ADVANCED CELL&GENE THERAPY

Workshop D
Ex Vivo Gene Therapy Analytics

Scott R. Burger, MD

Hanson Wade Gene Therapy Analytical Development conference
November 30, 2020

Agenda

1:00-1:10 PM	Welcome and introductions
1:10-2:00 PM	Presentation: Analytical Considerations for *Ex Vivo* Gene Therapy Products, Part I
2:00-2:30 PM	Break
2:30-3:15 PM	Presentation: Analytical Considerations for *Ex Vivo* Gene Therapy Products, Part II
3:15-4:00 PM	Roundtable Discussion and Q&A

ADVANCED CELL&GENE THERAPY

Analytical Considerations for *Ex Vivo* Gene Therapy Products, Part I

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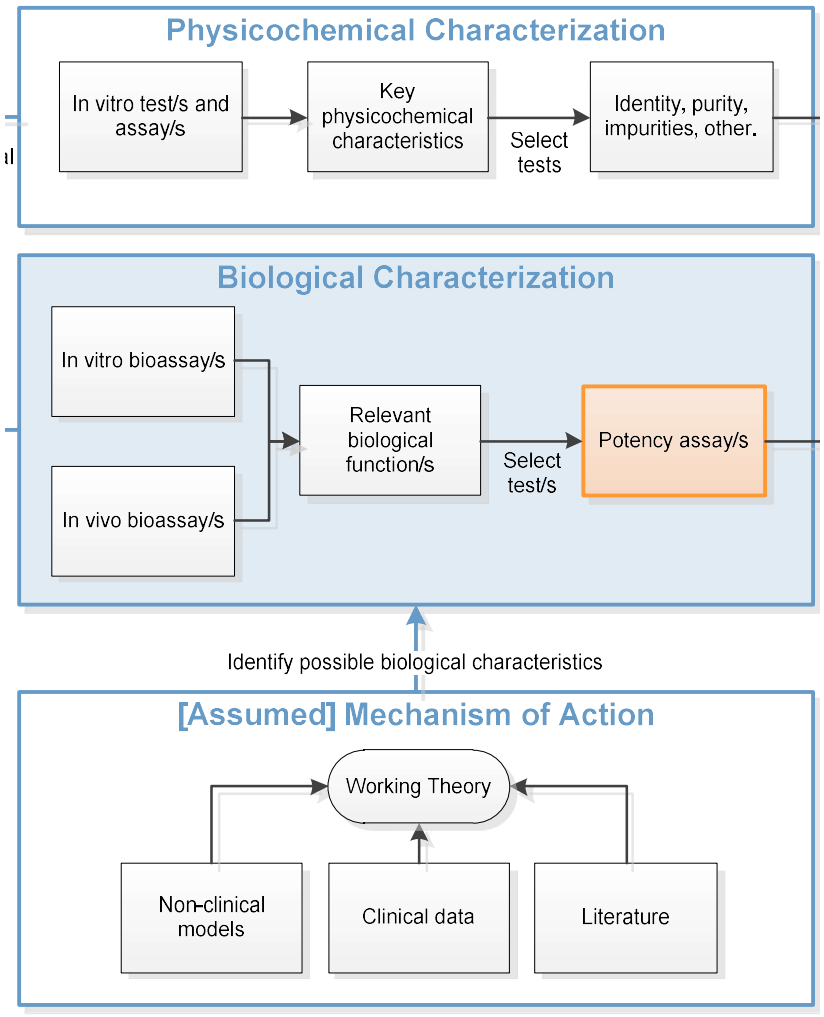
Characterization Strategy



Physicochemical characterization

Use of methods that measure physical and chemical characteristics

Physical: size, morphology, light scattering properties, tensile strength, cell number, confluence.

Chemical: identification of phenotypic markers and secreted substances, genotype, gene expression profile.

Biological characterization

Use of methods that measure biological function, such as how physicochemical characteristics influence biological systems.

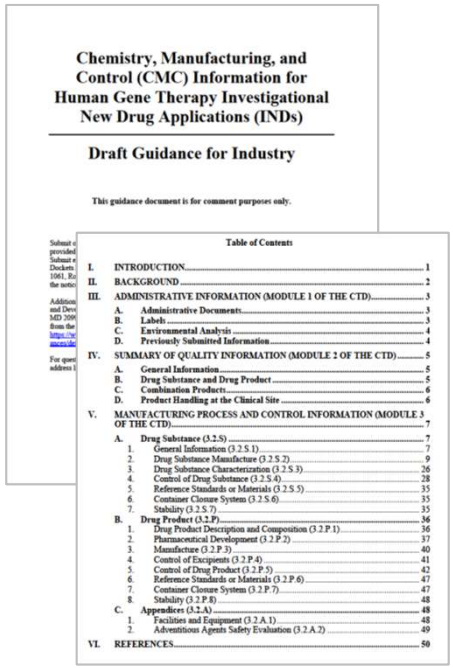
Biological: *in vitro* and/or *in vivo* measurements of cytotoxicity, cell growth, de/differentiation, proliferation, migration, immunomodulation.

Characterization Testing – FDA Requirements Based on 21 CFR 610

- Safety
  - Sterility cultures
  - Mycoplasma
    - PCR-based assay acceptable, if validated against PTC
  - Adventitious agents
    - Blood donor testing (21 CFR 1271) for human-derived cells/tissue
    - More extensive adventitious agent testing if extensively expanded or using animal-derived reagents
    - Replication-competent virus, if relevant
  - Tumorigenicity
- Purity, Identity
  - Measure intended product components, as well as contaminating cells and other undesired agents, including endotoxin.
  - Non-compendial analytical methods commonly used.
  - Cell viability, concentration, morphology, immunophenotype (flow cytometry), IFA, immunocytochemistry, RT-PCR, Q-PCR, microarray analysis…
- Potency
  - Relevant biological function(s). May require functional and nonfunctional assays.
- Stability

FDA Guidance: CMC Information for Gene Therapy INDs – January 2020

- Updates the 2008 FDA Guidance on CMC Information for Human Gene Therapy INDs to fit the Common Technical Document (CTD) format
- Still packed with useful information about CMC information FDA expects and advice about manufacturing and testing
- The checklist for CMC reviewers that was included in the 2008 guidance is not part of the 2018 version, however. Keep the old and new versions on hand.



Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)

Draft Guidance for Industry

This guidance document is for comment purposes only.

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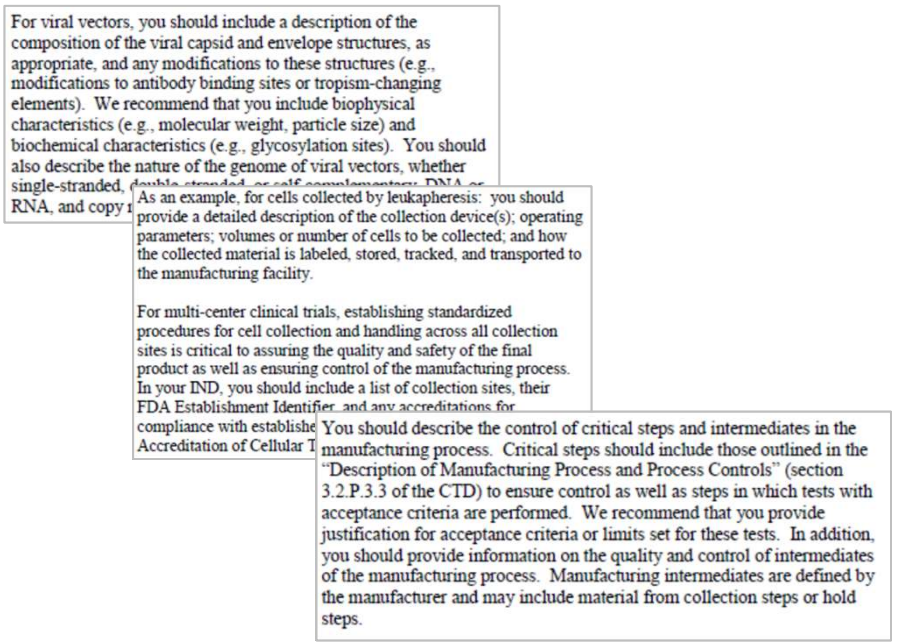


For viral vectors, you should include a description of the composition of the viral capsid and envelope structures, as appropriate, and any modifications to these structures (e.g., modifications to antibody binding sites or tropism-changing elements). We recommend that you include biophysical characteristics (e.g., molecular weight, particle size) and biochemical characteristics (e.g., glycosylation sites). You should also describe the nature of the genome of viral vectors, whether single-stranded, [illegible] RNA, and copy

As an example, for cells collected by leukapheresis: you should provide a detailed description of the collection device(s); operating parameters; volumes or number of cells to be collected; and how the collected material is labeled, stored, tracked, and transported to the manufacturing facility.

For multi-center clinical trials, establishing standardized procedures for cell collection and handling across all collection sites is critical to assuring the quality and safety of the final product as well as ensuring control of the manufacturing process. In your IND, you should include a list of collection sites, their FDA Establishment Identifier, and any accreditations for compliance with establishe Accreditation of Cellular T

You should describe the control of critical steps and intermediates in the manufacturing process. Critical steps should include those outlined in the "Description of Manufacturing Process and Process Controls" (section 3.2.P.3.3 of the CTD) to ensure control as well as steps in which tests with acceptance criteria are performed. We recommend that you provide justification for acceptance criteria or limits set for these tests. In addition, you should provide information on the quality and control of intermediates of the manufacturing process. Manufacturing intermediates are defined by the manufacturer and may include material from collection steps or hold steps.

USP Chapter <1047> Gene Therapy Products

Manufacturing overview
- Ancillary materials
- Characterization, qualification of cell and virus banks
- In-process controls, specifications
- Validation

Manufacturing gene therapy products
- Vector design, immunogenicity
- Manufacturing and purification
- Formulation

On-site preparation, administration
- Monitoring

Analytical methods
- Sampling, dose-defining assays

Stability

Storage and shipping

Labeling

Regulations and standards

Characterization Testing Development

- Establish patterns for purity/identity, function
  - Cell-surface marker expression, humoral factor production, functional assays, gene arrays…
  - Novel methods welcome, *if scientifically valid and controlled*
  - Multiple, orthogonal methods increase sensitivity, robustness
- Assess variability of raw material and product
  - Identify sources of variability, distinguish controllable *vs.* intrinsic/biological variability
  - Donor-to-donor, product-to-product, lot-to-lot variability
- Develop analytical standards and controls. Over time, qualify and validate analytical methods.
  - 21 CFR 610 methods, ***or demonstrate equivalence***
  - At BLA, 21 CFR 610 methods ***or validated alternative methods***

Characterization is expected to improve as clinical development progresses, but analytical rigor is needed from the outset

Consider assay variability and "worst case" in designing assays and setting criteria

Assays are sometimes qualified/validated under ideal or best case conditions, and may factor only one variable at a time. This can lead to overconfidence of an assay. Real world use may involve:

- **Different QC analysts**
- **Different batches of reagents**
- **Different equipment**
- **Samples held for different lengths of time**
- **Different interpretation of procedures due to vague SOPs**
- **Subjective parameters (such as flow cytometry gates, background cut offs, dilutions, etc.)**

Assay variability can confound efforts to demonstrate manufacturing consistency, comparability, or stability.

Safety Testing

- Sterility cultures
  - *Ex vivo* gene therapy products are, by definition, more-than-minimally manipulated, which requires aerobic, anaerobic, and yeast/fungal sterility testing
  - Automated blood culture often used, validate against CFR 610 or USP sterility by Phase III
- Endotoxin (21 CFR 610.13)
  - Specification <5 EU/Kg/hr for i.v. administration
- Mycoplasma (21 CFR 610.30)
  - PCR-based assay acceptable, if validated against PTC
- Adventitious agents
  - Allogeneic products require testing with human blood donor test panel, augmented per 21 CFR 1271 with updates from FDA OTAT as needed
  - Species-specific adventitious agent testing may be required if using primary animal-origin reagents

Replication Competent Virus Testing

- For allogeneic *ex vivo* gene therapy products, must be performed on product MCB, if using:
  - Retroviral-based products (including lentivirus and foamy virus-based products)
  - Adenovirus
  - AAV (unlikely to be used in *ex vivo* gene therapy setting, however)

Purity/Identity Testing

- Test for presence of target cell population(s), as well as potential contaminating cells and materials
- Establish expected pattern and specifications for positive and negative markers
- Multiple analytical methods may be used
  - Flow cytometry, IFA, immunocytochemistry
  - RT-PCR, Q-PCR
  - Microarray analysis
  - Epigenetic fingerprinting
  - Molecular or transcriptional profile
- Qualified assays at Phase I, validated assays by Phase III

Potency - a Measure of Relevant Biological Function

"The specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result."

- 21 CFR 600

Ideally, quantitative bioassay(s) directly related to the mechanism of action

- But the ideal is rarely feasible - multimodal mechanism(s) of action, multiple cell subpopulations potentially involved

- FDA Final Guidance: Potency Tests for Cellular and Gene Therapy Products, 2011
- EMEA CHMP Guideline on Potency Testing of Cell Based Immunotherapy Medicinal Products For the Treatment of Cancer, 2007

Roles of Potency Testing

- Monitoring product quality and lot-to-lot consistency
- Provides data to establish specifications for lot release
- Supports:
  - Product stability studies
  - Comparability studies
  - Clinical data interpretation
- Requires a flexible, progressive approach, begin *early*

Potency Testing: A Flexible Regulatory Approach…

"FDA regulations allow for considerable flexibility in determining the appropriate measurement(s) of potency for each product. Potency is determined based on individual product characteristics; therefore, the adequacy of potency assays is evaluated on a case-by-case basis."

FDA Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products, 2011

Potency Testing: … But There Are Core Requirements

- Potency testing must
  - Indicate product-specific biological activity/activities
  - Measure identity and activity of active components
  - Provide test results for product release
  - Meet pre-defined acceptance and/or rejection criteria
  - Include appropriate reference materials, standards, controls
  - Be feasible to validate (eventually)
    - Established, documented accuracy, sensitivity, specificity, reproducibility of test methods
  - Provide data to establish stability specifications
  - Provide quantitative data
  - Comply with biologics regulations and GMPs
  - Meet labeling requirements
- Correlation with clinical outcome advantageous, but not required

Testing *Ex Vivo* Gene Therapy Product Potency

- Any assay used for biological characterization could be a potency assay if it gives a meaningful indication the product will be ‘potent’.
- One assay alone is unlikely to reflect all the relevant biological effects.
- One or more biological assays may be needed together to define potency.
- Biological characterization allows identification of which assays are candidate ‘potency assays’

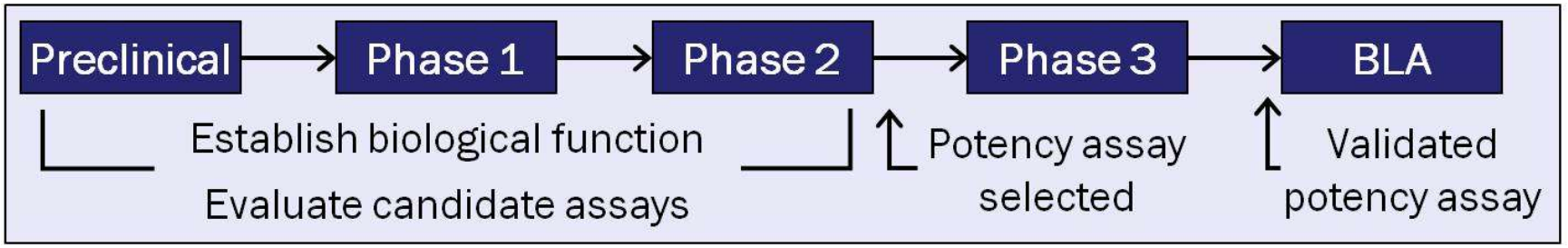
Analytical Methods for Potency Testing

- Biological assays (*in vitro, in vivo*)
  - Functional assay turnaround time may be problematic, requiring qualification of real-time surrogate assays for release
- Non-biological assays
  - Immunologic, biochemical, molecular characteristics
  - Correlate to functional biological assay results
- A matrix approach may be necessary, combining multiple assays, biological and non-biological
- Even semi-quantitative assays can contribute

  "Without quantitative data, demonstrating accuracy and precision could be challenging; however, with proper assay design (e.g., sufficient replicates), you might be able to demonstrate reproducibility."

Progressive Implementation of Potency Testing

- In the course of Phase I and Phase II trials, evaluate multiple candidate assays for *proposed* product function(s)
  - Cytotoxicity, cytokine release, antigen presentation, proliferation, differentiation…
- Adjust assay acceptance criteria throughout product development to reflect manufacturing and clinical experience



Potency Testing: Learn and Adapt

- Expect understanding of product function to be refined throughout preclinical and clinical development

  "Characterization data obtained during product development may provide support for the initial potency assay, or may lead to an improved potency assay."

  "…a considerable amount of data might be necessary to develop a suitable measurement of potency for your product, *and your assay(s) might change over time as you develop your product and learn new information and methods*."

Tumorigenicity Testing

- Required for cell and gene therapy products with potential tumorigenic risk
  - Cell banks isolated from certain types of stem cells, from genetically modified cells, or from extensively expanded cells
- Tumorigenicity testing should be performed under conditions that resemble the intended use of the cells

Testing Autologous *vs.* Allogeneic Products

Allogeneic "Universal Donor"

- Immunogenicity
  - Functional assays of immune response, proliferation, MLR, etc.
  - Immunophenotype, HLA expression
- Inter-donor variability, stability of product/intermediate
- Cell bank comparability
- Cell bank testing requirements

Autologous/Patient-Specific

- Establish magnitude of inter-patient variability, acceptable and unacceptable ranges
  - Variability of cell/tissue raw material, impact on manufacturability
- Release testing on each product, for each patient
  - Potential for process control/validation to reduce test battery and analytical costs

Cell Bank Testing – Allogeneic Products

- Requirements based on 21 CFR 610.18
- Safety, identity, purity
  - Cytogenetic characteristics and tumorigenicity
  - Growth characteristics
  - Presence of detectable microbial agents
  - Raw materials
- Cell banks from different donors must be tested for comparability
  - Identity, biological activity, immunogenicity, tumorigenic potential

Cell Bank Testing – Allogeneic Products

	Master Cell Bank	Working Cell Bank
Safety		
• Sterility	✓	✓
• Mycoplasma	✓	✓
• Human adventitious agent testing (+ xeno, if relevant)	✓	
• Adventitious agents, species-specific virus testing	*In vitro* and *in vivo*	*In vitro*
• Tumorigenicity (if required)	✓	
• Replication competent virus testing (if relevant virus)	✓	
Purity/identity*	✓	✓
Stability	✓	

* Examples of identity testing methods include cell surface markers, isoenzyme analysis, karyotype, short tandem repeat (STR) profiling, etc.

Final Product Release Testing

Overview of Analytical Tests for Cell and Gene Therapy Biological Products from USP <1047> Gene Therapy Products

Test	Gene-Modified Cellular Gene Therapy Product	Gene Therapy Products	
		Viral	Nonviral
Identity of Biological Substance	▪Surface marker determination ▪Species ▪Morphology ▪Bioassay ▪Biochemical Marker	▪ Restriction enzyme map ▪ PCR ▪ Immunoassay for expressed gene ▪ Sequencing	▪ Restriction enzyme map ▪ PCR ▪ Immunoassay for expressed gene ▪ Sequencing
Dose	▪Viable cell number ▪Enumeration of specific cell population ▪Total DNA ▪Total protein	▪ Particle number ▪ Transducing units (DNA hybridi-zation assay) ▪ Total protein ▪ HPLC assay using authenticated reference standard	▪ Plasmid–DNA weight ▪ Formulated-complex weight HPLC or capillary electrophoresis assay using authenticated refer- ence standard
Potency	▪Viable cell number (cells intended for structural repair) ▪Bioassays - Colony-formation assay - Function of expressed gene - Induction of secondary effect (e.g., human leukocyte antigen (HLA) induction, secretion of cytokines, and up-regulation of surface marker)	▪ Function of expressed gene (induction of secondary effect and other bioassays)	▪ Function of expressed gene (induction of secondary effect and other bioassays)
Purity	▪Percentage of viable cells ▪Percentage of transduced cells ▪Percentage of cells with specific surface marker ▪Process contaminants (e.g., se- rum)	▪ Residual host-cell DNA ▪ Process contaminants (e.g., serum and cesium chloride) ▪ Residual helper virus ▪ Optical density ratio ▪ Residual host-cell proteins ▪ Viral protein profile (HPLC assay for defective or immature particles) ▪ Residual RNA	▪ Percentage of specific physical form (e.g., percentage super- coiled) ▪ Residual host-cell DNA ▪ Residual RNA ▪ Residual host-cell proteins ▪ Residual solvents ▪ Optical density ratio ▪ Process contaminants (e.g., cesium chloride)
Safety	▪Mycoplasma ▪Sterility ▪Pyrogen and endotoxins ▪Adventitious viruses ▪Residual virus ▪Replication-competent vector	▪ General safety ▪ Sterility ▪ Pyrogen and endotoxins ▪ Adventitious viruses ▪ RCV	▪ Mycoplasma ▪ Sterility ▪ Pyrogen and endotoxins

30-Minute Break

ADVANCED CELL&GENE THERAPY

Analytical Considerations for *Ex Vivo* Gene Therapy Products, Part II

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Stability Testing

- Establishes how long the product remains within acceptable limits (purity, potency) for clinical use, when stored at specified conditions for defined periods
- Intended to assure the safety and efficacy of the product upon administration to the patient
- Should reflect duration and conditions of product storage and transport
- Test stability of:
  - Final product from product release to patient administration
  - Process intermediates for any in-process holding steps
  - Critical raw material -- cells, tissue explants
    - Other raw materials may be included in stability testing as clinical development progresses

Regulatory Requirements - Stability Testing

- Stability testing is required at all stages of clinical development, to demonstrate that the product is within acceptable chemical and physical limits for the planned duration of the proposed clinical investigation.
  - 21 CFR 312.23(a)(7)(ii)
  - If a very short-term clinical investigation is proposed, the stability data submitted may be correspondingly limited.
- Extent and rigor of stability testing is expected to increase as clinical development progresses. ***Validated stability testing prior to licensure.***

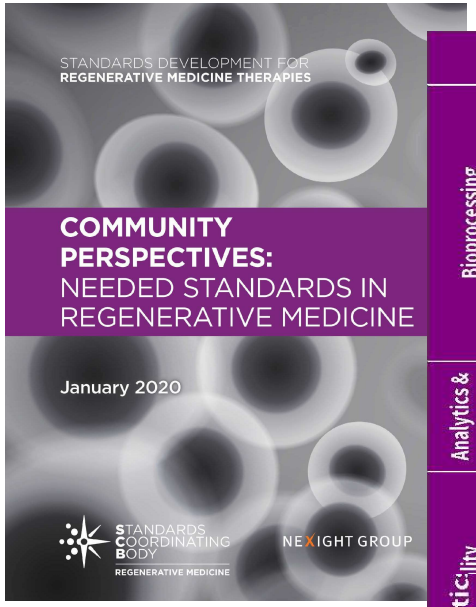
IND Requirements for Stability Testing

- Phases 1-3
  - INDs should include description of stability testing, and data indicating whether the product and components are likely to remain stable for duration of clinical trial.
- Phase 1
  - Basic stability testing protocol, preliminary data indicating product stability
- Phase 2
  - Formal stability protocol in place, acquire additional data
- Phase 3
  - Data from stability protocol supports establishment of dating period, storage conditions, shipping conditions.
  - Begin validation studies using conditions that stress the system. Complete validation studies prior to BLA submission.

Analytical Method Validation

- Appropriately controlled assays for Phase I. Safety testing should be qualified prior to Phase I. Validated assays required by BLA.
- Determine suitability of the analytical method for providing useful data
  - Quantify assay performance characteristics
  - Identify potential sources of error
  - Quantify potential errors
- ICH Q2 method validation parameters
  - Accuracy
  - Precision
  - Limit of Detection
  - Limit of Quantitation
  - Specificity
  - Linearity and Range
  - Ruggedness, Robustness
  - Suitability

Analytical Standards – Work in Progress



	Area of Standard Need	Cell Therapy	Tissue Engr.	Gene Therapy
Bioprocessing and Production	[C1] Ancillary Materials			
	[C2] Cell Collection Procedures			
	[C3] Cell Therapy Manufacturing Equipment			
	[C4] Knowledge Standard for Cell Types			
	[C5] Methods and Processes for Cell Identity & Cell Line Authentication			
	[G1] Framework for Gene Delivery Methods & Gene Editing Tools			
	[G2] Standards Regarding Ethical Considerations of Gene Therapy			
	[T1] Characterization of Scaffold Materials			
	[T2] Donor Tissue Sterilization			
	[T3] Properties of Bioinks used in Bioprinting			
Analytics & Testing Methods	[C6] Cell Counting Methods			
	[C7] Determining & Interpreting Cell Viability			
	[G3] Methods for the Evaluation of Endogenous T-Cell Therapies			
	[G4] Viral Vector Gene Quantification			
Analytic:ility Testin1zation Method	[C8] Human Cell Characterization			
	[C9] Product Potency Measurement			
	[C10] Test Methods to Measure Sterility, Mycoplasma, and Adventitious Agents			
	[C7] Determining & Interpreting Cell Viability			
	[G3] Methods for the Evaluation of Endogenous T-Cell Therapies			
	[G4] Viral Vector Gene Quantification			
Product Quality and Characterization	[C8] Human Cell Characterization			
	[C9] Product Potency Measurement			
	[C10] Test Methods to Measure Sterility, Mycoplasma, and Adventitious Agents			
	[C11] Acceptable Particulates in Regenerative Medicine Products			
	[C12] Release Criteria for Regenerative Medicine Products			
	[C13] Consistent Language and Testing Practices for Sterility Testing Methods			
	[G5] Revisiting Applicability of Standards for Replication-Competent Retrovirus (RCR) Testing			
	[G6] Methods for Assessing Product Activity and Comparability			
	[C14] Chain of Identity / Chain of Custody Recording			

Raw Materials for Manufacturing *Ex Vivo* Therapy Products

- Ancillary materials
  - Materials used in manufacturing, *not intended to be present in final product*
  - e.g., culture media, supplements, cytokines, cell separation reagents
- Excipients
  - Materials *administered as part of the product*, help maintain quality attributes of the cells
  - e.g., electrolyte solutions, cryopreservatives

USP Chapter <1043> Ancillary Materials for Cell, Gene, and Tissue-Engineered Products

- Qualification of ancillary materials
  - Identification, selection, suitability, characterization
  - Vendor qualification, particularly quality control, quality assurance
- Performance testing
  - Does the material function as intended *in your manufacturing process*? Standard functional assay for a reagent doesn't necessarily reflect how the reagent works in *your* process.
- Assess residual levels of ancillary materials
  - Must demonstrate removal/adequate reduction of ancillary material from final product
- Ancillary material qualification is risk-based
  - Higher-risk materials require more extensive qualification
  - 4-tiered risk classification, per USP <1043>

Risk-Based Approach to Raw Materials Qualification

- **Tier 1:** low risk, highly qualified materials
  - e.g. insulin, HSA, other pharmaceuticals
  - Qualify based on CoA, assess removal from final product
- **Tier 2:** low risk, well-characterized, GMP-manufactured materials, not animal origin, used as ancillary material in manufacturing process
  - e.g., clinical-grade growth factors, density gradient medium
  - Qualification as for Tier 1, plus supplier qualification
- **Tier 3:** moderate risk; diagnostic- or research-grade, not intended for use in therapeutic product manufacturing
  - e.g., research-grade growth factors, culture medium
  - Additional testing needed for qualification, to demonstrate quality, performance
- **Tier 4:** high risk, potentially toxic or animal-derived
  - e.g., FBS, animal-origin feeder cells
  - Source animal, documentation of country of origin, additional testing

USP Chapter <1043> Ancillary Materials for Cell, Gene, and Tissue-Engineered Products

Process residuals

- Test for residual ancillary materials (reagents) in final product. Often done as part of testing products of engineering runs.
  - Vector, cytokines, antibodies, sera, etc.
  - Evaluation should be risk-based. Testing is necessary for higher risk reagents. For lower-risk reagents, calculation of removal based on wash volumes may be adequate.
  - Testing should use suitably sensitive assays

Release Logistics: Fresh *vs.* Cryopreserved Products

- Cryopreserved products - preferable
  - Thaw and administer product when release testing complete
  - Release testing performed on pre-cryopreservation product
    - Validate cryopreservation and thaw
    - Clinical product thawed and administered ***without further testing (!)***
- Products administered fresh
  - Sample for sterility culture 24-48 hr before cell harvest, repeat at harvest
  - Stat Gram stain and endotoxin test at harvest
  - Release based on negative 48-hr culture, Gram stain, endotoxin, final results pending
    - Policy and action plan for positive culture results (or other QCT failures) obtained after product administration
- Cryopreserved product thawed and washed prior to administration
  - Validate thaw/wash
  - Stat Gram stain and endotoxin on washed product prior to administration, sample for sterility culture, and action plan as for fresh product

Contract Testing: Role of Quality Agreements

- Agreement between company (client) and contract service provider or supplier
- Establishes clear, mutually agreed expectations for quality, level of services to be provided, mechanisms for verifying quality, and communication
- Assigns responsibilities for QA oversight of operations, regulatory compliance
- Approved by senior management and QA
- The client is responsible for assuring that the vendor is in compliance with regulations - 21 CFR 1271.150(c).

Gene Therapy Products - Common Causes of Regulatory Delays and Hold Actions	

Phase I	• Vector sequence not provided
	• No *in vitro* adventitious agent testing of final vector product, or incorrectly performed *in vitro/in vivo* adventitious agent testing
	• Incomplete human pathogen testing on human cell lines
	• Inadequate QA/QC program
	• Segregation and cleaning procedures inadequately described
	  –Prevent cross-contamination from production of multiple vectors
	• Inadequate lot release testing
	  –RCR assays, endotoxin, sterility testing

Post-Phase 1	• Critical assays (potency, identity, other) are not…
	  –… validated, reproducible, quantitative, sensitive, specific, biologically relevant
	• Stability program inadequate, unsuitable, or absent
	• Characterization data insufficient to establish lot release specifications
	• Comparability not adequately demonstrated
	• Safety issues
	  –High levels of bioburden resulting from contamination

BLA	• *Significant* change(s) made late in development, without adequate product comparability data –Viral clearance evaluation studies may be needed • Process validation data incomplete, inadequate, or absent • Inadequate stability studies • Characterization data inadequate to support establishing specifications • Consistent manufacturing inadequately demonstrated • Compliance issues - contract manufacturers, finish-and-fill facilities, other

Wonnacott, *et al*. Investigational new drugs submitted to the FDA that are placed on clinical hold: the experience of the Office of Cellular, Tissue and Gene Therapy. Cytotherapy (2008) 10(3):312-316.

Summary

- *Ex vivo* gene therapy product characterization and definition are established through preclinical and clinical development.
- Clinical trial experience often is necessary to elucidate relevant biological function and support potency testing development.
- Product stability should be evaluated early in product development.
- Potency testing may require a matrix of methods, developed and refined through Phase III.

References and Resources

- FDA cell and gene therapy regulatory references
- FDA guidance documents specific to cell and gene therapy products
- FDA Guidance: CMC Information for Human Gene Therapy INDs, January 2020
- USP Chapter <1047> Gene Therapy Products
- USP Chapter <1043> Ancillary Materials
- BSI PAS 83 - Developing Human Cells For Clinical Applications in the EU and USA
- BSI PAS 93 - Characterization of Cell Therapy Products
- FDA Final Guidance: Potency Tests for Cellular and Gene Therapy Products, 2011
- EMEA CHMP Guideline on Potency Testing of Cell Based Immunotherapy Medicinal Products For the Treatment of Cancer, 2007
- FDA Guidance: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products, 2007
- Assay Validation International Conference on Harmonization; Validation of Analytical Procedures: Methodology; Q2B, 1996 (www.fda.gov/cder/guidance/ichq2b.htm)
- ICH Q6B: Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products