

CMC Considerations for Tissue Engineered Product Development

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Presenter Disclosure

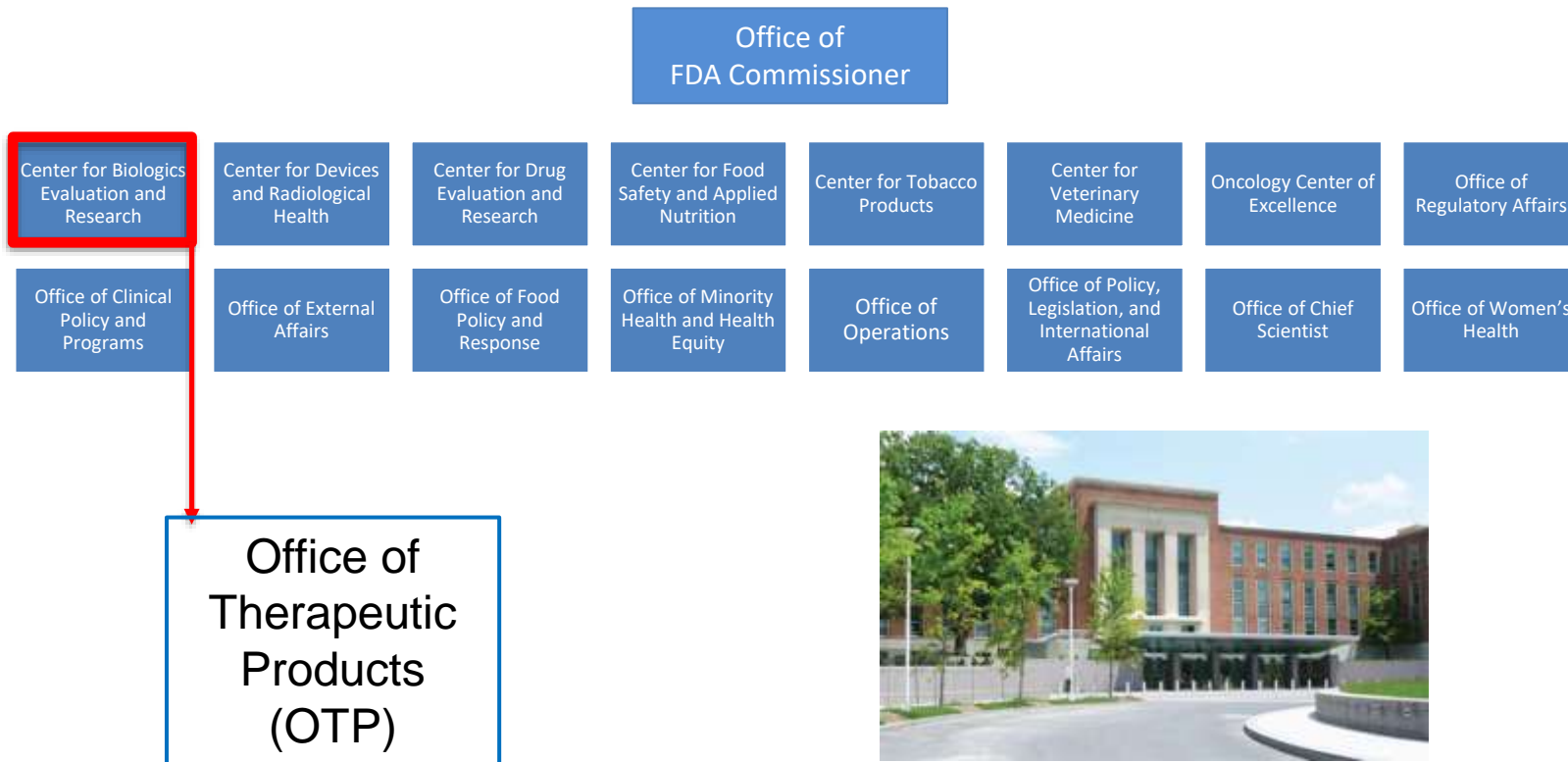


I have no conflict of interest to disclose.
This presentation reflects my views.
It does not bind or obligate FDA.

Learning Objectives

- Understand the advantages and the chemistry, manufacturing and control (CMC) challenges associated with tissue engineered products throughout product development.
- Understand the advantages and challenges associated with expedited product development programs.
- Be aware of key FDA guidance documents and other CMC resources available for manufacturers to assist in the development of tissue engineered products

FDA Organization



What We Do at the Office of Therapeutic Products (OTP)



We protect and enhance public health through the regulation of biological and related products including gene therapies, gene-modified products, tumor vaccines, stem cells, human tissues for transplantation, plasma products, bioengineered tissues and medical devices with biologic output.

<https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/establishment-office-therapeutic-products>

Diversity of Products Regulated by Office of Therapeutic Products (OTP) in CBER



- **Gene therapies (GT)**
 - Ex-vivo genetically modified cells
 - Non-viral vectors (e.g., plasmids)
 - Replication-deficient viral vectors (e.g., adenovirus, adeno-associated virus, lentivirus)
 - Replication-competent viral vectors (e.g., measles, vaccinia)
 - Microbial vectors (e.g., Listeria, Salmonella)
 - Genome-edited 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)
 - Induced pluripotent stem cells (iPSCs)
- **Products for xenotransplantation**
- **Functionally mature/differentiated cells (e.g., retinal pigment epithelial cells, pancreatic islets, chondrocytes, keratinocytes)**
- **Therapeutic vaccines and other antigen-specific immunotherapies**
- **Blood- and Plasma-derived products**
 - Coagulation factors, fibrinogen, thrombin
 - Fibrin sealants
 - Plasminogen
 - Immune globulins
 - Anti-toxins
 - Snake venom antisera
- **Combination products**
 - Engineered tissues/organs
- **Devices**
- **Tissue-based products**

Tissue Engineered Products – MACI

- **MACI** (Vericel): Autologous cultured chondrocytes on porcine collagen membrane; approved under BLA 125603 (2016)
- Indicated for the repair of single or multiple symptomatic, full-thickness cartilage defects of the knee with or without bone involvement in adults.
- <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/maci-autologous-cultured-chondrocytes-porcine-collagen-membrane>



<https://www.maci.com/>

Tissue Engineered Products – STRATAGRAFT

- **STRATAGRAFT** (Stratatech):
Allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen; approved under BLA 125730 (2021)
- Indicated for the treatment of adults with thermal burns containing intact dermal elements for which surgical intervention is clinically indication (deep partial-thickness burns).
- <https://www.fda.gov/vaccines-blood-biologics/stratagraft>



<https://stratagraft.com/>



REGULATORY REVIEW OF TISSUE ENGINEERED PRODUCTS

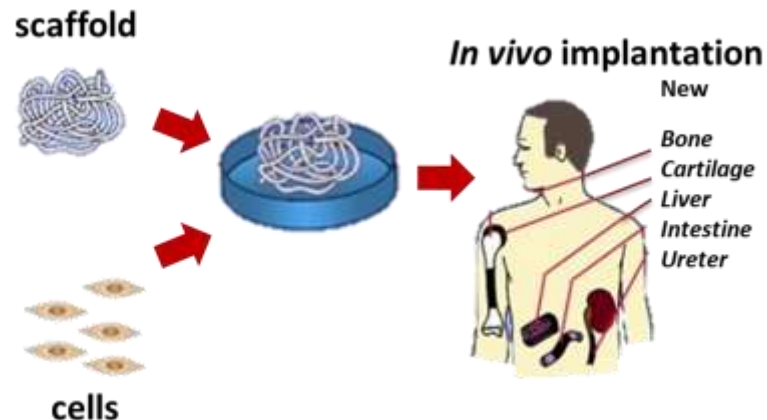
Regulatory Framework for Tissue Engineered Products



- **Human Cells, Tissues & Cellular and Tissue-Based Products (HCT/Ps)**
 - 21 CFR 1271
- **Biologics**
 - 21 CFR 600s
- **Drugs**
 - 21 CFR Part 312 Investigational New Drug (IND)
 - 21 CFR Parts 210/211 Current Good Manufacturing Practices

Regulatory Framework for Tissue Engineered Products

- **Device** (e.g., when a structural scaffold is used in combination with cells or when a delivery device is used)
 - 21 CFR 800s
 - 21 CFR 820 Quality System Regulations
- **Combination Products**
 - 21 CFR Parts 3 and 4





Regulatory Decision Making

- FDA's regulatory decisions in the pre-market and post-market review process are based on a benefit-risk assessment.
- Every regulatory decision involves a unique risk/benefit assessment for the disease, patient population, and agent(s) being evaluated.
- This assessment is informed by science, medicine, policy, regulations, relevant scientific literature and judgment.
 - Data-driven decision making

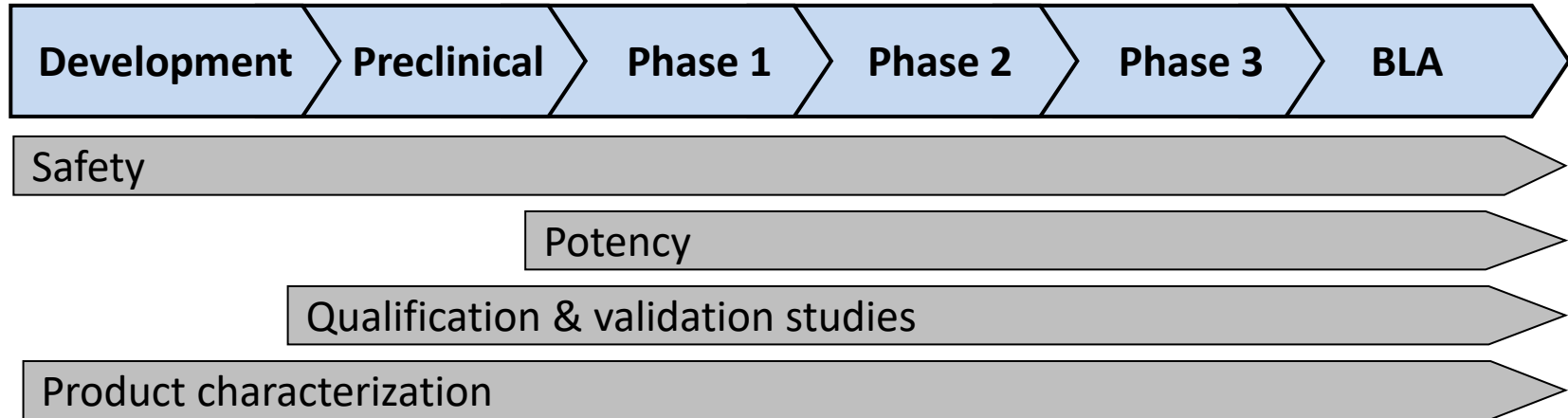
Regulatory Review at FDA is Highly Product Dependent



- Scale – one “lot” for some products could treat thousands of patients, whereas patient-specific products treat just one
- Manufacturing procedures, technologies, and methods can differ widely
- Comprehensive testing is challenging for products with little test material or very short shelf lives
- Risk of product depends greatly on source material and how the product is made
- High inherent variability of some product types makes demonstrating manufacturing comparability and consistency challenging

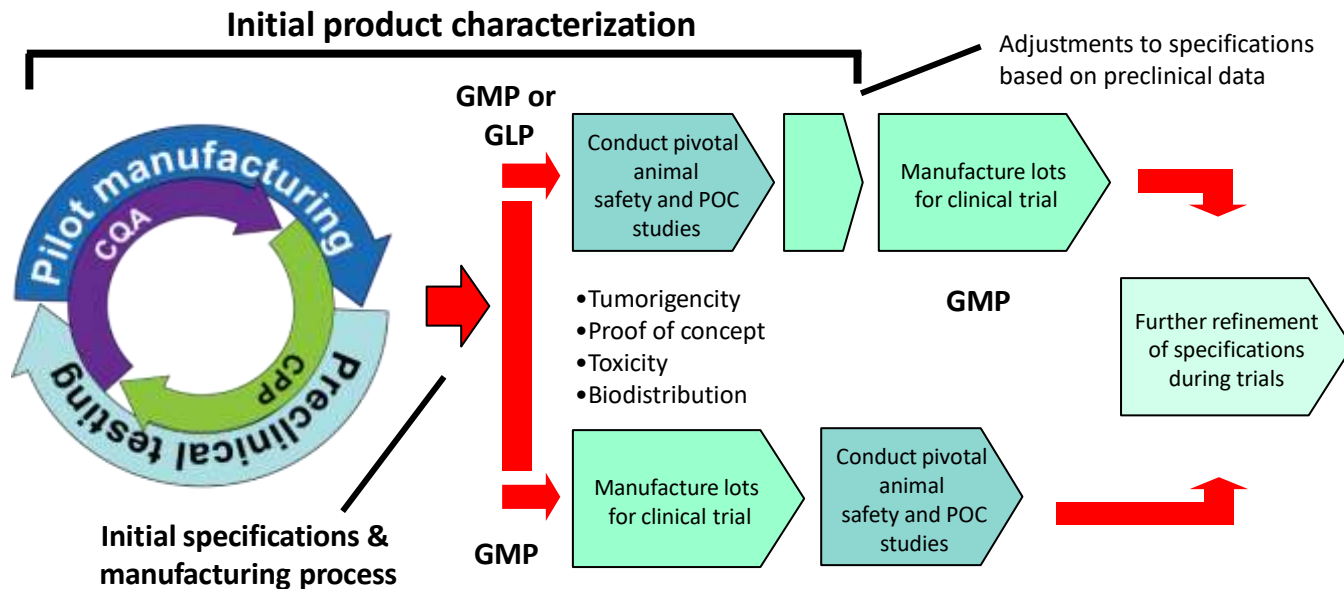
Product Development Lifecycle

- The stage of product development for tissue engineered products guides the review concerns, with safety being the primary concern at all stages



- Safety and quality must be designed into the product
- Sponsors are encouraged to qualify or validate their assays and processes, and develop a potency assay early

Typical Early Product Development Approach



- Early product development and preclinical data are used to justify safety and quality of the product for use in clinical studies
- FDA encourages continual improvements to product quality, but that must be balanced with maintaining product consistency
- Need to be sure that preclinical testing is representative of actual clinical lots

Moving Forward to Clinical Trials

- **Chemistry, Manufacturing and Controls**
 - Describe composition, manufacture, and control of the investigational product
 - Describe testing conducted to assure identity, quality, purity, and potency (biological activity) of the investigational product
 - Demonstrate capability to consistently and reproducibly manufacture the investigational product
 - Provide information on product stability, storage and shelf life
 - Provide information on container, label, and tracking information
- **Pharmacology/Toxicology**
 - Safety and proof of concept testing
 - Perform studies in animal models of human disease – results serve to support a rationale for conducting a clinical trial
 - Toxicological assessment
- **Clinical**
 - Phase of study
 - Describe clinical study and design parameters (objectives, study population, design, protocol)

CMC Expectations for Late-stage Tissue Engineered Products Development



- Have a controlled manufacturing process
 - Sufficient knowledge of the manufacturing process to determine Critical Process Parameters (CPP)
 - Sufficient knowledge to set in-process quality criteria: Action Limits and Rejection Limits
 - Sufficient knowledge to plan for future production scale up/scale out
- Have well developed and qualified/validated analytical assays
 - Have a biologically relevant potency assay in place
- Have sufficient manufacturing experience to refine product acceptance criteria



MANUFACTURING CONSIDERATIONS FOR TISSUE ENGINEERED PRODUCTS

Manufacturing Considerations for Tissue Engineered Products



CELLS

Cell Source

Donor eligibility, MCB testing

Cell Processing/Manufacturing

GMP, In-process testing

Testing & Characterization

Safety, Identity, Purity, Potency

SCAFFOLD

Starting Materials

Safety, Quality, Biocompatibility

Design & Properties

Mechanical/Physical Characteristics

Manufacturing & Testing

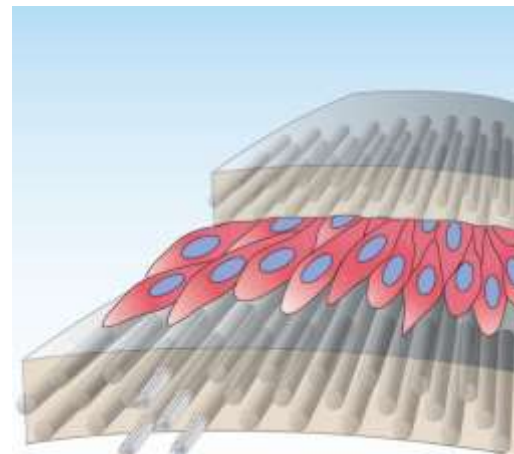
QSR, Design control, Performance

Cell + Scaffold Manufacture & Control

Dose Response, Cell Growth, Cell Functions, Cell-Scaffold Interactions

Final Product Testing & Characterization

Safety, Potency, Durability, Cell Fate, Structural and Biomaterial Decomposition



Manufacturing Considerations for Tissue Engineered Products



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Manufacturing & Testing

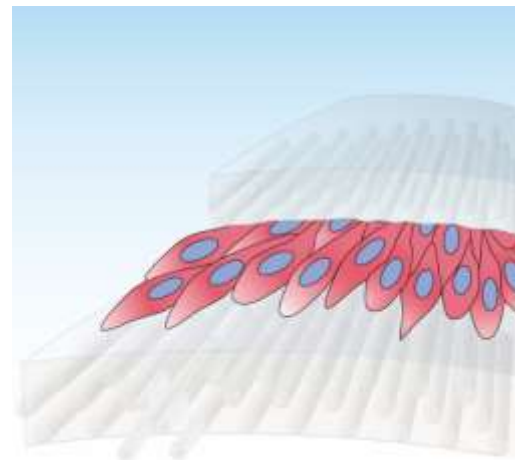
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Cell + Scaffold Manufacture & Control

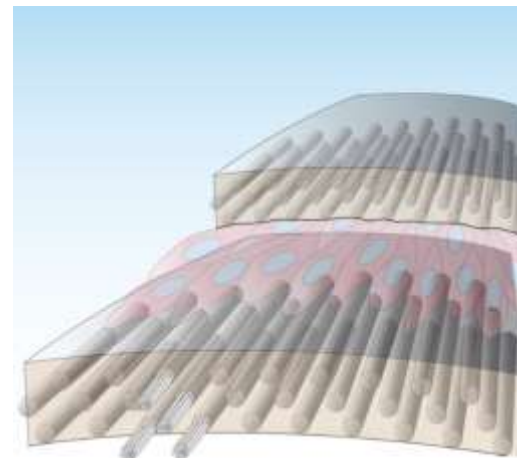
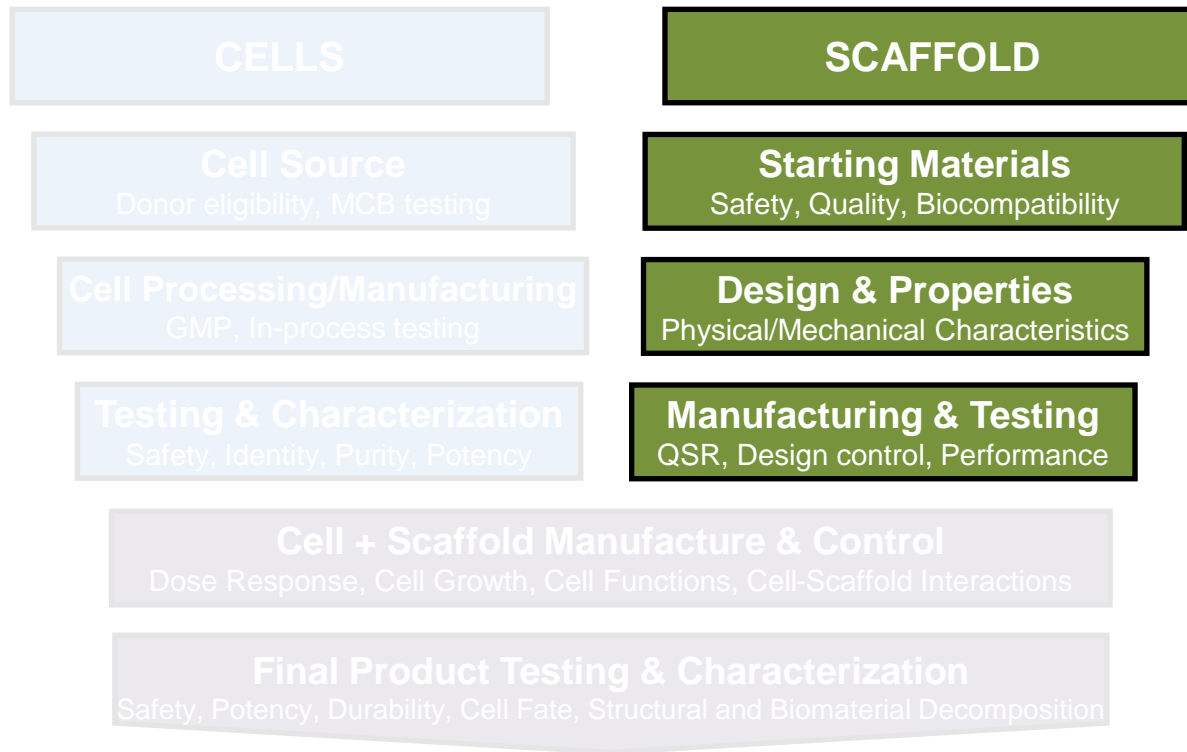
Dose Response, Cell Growth, Cell Functions, Cell-Scaffold Interactions

Final Product Testing & Characterization

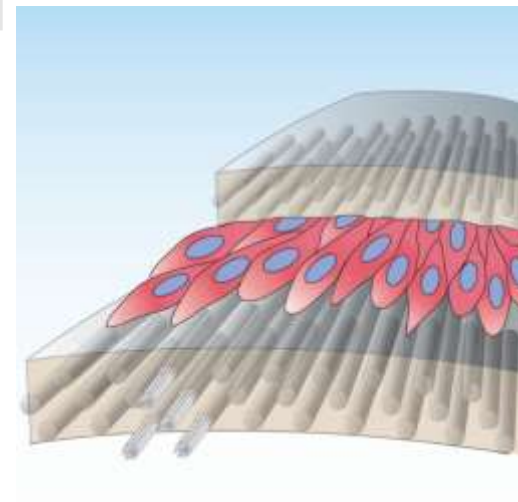
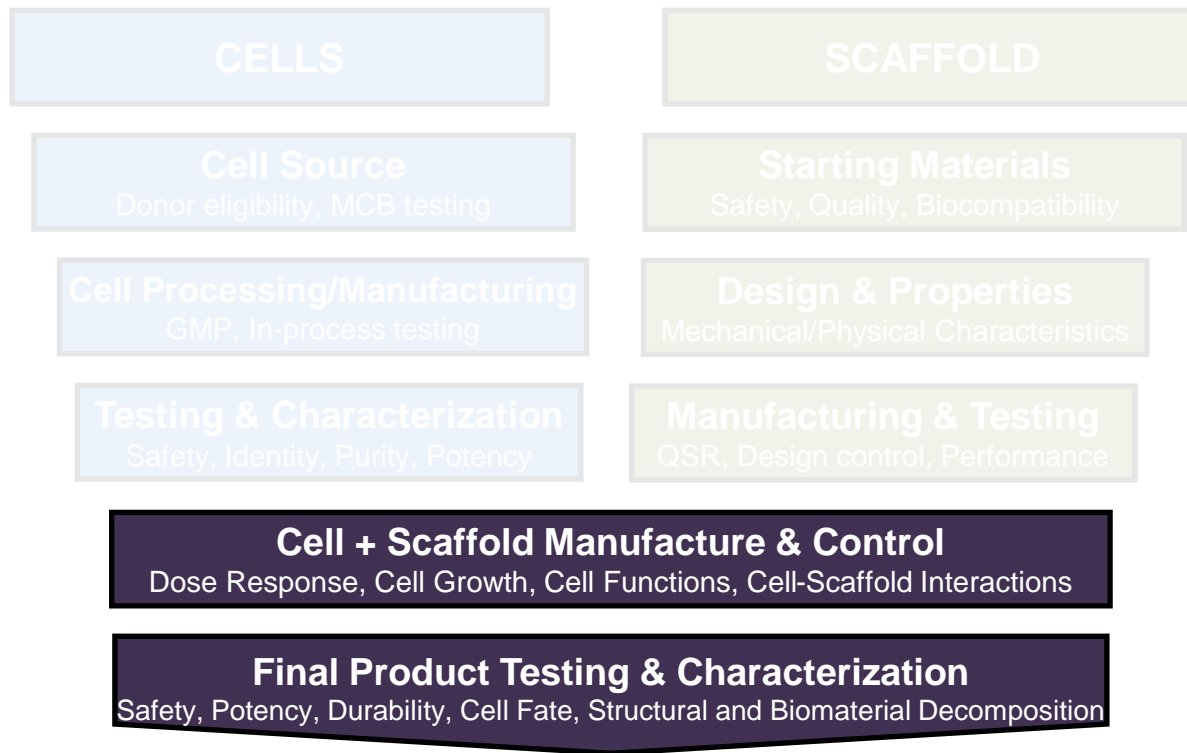
Safety, Potency, Durability, Cell Fate, Structural and Biomaterial Decomposition



Manufacturing Considerations for Tissue Engineered Products



Manufacturing Considerations for Tissue Engineered Products



Characterization Methods for Tissue Engineered Products



- **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.

Unique Manufacturing Challenges for Tissue Engineered Products



- Limited product manufacturing experience prior to licensure (incomplete knowledge of Critical Process Parameters (CPP), limited lots made)
- CQAs not entirely understood due to limited characterization of drug product, drug substance, and in-process material
- Assays not fully developed and qualified
- Product variability arising from source materials
- Reproducibility of replacement cell banks
- Increased demand for qualified reagents and materials
- Limited product testing due to limited material or short shelf-life
- Limited product stability data
- Complicated planning for advanced manufacturing, process automation, scale up / scale out
- Comparability studies in the absence of reliable reference standards and validated assays
- Direct impact of manufacturing failure on patient



Unique Manufacturing Challenges for Tissue Engineered Products



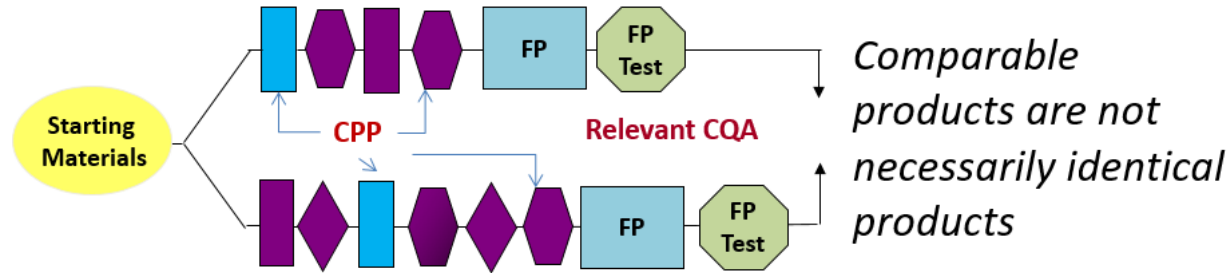
- Development of appropriate in vitro and in vivo testing and characterization methods due to:
 - Complexity in structure (3D)
 - Heterogeneity in composition
 - Small lot sizes (“lot of one”)
 - Remodeling of product post-implantation
- “Final” product specification from in vitro testing may not be predictive of clinical safety and/or efficacy
 - Product is not designed to be “stable”
- Defining potency/performance requirements
 - Multiple modes of action
 - Specific to both product type and intended use (cartilage, vascular graft, etc.)
- Manufacturing changes or scale up/out requiring comparability assessments

Comparability



FDA

- Manufacturing changes common in late phase studies: Scale-up, transfer, change in manufacturing platform/scheme, reagents, starting material, formulation etc.



- Highly similar quality attributes before and after change**
- No adverse impact on the quality, safety, or efficacy**

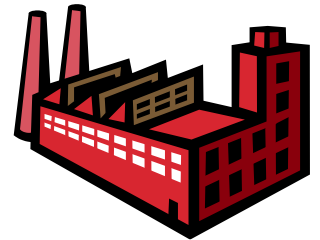
Think ahead about:

- Donor eligibility of source material
- Cell bank qualification
- Cell bank capacity
- Logistical issues for products with short shelf-lives
- Scale-up needs
- Second source for custom or critical materials
- Scaffold properties (e.g., composition, physicochemical properties, biocompatibility, degradation profile etc.)
- Qualification & validation

Manufacturing changes can be implemented at any stage, but the potential impact of a manufacturing change can increase the farther you are along in the product lifecycle.

Good Manufacturing Practices (GMPs) Considerations

- For phase 1 there is more flexibility in how GMPs compliance is achieved
- The suitability of a facility depends on the nature of the product – not all “state of the art facilities” are ideal for every product
- GMP may “improve” the product, but mostly it allows you to control product quality and safety, and to help ensure manufacturing consistency
- GMP cannot prevent manufacturing errors from happening, but can help ensure that controls are in place to catch them and take appropriate corrective actions



FDA Guidance

[Current Good Manufacturing Practice for Phase 1 Investigational Drugs \(2008\)](#)

Aligning Clinical and Product Development



- It is not advisable to begin studies intended to support licensure if you still are undecided about what your manufacturing process will be or what you intend to measure.
- Do not underestimate the time and resources needed to bring manufacturing up to the level of Phase 3 and commercial production
- Establishment of quality attributes, measurement of potency, and demonstration of product stability can be particularly challenging
- To approve a BLA, all assays and methods have to be validated and the facility has to be ready for commercial production



EXPEDITED PRODUCT DEVELOPMENT PROGRAMS

Expedited Development of Promising Treatments



Expedited Programs

- Accelerated Approval (1992)
- Priority Review (1992)
- Fast Track (FT) Designation (1997)
- Breakthrough Therapy (BT) Designation (2012)
- Regenerative Medicine Advanced Therapy (RMAT) Designation (2016)

FDA Guidance

[Expedited Programs for Serious Conditions—Drugs and Biologics \(2014\)](#)

[Expedited Programs for Regenerative Medicine Therapies for Serious Conditions \(2019\)](#)

Regenerative Medicine Advanced Therapy (RMAT)



- **21st Century Cures Act: Title III, Section 3033**
 - Signed into law in 2016 and creates pathway for designation as a regenerative medicine advanced therapy
- **Definition of Regenerative Medicine Therapy:**
 - Cell therapies, therapeutic tissue engineering products, human cell and tissue products*, or any combination product using such therapies or products
 - Combination product can be eligible for RMAT designation when the biological component provides the greatest contribution to the overall intended effects of the combination product
 - FDA interpretation of Section 3033 of the 21st Century Cures Act adds: “Gene therapies, including genetically modified cells, that lead to a sustained effect on cells or tissues”

* Except for those regulated solely under section 361 of the PHS Act

Comparison of Expedited Programs – Criteria

Accelerated Approval	Priority Review	Fast Track (FT)	Breakthrough Therapy (BT)	Regenerative Medicine Advanced Therapy (RMAT)
<p>-Serious condition</p> <p>AND</p> <p>- Meaningful advantage over available therapies</p> <p>- Demonstrates an effect on either: a surrogate endpoint or an intermediate clinical endpoint</p>	<p>-Serious condition</p> <p>AND</p> <p>-Demonstrates potential to be a significant improvement in safety or effectiveness</p>	<p>-Serious condition</p> <p>AND</p> <p>-Nonclinical or clinical data demonstrate the potential to address unmet medical need</p> <p>Note: Information to demonstrate <i>potential</i> depends upon stage of development at which FT is requested</p>	<p>-Serious condition</p> <p>AND</p> <p>-Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on one or more clinically significant endpoints</p>	<p>-Serious condition</p> <p>AND</p> <p>-It is a <u>regenerative medicine therapy</u></p> <p>- Preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition</p>

Comparison of Expedited Programs – Features



Accelerated Approval	Priority Review	Fast Track (FT)	Breakthrough Therapy (BT)	RMAT
<p>Approval based on surrogate or intermediate clinical endpoints</p> <p>Save valuable time in the drug approval process</p> <p>Reduce waiting period for patients to obtain clinically meaningful benefit.</p>	<p>Shortened Review Clock</p> <p>FDA will take action on an application within 6 months (compared to 10 months under traditional review)</p>	<p>Frequent meetings</p> <p>Eligibility for *:</p> <ul style="list-style-type: none"> ✓ Priority Review ✓ Rolling Review <p>*if relevant criteria are met</p>	<p>All FT Features, including:</p> <p>Actions to expedite development and review; Rolling review</p> <p>+</p> <p>Intensive guidance on an efficient drug development program</p> <p>Organizational commitment involving senior managers</p>	<p>All FT and BT Features, including early interactions to discuss any potential surrogate or intermediate endpoints</p> <p>+</p> <p>Statute addresses potential ways to support accelerated approval</p>

Tissue Engineered Products Expedited Development: CMC Expectations

- Clinical program advances rapidly for BT and RMAT products; timelines from early to late development may be compressed
- Accelerated clinical development does not change CMC and CGMP regulatory requirements and expectations
- Need to focus on all CMC and CGMP issues early if tissue engineered product received a BT or RMAT designation: e.g., CQA/CPP, assay & process development/validation, raw material qualification and supply chain, major manufacturing change
- Planning for commercial scale manufacturing including comparability studies (when needed) should be conducted early (Phase 1/2)
- **Aligning CMC with clinical development is crucial**



Tissue Engineered Products Expedited Development: CMC Approach Towards Licensure

- **Essential goal:** Ensure the availability of a quality product that can be consistently produced at the time of approval
- **FDA may exercise some flexibility** *on the type and extent of manufacturing information* that is expected at the time of submission or approval for certain components to a certain degree. Case by case and dependent on:
 - Product characteristics
 - Seriousness of condition and unmet medical need
 - Manufacturing processes
 - Robustness of quality system
 - Strength of the risk-based quality assessment
- **Areas of potential flexibility**
 - Validation strategies, manufacturing scale-up/ scale-out strategies, use of post marketing commitments or post marketing requirements



Pre-IND Meetings

- A non-binding, formal scientific discussion between all CBER/OTP review disciplines (CMC, P/T, and Clinical) and the sponsor
- **Goal:** To achieve a successful IND submission
- **Purpose**
 - To allow early communication between the sponsor and CBER/OTP
 - To comprehensively communicate the product/clinical development plan
 - Product characterization issues
 - Preclinical testing program (A pre-IND meeting should be requested prior to the conduct of the definitive preclinical safety studies)
 - The scope and design of the planned clinical trial
 - To discuss the format for the IND submission
- OTP grants one pre-IND meeting

INTERACT Meetings



INitial **T**argeted **E**ngagement for **R**egulatory **A**dvice on **C**BER product**T**s (*previously known as pre-pre-IND interactions*)

- **Goal:** To obtain early feedback on a product development program for a novel investigational agent
- **Purpose**
 - A mechanism for early communication with OTP
 - Non-binding, scientific discussion between CBER/OTP review disciplines and the sponsor
 - Initial targeted discussion of specific issues
- **Timing**
 - When you have generated preliminary preclinical data (POC and some safety), but are not yet ready to conduct definitive preclinical safety studies
- **Requests** for INTERACT meetings should be sent to INTERACT-CBER@fda.hhs.gov

*<https://www.fda.gov/media/84040/download>

Useful FDA Information



- References for the Regulatory Process for the Office of Tissues and Advanced Therapies (OTAT) (now Office of Therapeutic Products (OTP)):
<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>
- Combination Products Guidance: <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>
- Additive Manufacturing Guidance: <https://www.fda.gov/media/97633/download>

Summary



- Tissue engineered products are complex and require assessment of the cells, scaffold, and final cell-scaffold product.
- Depending on the tissue engineered product, 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.
- Seek FDA advice early and throughout product development.

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Questions?

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