for Biological Products.

A case-by-case assessment of CGTs is necessary for the design of each clinical trial because of the distinctive features of these products and may also reflect previous clinical experience. FDA encourages CGT innovators to meet with CBER prior to finalizing the design of the clinical studies. Meetings are outlined in FDA's Formal Meetings Between FDA and Sponsors or Applicants of PDUFA Products.

As mentioned above, FDA has implemented expedited programs designed to help ensure therapies for serious conditions are approved and available to patients as soon as FDA determines that the benefits justify the risks, while still preserving the standards for safety and efficacy. For this reason, most CGT products targeting rare diseases or unmet medical needs qualify for expedited programs and are frequently designated orphan drugs. In addition, the Accelerated Approval program allows for the earlier approval of drugs based on surrogate or intermediate endpoints, while confirmatory studies (late-phase clinical trials required to verify clinical benefits) are ongoing.

FDA generally asks for single-dose regimens for CGT **first-in-human** trials. Repeat dosing of CGTs is not usually allowed until there is a good understanding of the **toxicity** of the product. To be compliant with FDA toxicity study guidance, there must be follow-up after the first patient is treated to ensure safety before the next patient can start treatment. Add-on regimens can be allowed to help define dose-limiting toxicities; however, you would have to provide a strong justification for the risk-benefits of an additional dose and FDA needs to approve such a design.

Manufacturing a personalized medicine can pose additional challenges in the clinical study design, since you would need to consider the time frame for manufacturing when establishing eligibility criteria. CGT **drug products** can be heterogeneous regarding active, inactive, and toxic fractions. FDA frequently asks for data on various subsets in the final CGT product and a comparison to the **clinical outcomes**, to identify the important subsets.

3.1 Early-Phase Clinical Trials of CGT Products

In developing CGT products, well-designed, early-phase **clinical trials** are essential to establish the regimen and design of the late-phase clinical trials. This can also shorten the development period and ensure efficiency. The design of early-phase clinical trials of CGT products often involves issues that are less common in the development of other pharmaceuticals: among these are clinical safety issues, preclinical issues, and chemistry, manufacturing, and controls. This guide covers the issues specific to CGTs. For a more complete discussion of initiating drug clinical trials, please refer to Section 5 of the Regulatory Knowledge Guide for Small Molecules and Section 7 in the Regulatory Knowledge Guide for Biological Products.

FDA assesses a proposed CGT clinical trial design based on collective evidence presented in the IND submission. Together, the information should provide the justification for safe starting dose and/or dose-escalation schema and optimal ROA. The information you'll provide includes CMC issues, non-clinical pharmacology, and toxicology/safety studies in disease-specific animal species/models. Consult a regulatory expert or FDA if the **good laboratory practice** (GLP) animal **toxicology studies** show little or no toxicity, or if traditional pharmacokinetic studies are not enough to provide information on starting dose and are unable to guide clinical trial design.

You can consider conducting dose exploration/escalation **Phase I** studies in two arms—arm one of the studies will be a dose-escalation Phase I safety and tolerability study (three doses to be tested). Data generated from arm one will inform the conduct of arm two, which tests the safety/tolerability and efficacy at the optimal dose. In cases where there is no previous human experience with a specific CGT product, treating participants simultaneously could represent an unreasonable risk. FDA suggests staggering the treatment to limit the number of subjects that might be exposed to such risk. Failure to identify a **maximum tolerable dose** (MTD) during early development may lead to subsequent clinical trials using sub-therapeutic dose levels.

While the primary objective of early-phase clinical trials for CGT products is to identify a safe MTD and establish the safety profile, simply demonstrating safety data may be insufficient to move into later stage trials. In addition, for CGT products, the first-in-human (FIH) trial is usually conducted in a disease population and not in healthy volunteers. Furthermore, the trial design may get restrictive due to the limited size of a patient population available and the pursuit of **orphan drug** status for the product. Note that due to the limited pool of patients, Phase I studies for CGT products may not be powered adequately to produce a significant statistical safety signal. Carefully consider inclusion of specific short/long-term efficacy end points (selected features of **Phase II** study design) as one of the objectives in early phase trials so you can generate preliminary evidence of effectiveness of the CGT product.

Resources:

FDA: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products
FDA: Human Gene Therapy for Rare Diseases

3.2 Multiple CGT Product Versions in a Single Trial

A clinical development strategy should be driven by the individual targeted therapy portfolio and the indications of interest. As such, you can gather preliminary evidence of safety and activity of your CGT product by testing multiple versions of the product in a single clinical trial. In this scenario, each version of your CGT product is considered distinct and submitted to FDA in a separate IND. The objective of testing multiple versions of the product in these early-phase clinical studies is to guide the selection of optimal versions of the product that may be safer or more effective, which may expedite early and later stage clinical phase studies.

The goal of these studies is not intended to provide primary evidence of effectiveness in a market application: they may not be adequately powered to demonstrate a statistically significant difference in efficacy between the study arms.

These studies can be conducted under the so-called, FDA-designated "**umbrella trial Master Protocol**" for more efficient clinical development (e.g., using a common control group). When a primary IND is submitted as a part of an umbrella trial Master Protocol, it constitutes the clinical content for a multi-product development program. This would include a Master Protocol, informed consent document, **Investigators Brochure**, and secondary INDs that describe the product versions that will be studied under the Master Protocol. Any changes to the Master Protocol should be reported as an amendment to the primary IND, and the secondary INDs can cross-reference that amendment.

This approach does not change FDA's regulatory expectations from the innovator—you will still have to demonstrate adequate characterization of CMC and non-clinical evidence of safety/bioactivity for different product iterations. If you are using the umbrella trial Master Protocol, FDA recommends requesting a **pre-IND meeting** with the CBER's Office of Therapeutic Products to discuss your proposed clinical trial design.

Resource:

FDA: Studying Multiple Versions of a Cellular or Gene Therapy Product in an Early-Phase Clinical Trial

3.3 Long-Term Follow-Up of Patients Receiving CGTs

Pharmacovigilance and pharmacoepidemiologic assessment of observational data regarding drugs, including biological drug products (excluding blood and blood components), is used for safety signal identification and interpretation. As more understanding and experience are gained with CGT products, safety signals continue to be better understood and anticipated. A point of emphasis for regulators is discovering trends in safety events associated with similar product types or classes, so increased attention is placed on the pharmacovigilance plan development for CGT products.

A well-developed pharmacovigilance plan for CGT products should include trends in safety events associated with similar products.

Given the limited number of patients who have received CGT products to-date, and the limited number of CGT products approved, little is known about the long-term effects of these therapies. Furthermore, because CGT products may achieve the therapeutic effect by permanent or long-acting changes to the recipient, there may be an increased risk of undesirable and unpredictable outcomes resulting in delayed adverse events in patients receiving them. As a result, CGT products may be subjected to monitoring post-licensure for a **long-term follow-up** (LTFU) period lasting up to fifteen years. It is advisable to discuss with FDA as early as possible if LTFU studies are needed and if so when they should be conducted throughout clinical development.

Consult with a regulatory expert when you devise a pharmacovigilance plan (PVP)—submitted with the BLA—for monitoring the long-term safety and efficacy of the CGT product in humans (See section 5.2 for more details on a PVP). The PVP should include the LTFU protocol, statistical analysis plan, and schedule of anticipated study milestones for any proposed or required post-marketing observational studies or clinical trials. Assessment of risk should be viewed as a continuous process, as data accumulates, it may be necessary to revise existing (or initiate) LTFU observations.

On a case-by-case basis, long term studies in animals may be required for initiation of early phase clinical trials. These studies inform the clinical strategy and FDA review of *in vivo* product performance—especially safety, efficacy, immunogenicity signals. You can request clarity from FDA during INTERACT (see Section 2 for a discussion of INTERACT meetings) or pre-IND meetings.

Resources:

FDA: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment
FDA: Long Term Follow-Up After Administration of Human Gene Therapy Products
FDA: E2E Pharmacovigilance Planning
FDA: FDA Announces Program to Enhance Early Communications with Biological Product Developers
FDA: SOPP 8101.1: Regulatory Meetings with Sponsors and Applicants for Drugs and Biological Products
FDA: Long Term Follow-up After Administration of Human Gene Therapy Products

3.4 Replication-Competent Retrovirus Testing

For CGT products, there is an overall concern that the viral vector, once inside the patient, may recover its ability to cause disease and may elicit toxicity, inflammatory, immunogenicity, gene control, and targeting issues. To this end, pharmacovigilance studies consisting of LTFU must include safety monitoring of patients receiving the CGT treatment for **replication-competent retroviruses** (RCR) even after product licensure. Retroviral vector-based human gene therapy products should be tested for RCR during manufacturing, and follow-up safety monitoring of patients who have received the product is essential even after product approval.

The potential for contamination by a RCR during manufacturing remains a concern. Manufacturers must ensure that the various clinical manufacturing batches are not contaminated with RCR during the production process and meet release specifications. You must address the threat of RCR in the IND/BLA submission and outline the steps taken to address RCR concerns.

RCR testing results from production lots and patient monitoring are documented in amendments to the IND file. Positive results from patient monitoring must be reported immediately as an adverse experience in the form of an IND safety report (21 CFR 312.32). Negative results must be reported in the IND annual report (21 CFR 312.33) or Development Safety Update Report, if used instead of reporting in annual reports. In addition, to enhance the accumulation of data on RCR testing assays,

CBER encourages members of the CGT therapy community to publish data and/or discuss data publicly regarding their experience with different vector producer cell lines, patient monitoring, and safety.

Resources:

FDA: Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up
FDA: Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)
FDA: Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up

3.5 Pediatric Patients Versus Other Patient Populations

Many CGT products target rare pediatric diseases that are severely life-limiting. If you are developing a CGT product to treat pediatric patients, consider the risk-benefit of the treatment to the child, the prospect of clinical benefit, and how you will incorporate additional safeguards and monitoring for children in clinical investigations into the overall development program. Review 21 CFR Subpart D to understand these requirements.

As is the case with clinical studies on adults, FDA requires **Institutional Review Board** (IRB) approval of any studies on pediatric patients. The IRB determines the risk-benefit analysis for the pediatric population and whether the designed trial meets additional requirements necessary for this group of patients. IND/BLA submissions for pediatric trials must provide additional information related to plans for assessing pediatric safety and effectiveness (21 CFR 312.23(a)(10)(iii)). The IND regulations also require the sponsor to submit an investigational plan to FDA, including the rationale for the drug or the research study (21 CFR 312.23(a)(3)(iv)(a)).

Note that you may need to address specific vulnerabilities in different populations (e.g., adults/elderly versus children, pregnant women). In some situations, it may be appropriate to initiate clinical studies of CGT products in children based only on the results of preclinical studies. For example, suppose you plan to conduct a pediatric trial with no prior safety or efficacy study in adults. In that case, the IND/BLA package should explain the rationale as to why previous adult studies are not feasible or unethical under human subjects' protections regulations and guidelines. In addition, you must address ethical considerations for conducting studies in vulnerable pediatric populations. To justify conducting a pediatric first-in-human clinical trial associated with more than a minor increase over minimal risk, the non-clinical program should include studies designed to demonstrate a prospect of direct benefit (see 21 CFR 50.52 section V.A.) of the investigational CGT product. Non-clinical evidence of an opportunity for direct benefit is most important when clinical effectiveness is unavailable from adult subjects with the same disease.

Resources:

FDA: E11 Clinical Investigation of Medicinal Products in the Pediatric Population
FDA: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products
FDA: Human Gene Therapy for Rare Diseases
CFR: Final Rule: Additional Safeguards for Children in Clinical Investigations of Food and Drug Administration-Regulated Products

3.6 Shedding Studies

The potential for viral **shedding** should be addressed early in CGT product development. During shedding, the virus or bacteria-based gene therapy products or oncolytic products from the patient can be released via excreta (feces); secreta (urine, saliva, nasopharyngeal fluids, etc.); or through the skin (pustules, sores, wounds), raising the possibility of transmission from treated to untreated individuals. Shedding studies are required as they can elucidate how the number, route, mode of transmission, and stability of an infectious agent outside the host determines its infectivity.

Shedding studies (virus and vector) should be conducted per **International Council for Harmonisation** (ICH) considerations to determine the risk of a CGT product being transferred from the patient to an untreated person in close contact, such as a healthcare professional. A shedding study report should be included in the IND/BLA submission package. FDA provides guidance on design considerations for shedding studies, including both how and when shedding data should be collected (frequency, duration, type of samples) and how shedding data can be used to assess the potential for transmission to untreated individuals.

Resource:

ICH: General Principles to Address Virus and Vector Shedding

3.7 Safety Measures for AAV Vector-Based Gene Therapy Products

Adeno-associated virus (AAV) and **lentivirus vectors** are the most common viral vectors currently used in gene therapy development. Because of their low immunogenicity in humans, AAV vectors are seen as the most promising gene delivery candidate for severe nonlethal conditions that need long-term treatment. However, given the recent aggregated clinical/preclinical data in different CGT products and the toxicity risks of AAV vector-based gene therapy products in humans, you should have a clear understanding of the underlying treatment-specific **adverse events** related to product-specific vector administration. You should consider the following factors:

- Dose-related toxicity
- Host immune system responses and pre-existing neutralizing antibodies
- Short-lived or insufficient transgene expression and transgene expression in off-target tissues
- T-cell response to transgene or capsid protein and its effect on transgene expression

- Vector integration and oncogenicity risks
- Hepatotoxicity issues
- Thrombotic microangiopathy issues
- Non-clinical findings of neurotoxicity, especially related to dorsal root ganglion toxicity issues
- Clinical findings of neurotoxicity based on brain magnetic resonance imaging studies

Engage with FDA on additional safety measures and when any studies should occur during development. Also, review strategies to evaluate and mitigate risks in the context of AAV vector-based product design and quality, preclinical studies, and clinical trials.

Resource:

FDA: FDA Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) Meeting #70 Toxicity Risks of Adeno-associated Virus (AAV) Vectors for Gene Therapy

3.8 Clinical Objectives and Endpoints

Depending on the stage of clinical development and the disease **indication** under investigation, objectives and endpoints should be separated into primary, secondary, and potentially exploratory objectives. For additional information, see Section 9.3 in the Regulatory Knowledge Guide for Biological Products.

A regulatory consultant or **contract research organization** can help identify and improve the objectives and endpoints that will satisfy the regulatory requirements for CGT products (e.g., LTFU studies, prolongation assessments, the requirement for RCR assessments in cell therapy products, shedding studies, pediatric population considerations), as well as the standard objectives and endpoints common to biologics. They can also advise you on the proper handling of the finished drug product, which is critical to the investigational studies. This includes how the CGT product will be shipped to, received, and handled at the clinical site to ensure safety, product quality, and stability.

4 Chemistry, Manufacturing, and Controls Considerations

The CMC is among the most critical components of CGT products development and IND/BLA application, and an incomplete CMC package can be a significant problem in expediting the development of CGT products. Regulatory assessment of CGT product testing occurs on a case-by-case basis, depending on the current scientific knowledge, regulatory precedents and experience with similar products and indications, the phase of product development (e.g., preclinical, Phase I, End-of-Phase II), and the benefit-risk profile in the target patient population.

The FDA has shown considerable flexibility in CMC regulatory requirements for CGT products; however, you should be aware that these requirements usually increase and become progressively more stringent as a product development program advances toward marketing.

FDA's manufacturing requirements for CGTs become progressively more stringent as a product development program advances toward marketing.

For additional information, see Sections 5 and 6 in the Regulatory Knowledge Guide for Biological Products.

Resources:

FDA: Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications
FDA: Consideration for Early Phase Clinical Trials of Cellular and Gene Therapy Products
FDA: Advanced Topics: Successful Development of Quality Cell and Gene Therapy Products
NIH SEED: Quality Management Systems for Biological Products

4.1 Bioprocess Development and Manufacturing Procedures

Manufacturing of CGT products to support IND studies and BLA submission involves many materials, procedures, and challenges. Therefore, FDA requires thorough descriptions of processes and procedures, controls, and testing. Having a CMC consultant available to develop the overall CMC strategy, including **upstream** and **downstream unit operations** based on individual circumstances, can be valuable in advancing to IND/BLA enabling phase-appropriate **clinical trial material** manufacturing and market approval for CGT products.

You should ensure the following are addressed during the manufacturing process:

- **Cell Culture (Vector Production):** All steps to manufacturing and inserting a CGT vector must be thoroughly described. Documentation should include details on the gene, promoters, selection markers used, and all actions involving cell lines and cell culturing, harvesting, vector purification, and in process testing. The entire vector must be sequenced for vectors less than 40 kilobases; for larger vectors, minimum sequencing should include the gene insert, flanking regions, and any other modified regions.
- **Genetically Modified Cell Production:** Producers of CGT therapy products must describe the cell processing method, including the source material, collection of cellular material, and storage at the collection site. A description of shipping and handling procedures must be included. Cell selection, isolation, and enrichment steps are required in the documentation, as are cell expansion conditions, hold times, and transfer steps, as well as any cell harvest and purification procedures used.
- **Irradiated Cells:** FDA requires you to provide details on the irradiator source, including calibration. You must include data showing the irradiated cells are unable to replicate but that they still retain the desired characteristics.

- **Filling, Storage, and Transportation:** Documentation of process controls associated with the product's filling, storage, and shipping must be provided. This should include a description of the container closure system used, the materials it's made of, and whether the container has been approved for use with similar products. FDA recommends using materials that protect from moisture, gases, and light and that are safe and perform well under the expected storage and transport conditions. In addition, report the elapsed time for each vector production step and the cryopreservation of the final vector product. If cryopreservation is to take place, you should conduct stability studies. If leaching or adsorption to the container is a concern, address it before the filling stage.
- **Final Formulation:** The final formulation of the product, including excipients, should be included in the IND, along with all sources, vendors, and concentrations of components. Container closures should be compatible with the formulation.
- **Allogeneic Donors:** If T-cells from allogeneic donors are the source of the donor cells, they should meet the requirements of relevant national laws, regulations, and ethics. You should establish validated procedures for acquiring, transporting, sorting, testing, and preserving these donor cells. Formulate precise specifications and requirements for characteristics, culture conditions, generation, growth characteristics, preservation status, preservation conditions, and quality testing of donor cells. If feasible, establish cell banks to preserve and produce donor cells. The tiers of a cell bank would depend on full consideration of the cell characteristics, production, and clinical application. Cell bank testing standards should be established to meet basic safety, quality control, and efficacy requirements.
- **Autologous Donors:** If autologous donors are the source of the donor cells, qualification and the screening and testing of pathogens are recommended but not mandatory. The cells used in the production process, such as those used to produce viral vectors, should meet specific basic requirements: a clear source and culture history, controllable safety risks, adequate quality for production processes, and well-managed cell banks. Viral vectors (retroviral vectors or lentiviral vectors) used in the production of CAR-T cells have to be appropriately manufactured (suitability of production systems such as producer cell lines in combination with adeno- or HSV-helper viruses, or upcoming helper virus-free producer cell systems) and appropriately quality controlled. Each substance used in the production of CAR-T cells, such as the culture medium, serum, cytokines, enzymes, antibodies, antibiotics, and magnetic beads, should be clearly defined and assessed for applicability. To demonstrate quality, you should test the identity, purity, bacterial endotoxin, sterility, adventitious factor, and biological activity of the autologous donor cells.
- **Viral Vectors:** The quality of the vector used for gene modification in development is extremely important. It is different from the other raw materials used in production and should be managed as a product component. The production and quality control of vectors for genetic modification should meet the current FDA requirements for CGT products.

- The vector used for gene modification should be a clinical-grade product that has been produced under **current Good Manufacturing Practice** (cGMP) conditions and that has passed comprehensive quality tests. The vector production process must be validated to ensure its reproducibility with increased safety, efficiency, and quality consistency through controlled process flows.
- The critical raw materials commonly used for vector production are cells (allogeneic or autologous used for *ex vivo* transduction), media and serum, and **plasmids**. Each must come from an approved supplier and undergo rigorous testing procedures to reduce the risk of introducing adventitious factors into the production process. You must ensure all banks are managed and tested according to their corresponding regulatory requirements. The established cell bank, virus seed bank, bacterial seed bank, and animal-derived components in the culture medium require extensive testing.
  - A cell bank system is required for the retrovirus packaging for stably transfected cells.
  - Both a bacterial seed bank and a cell bank system are necessary for lentiviral vectors prepared by the transient transfection method.

- **Viral Clearance Studies:** Viral clearance from unprocessed bulk/**harvest material** is essential in the downstream purification process and is vital to ensure CGT product safety and efficacy. The type and extent of viral tests and clearance studies required at different production steps will depend on various factors and should be considered case-by-case and step-by-step. Review the following ICH guidelines for more guidance on viral clearance studies and FDA requirements: ICH Topic Q 5 A (R1) Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin. You can also consult with FDA on the proposed viral clearance studies and their suitability during early development for the developed CGT product.

4.2 Process Validation for CGT Products

Effective process validation contributes significantly to assuring CGT product quality. Compared to conventional biologics manufacturing, FDA may require a higher number of validation batches and adequate supporting data for CGT products. Therefore, you should consult with FDA regarding the manufacturing lot requirements (number and batch size) needed to demonstrate and confirm that the commercial process and product are robust and reproducible and afford a safe, high-quality final product.

Process validation is generally recognized to have happened when three consecutive batches, meeting acceptance and release criteria, have been manufactured. Comprehensive process characterization, appropriate process parameters, and quality standards should be established (based on prior developmental work) and compared to **reference standards** to ensure the effective control of each process. For process validation batches, the intermediate and finished products should also be tested, analyzed, and identified more extensively than regular batches, providing a basis for setting up test

items and quality standards for in-process testing and release testing of regular batches. For additional information, see Sections 2.6 and 2.9 in the Regulatory Knowledge Guide for Biological Products.

Resource:

FDA: Process Validation: General Principles and Practices

4.3 Manufacturing, Product Quality, and Lifecycle Management

Like other biological products, the manufacturing and quality risks associated with CGT can be mitigated to a large extent through tightly controlling starting materials and the manufacturing process and suitably evaluating intermediates and the final product. However, depending on the category of CGT products (e.g., cell-based therapies, virus-based gene therapy vectors), you will need to ensure that the manufacturers have a sound drug development plan that covers the product's lifecycle. They should also have sustainable manufacturing control strategies for each product class as well as established risk mitigation strategies aligned with current regulatory expectations for manufacture of these products. Depending on the nature of the product, lifecycle management of CGT products can vary widely.

The risks of failure for CGT products in later stages of clinical development can be high, and you may need to continuously refine your process parameters and critical quality attributes (CQAs). Therefore, the IND package should include the following assessments:

- Process/manufacturing consistency, batch-to-batch variability, and complexity of manufacturing
- Effect of **critical process parameters** on CQAs and in process testing and variability
- Understanding of mechanisms of action and their links to measurable product attributes
- Risk-benefits analysis of safety and efficacy

Significantly, this necessitates a phase-appropriate pragmatic approach to defining CGT in-process controls and quality product specifications.

Since the risks of failure for CGT products in later stages of clinical development can be high, you may need to continuously refine your process parameters and critical quality attributes.

Note that a CGT with an expedited drug development designation should likely pursue a rapid manufacturing development program. The quality and CMC teams should initiate early communication with FDA to ensure the manufacturing development programs and submissions meet licensure or marketing approval expectations. When you receive an expedited drug development designation, you should be prepared to propose a commercial manufacturing program. In contrast to other biologics manufacturing, CGT products should have robust product quality testing at the earliest possible stage

rather than simply testing the product for quality towards the end of the process. For additional information, see Section 8 in the Regulatory Knowledge Guide for Biological Products.

Designing, planning, and establishing lifecycle management for CGT products is critical to support phase-appropriate clinical trial and marketing clearance for CGT products. Consultants experienced in assessing the developability, manufacturing, and essential attributes of the quality of CGT products can be helpful in this regard.

Establishing product specific CQAs is relevant to the safety and biological activity of the product. CQAs are an essential part of establishing manufacturing control and are necessary for process optimization. They will be a central reference point for a comparability plan and the associated metrics as manufacturing evolves over the course of development.

Given the evolving nature of the CGT space, consult with FDA early in the manufacturing process to formulate a strategy and plan for testing requirements for comparability and before implementing proposed process changes. Simply demonstrating a product manufactured by a new process meets predetermined release specifications may not be sufficient to establish product comparability. Determinations of product comparability will have to be assured by the manufacturer based on the assurance of critical product quality attributes through robust analytical studies. For additional information, see Sections 2 and 5 in the Regulatory Knowledge Guide for Biological Products.

For CGT products, you should consider the impact of changes to a plasmid or its manufacturing process on safety and efficacy, a side-by-side comparability approach for autologous products (where there is likely to be significant donor variability), how to address deviation from the acceptance criteria or specifications or CQAs or critical process and performance indicators or CQAs, and **natural history studies**.

Resources:
FDA: Potency Tests for Cellular and Gene Therapy Products
FDA: Characterization and Qualification of Cell Substrates and Other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease Indications Products
FDA: Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process
FDA: Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) Meeting
FDA: Rare Diseases: Natural History Studies for Drug Development
USP: <1043>—Ancillary Materials for Cell, Gene and Tissue-Engineered Products
Website: The Regenerative Medicine Standards Landscape
Website: US Pharmacopeia USP29

4.4 CGT Aseptic Manufacturing

As is the case with biologics, new CGT products (especially autologous or allogeneic cells) must have established appropriate conditions for aseptic processes early in development. The decision to use open or closed systems or single-use components, the appropriate connection technology, and isolators, while maintaining a fully closed aseptic system - will be largely dependent on the product type, cell manipulation treatment (manual or automated), and handling required to minimize the bioburden/ contamination levels in the final drug product. Simulating appropriate aseptic procedures, defining aseptic boundary for cell/tissue processing, and demonstrating comparability of lot-to-lot process and drug product consistency and quality are critical components to address during development.

In addition, you should assess how the aseptic system can reduce the risk associated with direct product manipulation, and whether it allows for an increase in the number of product batches that a production operator can control at a given time. Selection of an unsuitable aseptic technology system can severely affect the process's scalability, reproducibility, and safety. For additional information, see Section 8.6 in the Regulatory Knowledge Guide for Biological Products.

Resources:

FDA: Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice
FDA: cGMP for Phase 1 Investigational Drugs
FDA: FDA Perspective on Aseptic Process Simulation for Cell Therapy Product Manufacturing

4.5 Freeze-Thaw Process

CGT products are unusually sensitive to freeze-thaw conditions. During clinical development, develop a qualified freeze-thaw process. The CGT products recommended in-use period will have to be justified, including its compatibility with any diluents used in reconstitution, with appropriate devices used for administration.

It is likely that the CGT **drug substance** is manufactured at one site and shipped to another contract manufacturing organization (CMO) for fill-finish operations. Therefore, you will have to demonstrate that the manufacturing process's shipping, thawing, filtration, and filling steps are controlled effectively at the CMO site and appropriate scale to produce a drug product that consistently meets the established product quality acceptance criteria.

5 Post-Market Authorization

You will need to conduct **post-market studies** to ensure safety, efficacy, optimal use of the drug, production consistency and reliability of the product quality. Consult with FDA on the requirements of post-marketing studies for your CGT product.

5.1 Manufacturing and Label-Claim Changes

In an annual report to FDA, you will need to document any post-approval changes in the product specifications, components, manufacturing process (batch size, container closure systems), labeling, quality controls, equipment, manufacturing facilities, or any other changes that may impact product quality. Any changes in the process or at the facility will have to be supported by a prospective comparability study using established protocols. Such studies need to demonstrate—by a combination of analytical testing and limited animal or clinical studies—that the changes do not negatively impact product similarity and product attributes (such as efficacy, stability, and safety). Note that it is rare for analytical comparability to be sufficient for complex CGT products and that a limited animal or clinical study is often required to determine if a change impacts product attributes. For additional information, see Section 8.5 in the Regulatory Knowledge Guide for Biological Products.

Resources:

FDA: CBER Advanced Technologies Team (CATT)
FDA: Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products

5.2 Post-Marketing Activities of CGT Products

The aim of pharmacovigilance within the industry is to protect patients from unnecessary harm by identifying previously unrecognized drug hazards, elucidating pre-disposing factors, refuting false safety signals, and quantifying risk in relation to benefit. There is considerable uncertainty about the nature and frequency of safety problems that might be associated with specific types of CGT products. These CGT-specific safety concerns include rejection and graft versus host reactions (e.g., for allogeneic products), transformation of tissues into different lineages, oncogenic potential, and migration or distribution. As a result, you will have to conduct additional pharmacovigilance monitoring activities for several years after **Market Authorization**. The specific pharmacovigilance monitoring program will depend on multiple factors, such as the nature and mechanism of action of the product, the study population, the results of animal studies, and any related human experience. Post-approval monitoring is a critical component of lifecycle management for CGT products.

These publicly available pharmacovigilance program for previously approved CGT products (examples below) may be useful to review:

- Summary Basis for Regulatory Action Yescarta (CAR-T)
- Summary Basis for Regulatory Action Zolgensma (AAV product)
- Summary Basis for Regulatory Action Kymriah (CAR-T)
- Summary Basis for Regulatory Action Luxturna (AAV)

Resources:

FDA: Consideration for Early-Phase Clinical Trials of Cellular and Gene Therapy Products
FDA: Long Term Follow-Up After Administration of Human Gene Therapy Products
FDA: E2E Pharmacovigilance Planning

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Appendix A. CMC Readiness Checklist for Expedited Pathways

Y/N	**Chemistry Manufacturing and Control Readiness Checklist for CGT Product Expedited Pathways**
	Have you devised a plan for commercial manufacturing scale-out or scale-up considerations? Has the plan about commercial scale manufacturing been discussed with the regulatory agency?
	Have you performed a careful review of your manufacturing process to ensure that you are entering pivotal clinical trials with a product that is optimal?
	Have you introduced major manufacturing changes that may require conducting comparability studies and if so, what is your plan for conducting those studies?
	What is the status of your analytical method development? Have you qualified or preferably validated your assays prior to initiation of your pivotal trial?
	Do you have appropriate potency assays in place for the final drug product?
	Do you understand your product's **critical quality attributes** and critical process parameters?
	Have you determined the shelf life of the final drug product by conducting stability assays using assays that are appropriate and qualified/validated?
	Do you have a well-defined plan to collect materials and reserve samples for in process and the final drug product?
	What is your plan of action for conducting process validation to demonstrate that the final drug product can be successfully manufactured consistently?
	Have you defined standard operating procedures, protocols, and/or instructions for use in outlining any additional manufacturing, processing, formulation, or thaw/dilution of the final drug product at clinical sites?
	Do you plan to gain a better understanding of the requirements for conducting leachable and extractable studies for materials that are in direct contact with your product?
	What is your plan for manufacturing of the final drug product? Do you anticipate needing to make a change to your existing facility or ship the drug substance for fill finish activities?
	Do you plan for automation, scale-out, or scale-up post approval or prior to initiation of the pivotal clinical study?
	Are there any existing, functionally closed platforms that allow manufacturers to manufacture products requiring less environmental control and monitoring? Can isolators be used as part of the manufacturing process?
	What is the appropriate and flexible environment for product manufacturing based on the current state of manufacturing? Can they move to manufacturing platforms earlier which are less open to the environment and more amenable to aseptic sampling?
	Is it feasible to perform manufacturing near patient sites? Is it possible to manufacture the drug product at point of care?

Y/N	Chemistry Manufacturing and Control Readiness Checklist for CGT Product Expedited Pathways
	Have you made a final determination of whether the current release specifications are adequate for ensuring safety and potency of your final drug product?
	Have you conducted shipping validation for source materials and the final drug product under worst-case scenarios or conditions of transport?
	Have you developed a qualified freeze-thaw process prior to its implementation, and it's recommended in-use period?
	Have you reviewed the quality of ancillary materials as well as the reliability and sustainability of your supply chain. Do you have a plan to review your quality agreements and standard operating procedures that are in place for material qualification and vendor qualification? Have you developed an identity test for your critical ancillary materials?
	Have you confirmed your choice of the final container and have a plan for how to affix the label on the final drug product?
	What is your plan for testing of the source material, in process materials, or the final drug product? Do you plan to outsource your testing, or will it be conducted in-house?
	Do you need to develop any in-house standards (physical or performance standards) for your assays? Do you know what reference standards are needed for your product development and release testing?
	Have you had an End-of-Phase 2 meeting with FDA to assess your CMC readiness?
	Do you have enough product to support the phase-appropriate Phase I clinical trials and material overage to support stability and ancillary studies?
	Does the process development, engineering batch, and GMP manufactured batch meet the equivalence/comparability criteria for process and product critical quality attributes and dose requirements?
	Are special formulation, dose, and packaging considerations required for pediatric populations and adult populations?
	Do you have all the relevant information to support IND filing related to Module 3 for manufacturing process and control information for drug substances (3.2.S) and drug products (3.2.P)?
	Do you have all the relevant source documentation from the manufacturer to support the investigational new drug and biological license application filing?

Appendix B. Decision Making Flow Chart for Regulating Human Cells, Tissues, and Cellular-Based Products

Flow chart describing decision-making process for whether human cells, tissues, and cellular and tissue-based products (HCT/Ps) are regulated as "351" versus "361" under the Public Health Services (PHS) Act. Also see the FDA webpage for following examples: FDA Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P's) Product List. HCT/P Regulation Solely Under Section 361 and 21 CFR 1271.