U.S. FOOD & DRUG ADMINISTRATION

Characterization of Tissue Engineered Medical Products

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Workshop on Measurement Needs for Biofabrication of Tissue Engineered Medical Products
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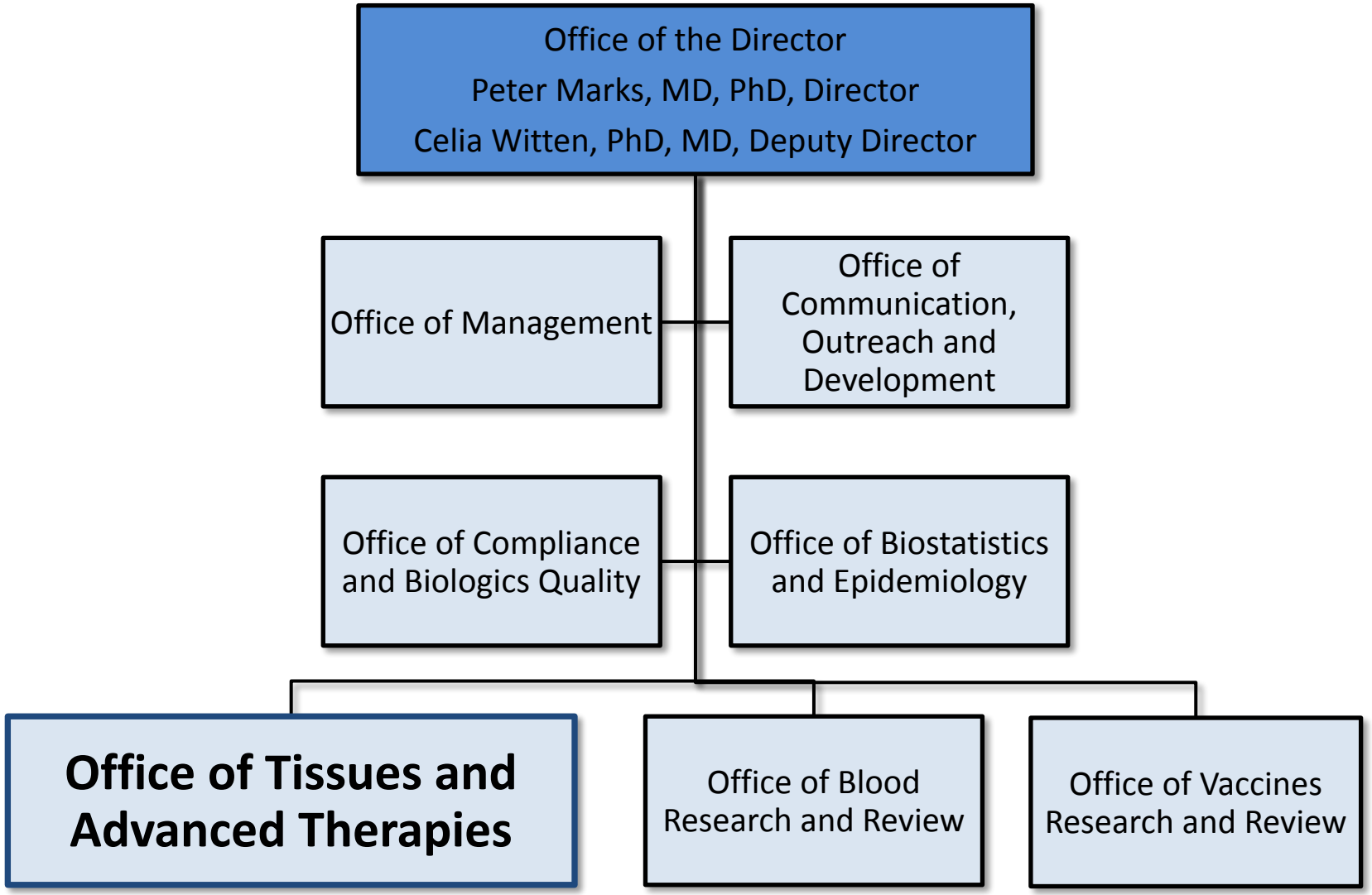
Center for Biologics Evaluation and Research (CBER)



Examples of OTAT-Regulated Products

- Stem cells/stem cell-derived
  - Adult (e.g., hematopoietic, neural, cardiac, adipose, mesenchymal)
  - Perinatal (e.g., placental, umbilical cord blood)
  - Fetal (e.g., neural)
  - Embryonic
  - Induced pluripotent stem cells (iPSCs)
- Functionally mature/differentiated cells (e.g., retinal pigment epithelial cells, pancreatic islet cells, chondrocytes, keratinocytes)
- Products for xenotransplantation
- Tissues
- Devices
- Combination products
  - Tissue-engineered and regenerative medicine products
- Therapeutic vaccines and cellular immunotherapies including antigen-specific and active immunotherapies
- Gene therapies
  - Genetically-modified cells
  - Replication-competent vectors
  - Non-viral vectors
  - Viral vectors
  - Genome editing products
  - Genetically modified organisms
- Blood products
  - Coagulation factors
  - Fibrin sealants
  - Fibrinogen
  - Thrombin
  - Plasminogen
  - Immune globulin
  - Venom antisera for snakes, scorpions, and spiders

REGULATORY CONSIDERATIONS FOR TISSUE-ENGINEERED MEDICAL PRODUCTS (TEMPs)

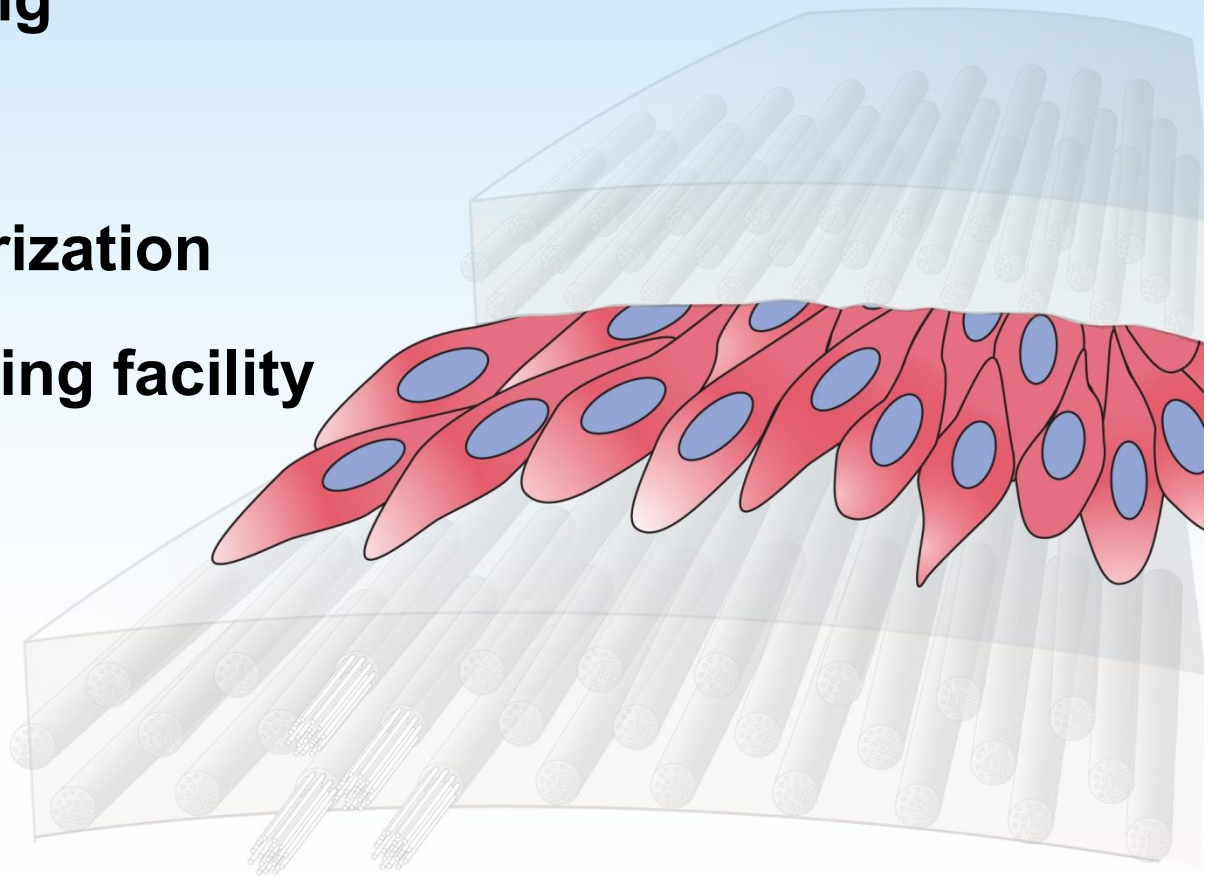
Combination Products

21 CFR 3.2(e)

- A product composed of different categories of regulated articles:
  - Device-biologic, biologic-drug, drug-device, biologic-drug-device (not biologic-biologic, etc.)
- Constituents are:
  - intended for use together
  - required to mediate the intended therapeutic effect
- Can be:
  - Physically or chemically combined
  - Co-packaged; or packaged separately but cross-labeled
- Jurisdiction is assigned based on Primary Mode of Action (PMOA), 21 U.S.C.§ 503(g). PMOA is the primary reason for assignment.
- PMOA is defined as the single mode of action of a combination product that provides the most important intended therapeutic action of the combination product.
  - Final Rule: http://www.fda.gov/OHRMS/DOCKETS/98fr/05-16527.pdf
  - 21 CFR 3.2(k) and (m)

Regulatory Concerns Related to Cells

- Quality of reagents used to prepare cells
- Cell bank safety testing
- Use of feeder layer
- Level of cell characterization
- Quality of manufacturing facility
- Aseptic processing
- Cell viability
- Cell stability



Regulatory Concerns Related to Scaffolds

Quality of materials used to synthesize scaffold

Residual reagents

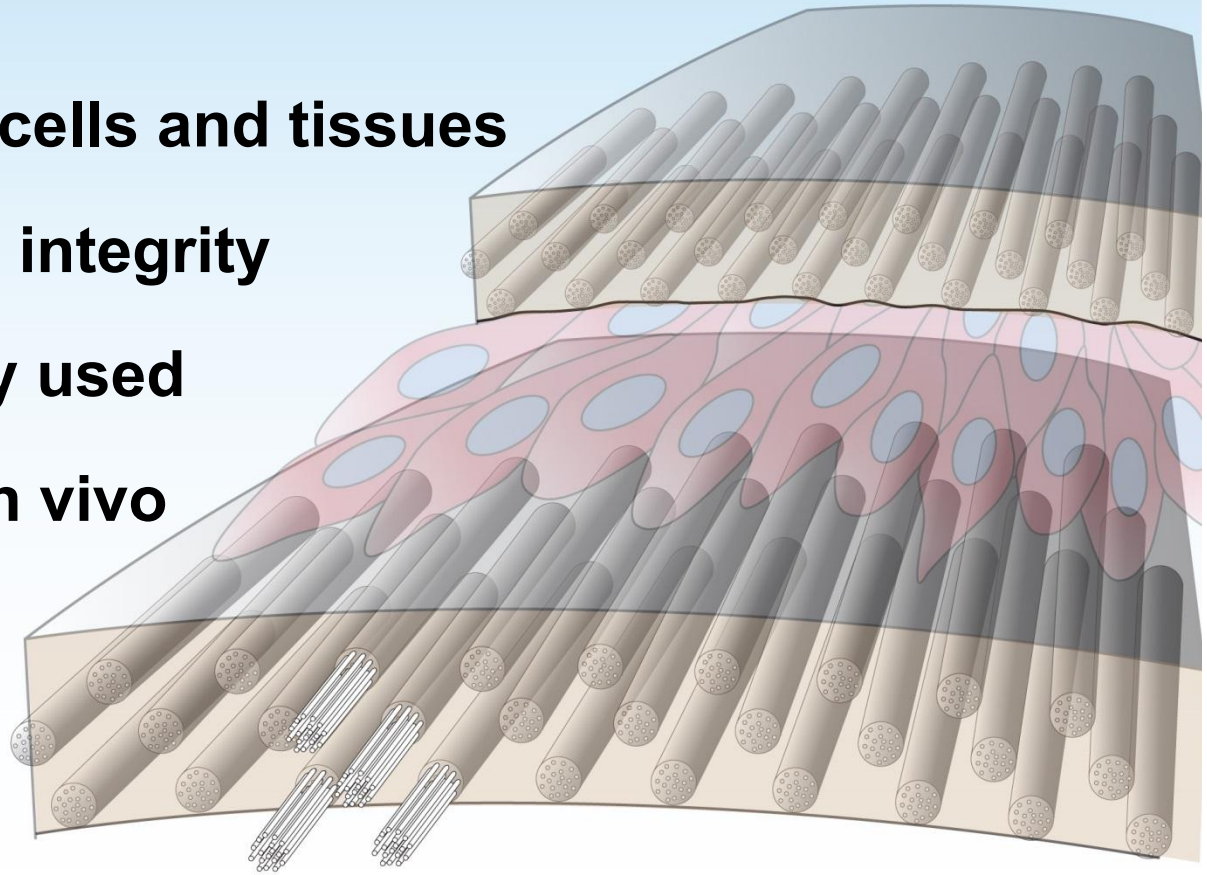
Biocompatibility with cells and tissues

Physical strength and integrity

Equipment and facility used

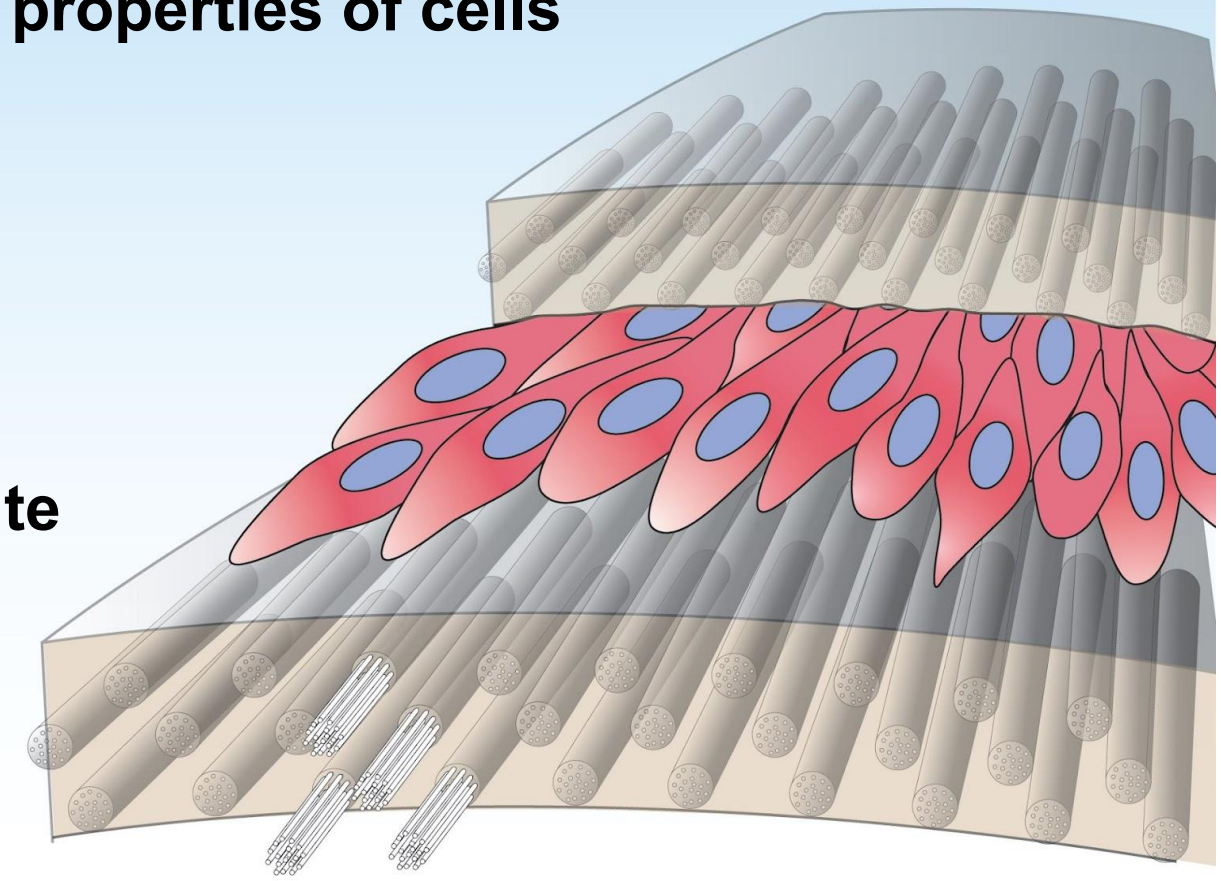
Stability in vitro and in vivo

Scaffold sterilization



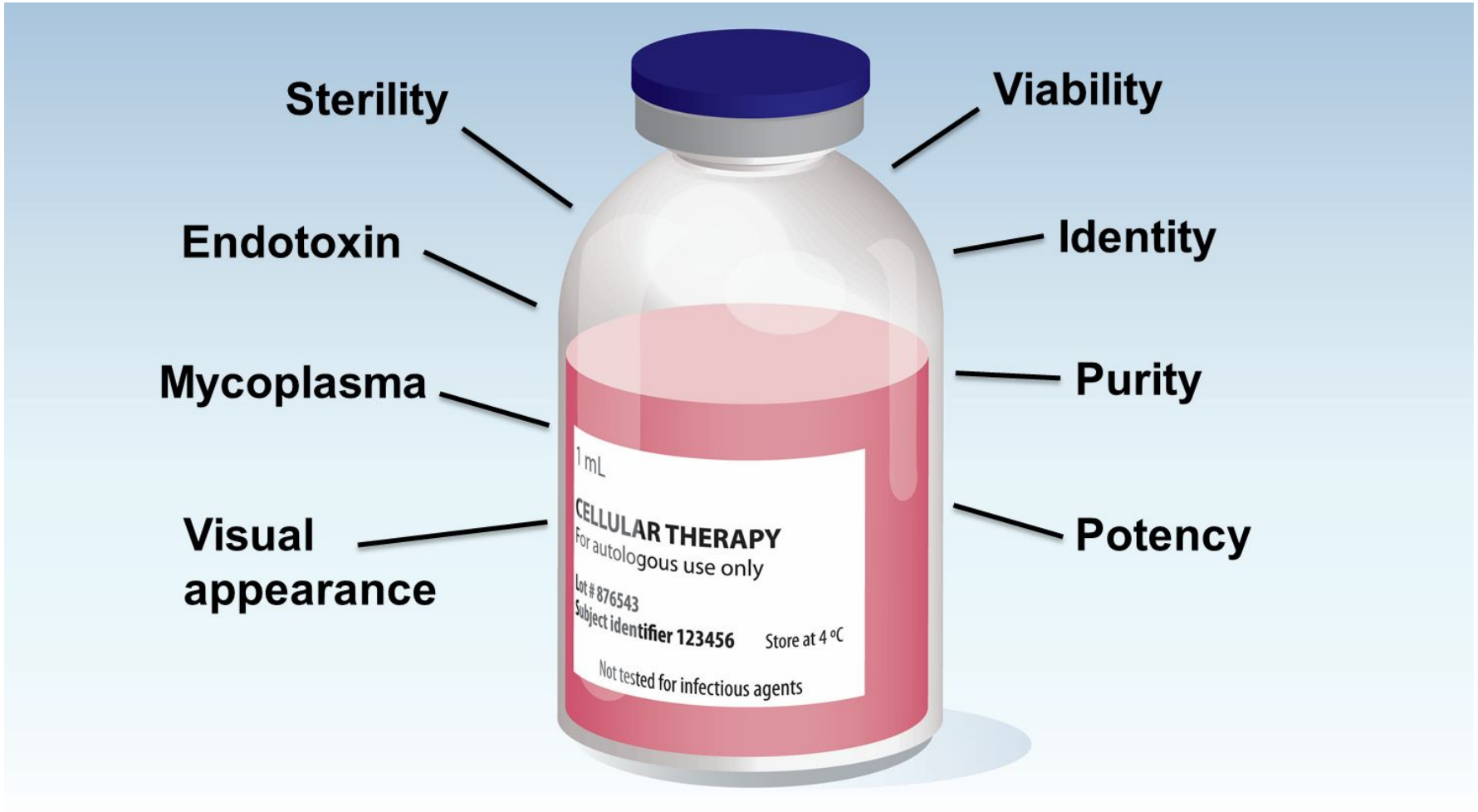
Regulatory Concerns Related to Combined Cell-Scaffold Product

- Impact of cells on properties of scaffold
- Impact of scaffold on properties of cells
- Testing of construct
- Uniformity
- Reproducibility
- Handling at clinical site
- Construct stability
- Shipping



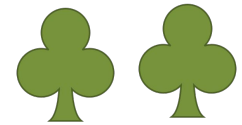
Lot Release Specifications

- Exist to set expectations for product safety and quality
- Lots that don't meet these cut-offs should not be distributed and used



Characterization Methods for TEMPs

- Methods using clinical product
  - Surrogate samples
    - Sample product made using identical materials and manufacturing method, ideally manufactured at the same time as the clinical product.
    - Requires additional data to demonstrate that surrogates are adequate representations of the final clinical product.



  - Portion of clinical product
    - Unused or extra part of clinical product used for testing prior to administration
    - Must demonstrate that portion of clinical product is representative of whole clinical product.

  - Separation of cells from scaffold to evaluate cell characteristics (viability, identity, potency) and scaffold parameters (porosity, strength, degradation)
    - Impact of dissociation of cells from scaffold should be considered

  - Utilization of entire product for lot release testing (sterility, potency, endotoxin, mycoplasma, identity, etc.)

- Lot release testing should be conducted on final product after all manufacturing steps.

Summary

- Tissue engineered medical products are complex and require assessment of the cells, scaffold, and final cell-scaffold product.

- Depending on the TEMP, final product release testing may require use of parts or entire final product. When only parts of the final product or surrogate products are used, sufficient supporting data may be necessary to demonstrate that they adequately represent the clinical product.

- Ensure product quality attributes (e.g., sterility) are not compromised when final product is tested prior to administration by utilizing non-destructive methods (e.g., visual assessment of cells, using portions of the product).

- Seek FDA advice early and throughout product development.

Useful FDA Information

- References for the Regulatory Process for the Office of Tissues and Advanced Therapies (OTAT): http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/ucm094338.htm
- Cellular & Gene Therapy Guidances: https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances
- Additive Manufacturing Guidance: https://www.fda.gov/media/97633/download
- Combination Products Guidances: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/combination-products-guidance-documents
- Interactions with Office of Tissues and Advanced Therapies: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/interactions-office-tissues-and-advanced-therapies

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- **OTAT Learn Webinar Series:**

  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

- **CBER website:** www.fda.gov/BiologicsBloodVaccines/default.htm
- **Office of Combination Products (OCP):** http://www.fda.gov/CombinationProducts/default.htm
- **Phone:** 1-800-835-4709 or 240-402-8010
- **Consumer Affairs Branch**: ocod@fda.hhs.gov
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