US Regulatory Update 2024: New Guidance Documents From FDA OTP

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CGT-Related Guidance Documents – August 2023-August 2024

Potency Assurance for Cellular and Gene Therapy Products

- Expands on the existing potency testing guidance, describing a comprehensive <u>potency assurance strategy</u>
  - "a multifaceted approach that reduces risks to the potency of a product…"
  - "…help ensure that every lot of a product will have the potency necessary to achieve the intended therapeutic effect."
  - Process designed to consistently produce a potent product
  - Process control - "[control] aspects of the manufacturing process that may affect potency"
    - Materials quality, control or monitoring of process parameters, in-process testing
  - Lot release testing for quality attributes related to potency
- Quality Risk Management-based approach
  - QTPP
  - Control strategy – process controls and product quality controls
  - Understanding of CQAs and CPPs
  - Risk assessment and risk reduction

Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products

Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products

- Cellular Starting Material
  - "**Particular consideration should be given to patients who have received CAR T cells previously.**
  - "…due to lack of response to the previously administered CAR T cells, relapse of the same condition, or treatment for a different malignancy."
  - "CAR T cells manufactured using cellular starting material (e.g., leukapheresis) from patients who have received CAR T cells previously may differ from the same type of CAR T cells manufactured using cellular starting material from patients who have not."
  - Previously administered CAR T cells in the starting material may have unexpected effects on CAR T cell manufacturing (e.g., expansion or transduction rates), potency, *in vivo* expansion, safety, and efficacy.
  - "…**evaluation of the previously administered CAR T cell levels in the cellular starting material** may be appropriate. This may be accomplished by **detection of common vector or CAR features to evaluate the presence of previously administered CAR T cells.**"
- CAR T cell analytical testing
  - "For allogeneic CAR T cells, where each product lot is meant to treat multiple patients, additional testing… may be appropriate. For example, additional adventitious agent testing, stringent acceptance criteria for the number of potentially alloreactive lymphocytes, and absence of aberrant growth should be included in lot release testing."

Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products

- Vector Copy Number
  - "We recommend that the VCN release criterion be justified based on a risk assessment. The risk assessment may include supporting data from studies such as insertion site analysis, clonal dominance, dose, indication, study population, etc. Supporting experimental data may be obtained from developmental and engineering manufacturing runs.
  - **For CAR T cells manufactured without extended culture, determining the stably integrated VCN at the time of lot release testing may be difficult** (e.g., due to persistence of episomal copies of non-integrated vectors). In some cases, **an interim VCN assessment at the time of lot release, followed by subsequent VCN assessment(s) on cultured CAR T cells, may be needed to determine the stably integrated VCN.**"
- Potency testing
  - "If the CAR T cells express multiple transgene elements, each transgene may contribute to product safety and efficacy and therefore should be adequately controlled. **A potency assay to measure the intended biological activity of each element may be needed**, depending on the contribution of each transgene to the product's activity.
    - If the CAR T cell targets multiple antigens (e.g., CD19 and CD22), you should assess the activity of the CAR T cells against each individual target antigen…"
    - If the CAR T cell includes a cytokine transgene to enhance the CAR activity, you should assess the activity of the CAR T cells against the target antigen and production of the transgenic cytokine…
    - If the CAR T cell includes a transgene conferring drug resistance, you should assess drug resistance and CAR T cell activity because they have independent mechanisms of action."

Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products

- Multisite manufacturing
  - Demonstrate product and analytical method comparability across manufacturing sites
  - Confirm GMP compliance at all sites
  - "We recommend using the same standard operating procedures (SOPs), training, reagents, and equipment across manufacturing facilities, when possible."
  - "…demonstrate analytical comparability of the products manufactured at each site by submitting data from CAR T cells manufactured using the same cellular starting material (e.g., splitting the leukapheresis starting material from the same donor)."
  - "list …methods used for testing and the predefined acceptance criteria used for determining analytical comparability."
  - "…identify a reference site to which all other sites are compared."
- Multisite testing
  - "…assay transfer protocol to ensure that non-compendial testing performed at each site is suitable for the intended purpose and is reproducible among all testing sites."
  - "…same SOPs, reference materials, reagents, and equipment… across testing facilities, when possible."
  - "When available, standard materials should be used to calibrate equipment at multiple sites…"

Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products

- Target identification
  - "The anti-tumor effect of the CAR T cells depends on the binding of the CAR with the cognate antigen expressed on the cancer cell. Therefore, **it is essential to enroll patients whose tumors express the antigen targeted by the CAR T cells**. If a test for the target antigen is not commercially available, **a companion diagnostic test may need to be developed to appropriately select subjects for the study.**"
  - Not stated but must be needed for approval and Phase IV. Guidance references:
    - Investigational *In Vitro* Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk Determination: Guidance for Industry, October 2019, https://www.fda.gov/media/112605/download.
    - Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product: Draft Guidance for Industry and Food and Drug Administration Staff, July 2016, https://www.fda.gov/media/99030/download.

Safety Testing of Human Allogeneic Cells Expanded for Use in Cell-Based Medical Products

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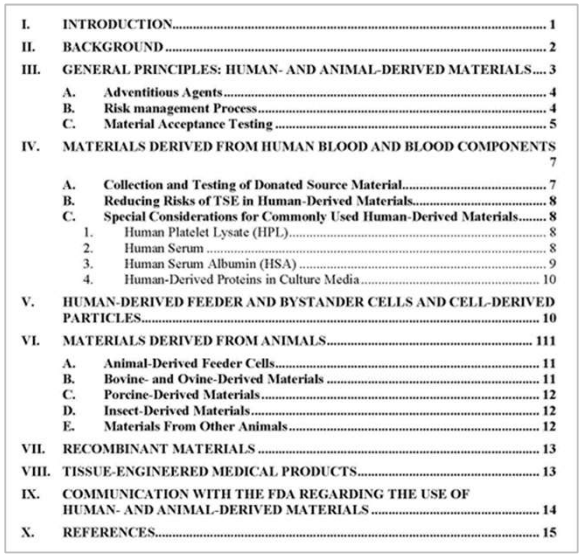
Cells	Cell Culture and Preparation	Product Use	Safety Testing
ES cells and allogeneic iPSCs	Cells expanded into MCB and WCBs. WCBs differentiated into final cell therapy product.	Potentially, many individuals	Test MCB and WCBs per section V, "Highly Expanded Cells"
Immortal cancer cell lines and transformed cell lines	Cells expanded into an MCB and WCBs. Cell-based product derived from WCBs.	Potentially, many individuals	Test MCB and WCBs per section V
Primary allogeneic cells capable of extensive expansion (highly expanded)	Cells expanded to make MCB. MCB vials thawed and expanded to make final product.	Potentially, many individuals	Test MCB and WCBs (if any) per section V
Primary allogeneic cells, including some genetically engineered cells, capable of limited expansion before loss of cell quality	Cells expanded several passages to make a small to midsized MCB or a single lot of cells that is the cell therapy product.	Limited number of individuals	Test MCB or lot of expanded cells, or EOP cells per section VI
Primary allogeneic cells expanded in culture	Cells expanded to make product lots of cells for a few subjects or a single subject.	A few individuals or a single individual	Test expanded cells for sterility, mycoplasma, and endotoxin

Safety Testing of Human Allogeneic Cells Expanded for Use in Cell-Based Medical Products

Partial Summary of Required/Recommended Testing

Testing	Extensively Expanded Cells (Section V)		Cells With Limited Expansion Potential (Section VI)
	MCB	WCB	X
Sterility	X	X	X
Mycoplasma	X	X	X
Specific pathogens: HIV 1&2, HTLV 1&2, HBV, HCV, CMV, EBV, Parvo B19, HPV, HHV-6, -7, -8, JCV (human polyomavirus 2), BK virus "as appropriate"	X		X
In vitro adventitious virus testing	X	X	X
In vivo adventitious virus testing	If "specific risk factors that are not fully mitigated by other types of testing"		
TEM	X		
Retroviral testing	If cultured on non-human cell feeder layers		
Species-specific virus testing	X		
Bovine- or porcine-derived virus testing (CFR 113.47, CFR 113.53(d))	If bovine– or porcine-derived reagents are used.		Additional safety testing if animal-derived reagents are used
Residual viral and plasmid reprogramming vectors –iPSC lines	Cell bank, DS, or DP		
Whole genome sequencing and analysis	Cell banks of continuous cell lines and genome edited cells		

Considerations for the Use of Human- and Animal-Derived Materials in the Manufacture of Cellular and Gene Therapy and Tissue-Engineered Medical Products



- Materials Derived From Human Blood and Blood Components
  - "…human AB serum can be manufactured from whole blood, single-donor plasma, or Source Plasma.
  - Testing requirements for Source Plasma are different than those for whole blood and plasma.
  - Source Plasma intended solely for further manufacturing use
  - Not required to be tested for HTLV, WNV, and Chagas disease. Less stringent requirements for syphilis testing.
  - Regulatory submission should document the type of donated source material (e.g., blood, plasma, platelets, Source Plasma, etc.) used to manufacture the human-derived material.

Considerations for the Use of Human- and Animal-Derived Materials in the Manufacture of Cellular and Gene Therapy and Tissue-Engineered Medical Products

- Reducing Risks of TSE in Human-Derived Materials
  - Recommendations to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease by Blood and Blood Components; Guidance for Industry, May 2022, https://www.fda.gov/media/124156/download
- Special Considerations for Commonly Used Human-Derived Materials
  - HPL, human serum, HSA, human-derived proteins in culture media
  - "Presence of a human-derived protein in cell culture media… may not be immediately apparent on the COA supplied for the medium."
  - "Document in the submissions to FDA the presence of human-derived proteins in all media used to manufacture CGT products and TEMPs."
  - "Include information to document conformance to donor testing requirements specified in 21 CFR 610.40 and that the human-derived material has been manufactured using procedures that have been validated to clear or inactivate human adventitious agents."

Considerations for the Use of Human- and Animal-Derived Materials in the Manufacture of Cellular and Gene Therapy and Tissue-Engineered Medical Products

- Recombinant Materials
  - "Recombinant human or animal proteins, such as growth factors and antibodies, particularly growth factors marketed for research purposes, may contain impurities or contaminants from the expression system. This may also include adventitious agents."
  - "Monoclonal antibodies may be used as reagents in drug manufacturing… Refer to Guidance… "for considerations to ensure that monoclonal antibodies are free of adventitious agents or process-related impurities."
    - Guidance for Industry: Monoclonal Antibodies Used as Reagents in Drug Manufacturing, (2001)
  - "Some growth factors may be purified by affinity chromatography using monoclonal antibodies that have not been tested for adventitious agents."
  - "It is your responsibility to obtain appropriate information regarding any purification of all recombinant materials used in the manufacture of your CGT products or TEMPs."

Human Gene Therapy Products Incorporating Human Genome Editing

CGT-Related Guidance Documents – August 2023-August 2024

- Potency Assurance for Cellular and Gene Therapy Products; Draft Guidance – December 2023
- Advanced Manufacturing Technologies Designation Program; Guidance for Industry – December 2023
- Considerations for the Development of CAR-T Cell Products – January 2024
- Human Gene Therapy Products Incorporating Human Genome Editing – January 2024
- BLAs and Master Files – final rule
- Safety Testing of Human Allogeneic Cells Expanded for Use in Cell-Based Medical Products; Draft Guidance – April 2024
- Considerations for the Use of Human-and Animal-Derived Materials in the Manufacture of Cell and Gene Therapy and Tissue-Engineered Medical Products; Draft Guidance – April 2024
- Platform Technology Designation Program for Drug Development; Draft Guidance – May 2024
- Risk Evaluation and Mitigation Strategies (REMS) for Autologous CAR-T Cell Immunotherapies Modified to Minimize Burden on Healthcare Delivery System – June 2024
- Essential Drug Delivery Outputs for Devices Intended to Deliver Drugs and Biological Products – June 2024 (includes 351 products)

More CGT Guidance Documents on FDA-CBER's 2024 Agenda

- Frequently Asked Questions — Cell and Gene Therapy Products; Draft Guidance for Industry
- Accelerated Approval of Human Gene Therapy Products for Rare Diseases; Draft Guidance for Industry
- Use of Platform Technologies in Human Gene Therapy Products Incorporating Human Genome Editing; Draft Guidance for Industry
- Potency Assessment of Therapeutic Vaccines; Draft Guidance for Industry
- Recommendations to Reduce the Risk of Transmission of Mycobacterium tuberculosis by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps); Guidance for Industry
- Recommendations to Reduce the Risk of Transmission of Disease Agents Associated with Sepsis for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps); Guidance for Industry
- Recommendations to Reduce the Risk of Transmission of Human Immunodeficiency Virus (HIV) by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps); Draft Guidance for Industry
- Recommendations to Reduce the Risk of Transmission of Hepatitis C Virus (HCV) by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps); Draft Guidance for Industry
- Recommendations to Reduce the Risk of Transmission of Hepatitis B Virus (HBV) by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps); Draft Guidance for Industry