# Understanding The Regulatory Framework For Stem Cell-based Products And Regenerative Medicine: FDA Perspectives

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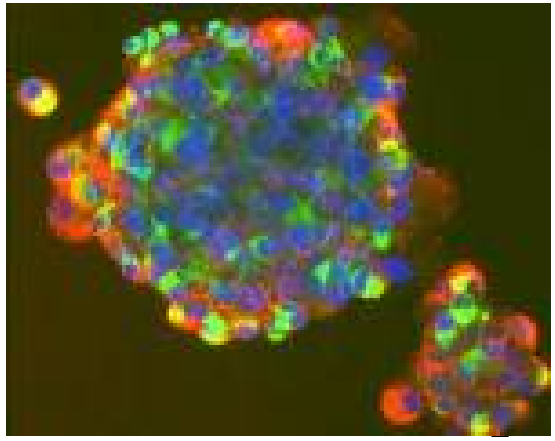
**Office of Cellular, Tissue and Gene Therapies**

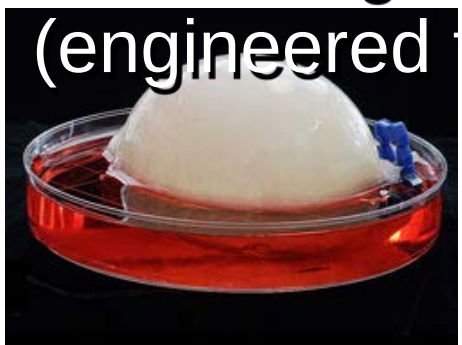
# Outline

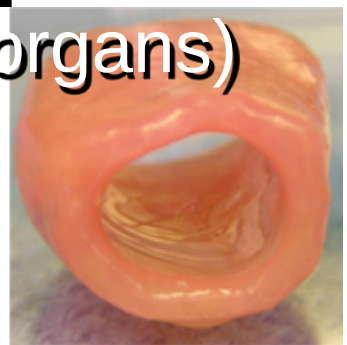
- Regulatory frameworks applicable to stem cells and regenerative medicine products
- Product considerations
- Preclinical/clinical considerations
- CBER activities in international harmonization
- OCTGT resources and contact information

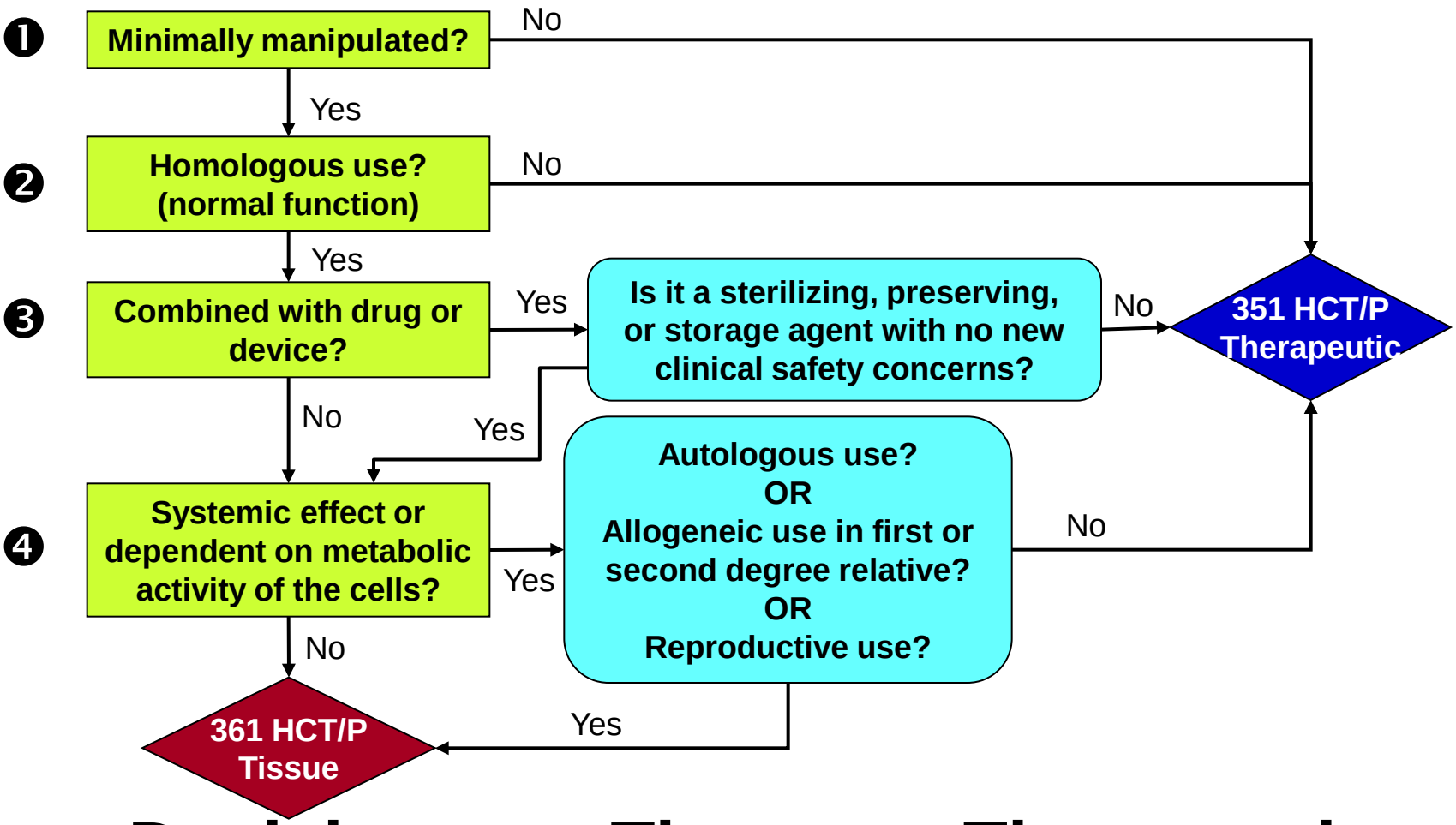


# Regenerative Medicine Products

- Pluripotent Stem Cells (hESC and iPS)
- Stem cells (mesenchymal, hematopoietic, etc)
- Functional and structural cells (chondrocytes, pancreatic islets, cardiomyocytes, etc)
- Modified human/animal tissues
- Cells delivered by devices
- Tissue engineered and combination products (engineered tissue and organs)







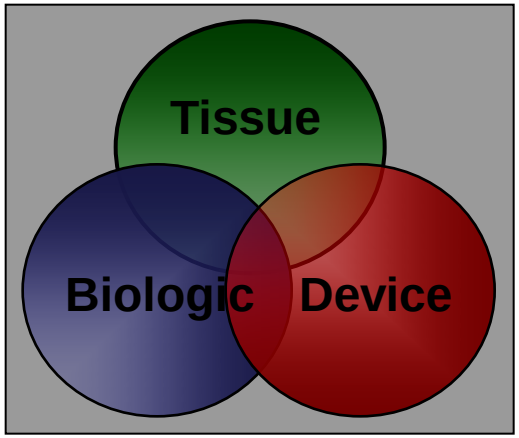

# Decision tree-Tissue vs Therapeutic Biologic

# Cell/Tissue-Based Regenerative Medicine Products

- **Fit regulatory definitions of the following:**
  - **Human cells, tissues, or cellular and tissue based products (HCT/P) (21 CFR 1271.3(d))**
    - **Section 361 Public Health Service Act, infectious disease**
  - **Biologics (21 CFR 600)**
    - **Section 351 Public Health Service Act, premarket approval, safety and effectiveness**
  - **Drugs (21 CFR 200)**
    - **Food Drug and Cosmetic Act**
      - **IND requirements**
- **May fit regulatory definition of:**
  - **Medical Device (21 CFR 800)**
  - **Combination Product (21 CFR 3.2 (e)(1))**

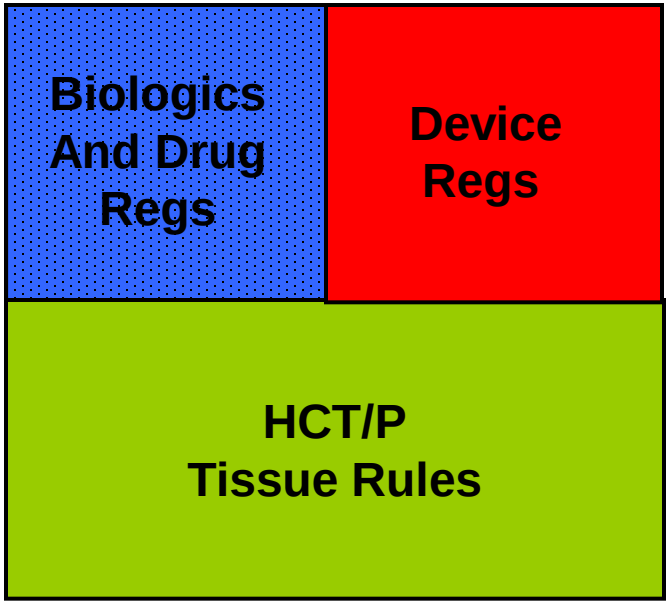
# Combination Products
# 21 CFR 3.2(e)

- Two or more regulated articles
  - Drug/device
  - Biologic/device
  - Drug/biologic
  - Drug/biologic/device

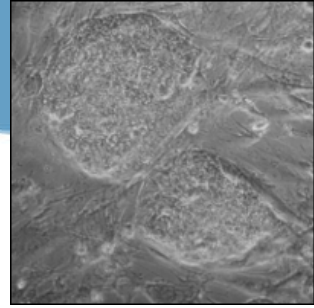



- Components under different regulatory authorities
- Specifically intended for use together
- Both components required for therapeutic effect

# What Regulatory Pathways are available for Cell/Tissue Based Regenerative Medicine Products?




Tissue rules would apply uniformly.



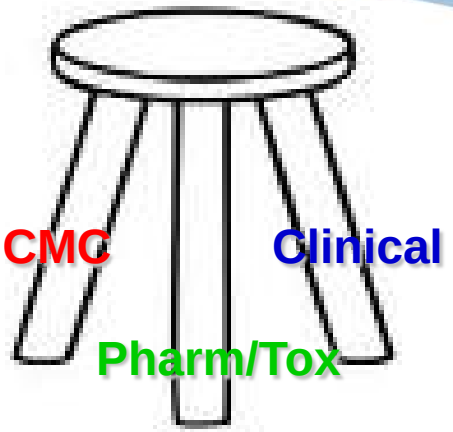
# iPS Cells Fit Within Existing Regulatory Framework

- Reprogrammed using gene transfer via vectored delivery mechanisms (i.e.retrovirus, adenovirus, plasmid)
  - Would be considered a gene therapy product
  - FDA review will include assessment of risks associated with gene delivery
  - NIH/OBA/RAC review of scientific and ethical considerations of proposed clinical trial

# OCTGT Approach

- Cell/Tissue-Based Regenerative Medicine Products do not lend themselves to a “one size fits all” concept of product development and regulation
- Regulations set framework of criteria that must be fulfilled.
- Flexibility in how to fulfill the criteria, needed for diverse and novel products in evolving fields

# FDA Review of Safety and Effectiveness




- FDA review is product-based
  - Parallels prudent product development
  - Early interactions with sponsors facilitate effective product development
  - Detailed manufacturing information is needed during product development
  - Preclinical studies designed to support the use of specific products
  - Clinical trial design supported by manufacturing, preclinical data

# Donor Testing of HCT/Ps

- Screening and testing for relevant communicable diseases agents or diseases (RCDADs) is required for cell and tissue donors

- A donor-eligibility determination must be made based on results of:
  - Donor Screening (1271.75)
  - Donor Testing (1271.80 and 1271.85)
    - At time of recovery or 7 days pre or post recovery
    - PBSC, BM, and oocyte donors: up to 30 days before recovery

- Donor eligibility determination is required for clinical use of HCT/Ps
  - Limited exceptions (1271.155 Exemptions and alternatives)

# Source control

- Qualify all materials that come in contact with the cells
  - Feeder layers
  - Human serum or serum proteins- licensed or qualified source
  - Animal serum- zoonotic viruses, TSE
  - Affinity purified proteins – adventitious agents in antibodies
  - Cell or tissue extracts – possible viral contaminants
  - What about when it says “For research purposes only, not for human use” - you need to establish that these are safe, which may mean additional testing (sterility, endotoxin, etc.)

# Cell Banks for Biologics Require Testing

- **Cell banks**
  - **Master Cell Banks**
    - Adventitious agent testing: HIV 1&2, HTLV 1 &2, CMV, EBV, B19, HCV, and HBV, in vivo, in vitro virus testing (inapparent virus testing). Other adventitious agents based on reagents cells have been exposed to (e.g.mouse feeder layers: murine viruses, fetal calf serum: bovine viruses, porcine trypsin:porcine viruses)
    - Sterility (bacteria, mycoplasma, fungus)
    - Characterization-viability, identity by molecular markers that define cells (e.g. cell surface markers), purity
    - Stability of cell line
      - number of passages/ doublings over time
      - maintain intrinsic properties
      - karyotypic alterations
    - Retroviral testing, when required
    - Tumorigenicity, when required
  - **Working Cell Bank**
    - in vitro virus testing (inapparent virus testing)
    - viability, purity, sterility, mycoplasma and endotoxin

# Product Quality Testing

- In-process testing
  - Should provide meaningful insight into process and product quality
  - Should contribute to the safety and quality of the final product
- Final product testing (Lot release)
  - Needs to be performed on the final product, not intermediate
  - Establish proper specifications
    - Should be based on experience and may change with new data obtained as clinical development progresses

# Who decides on lot release specifications used to define a product?

Some lot release specifications are dictated by regulations:

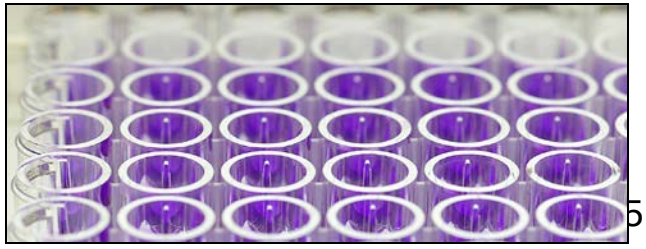
- Sterility – 14 days by either CFR or USP method, or equivalent test method

Some are based on recommendations in guidance documents:

- Viability of at least 70% for cell therapies

However, most lot release specifications are established by the sponsor and justified based on their manufacturing experience and clinical need- sponsor is responsible.

- Identity/product characterization
- Potency
- Dose/volume/concentration
- Purity/level of contaminants



# Development of Cell-Scaffold Combination Products

**CELLS**

**SCAFFOLD**

**Cell Source**
Donor eligibility, MCB/WCB testing

**Starting Materials**
Safety, Quality, Biocompatibility

**Cell Processing/Manufacturing**
GMP, In-process testing

**Design and Properties**
Mechanical/Physical Characteristics

**Characterization and Testing**
Safety, Identity, Purity, Potency

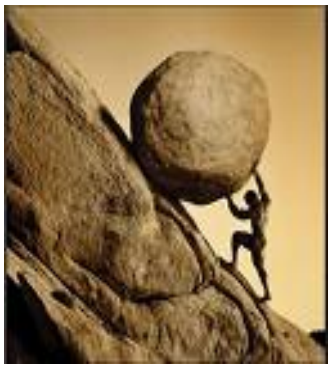
**Manufacturing and Testing**
QSR, Design control, Performance

**Cell and Device Combined**
Dose Response, Cell Growth, Cell Functions, Cell-Scaffold Interactions

**Final Product**
Safety, Potency, Durability, Cell Fate, Structural and Biomaterial Decomposition

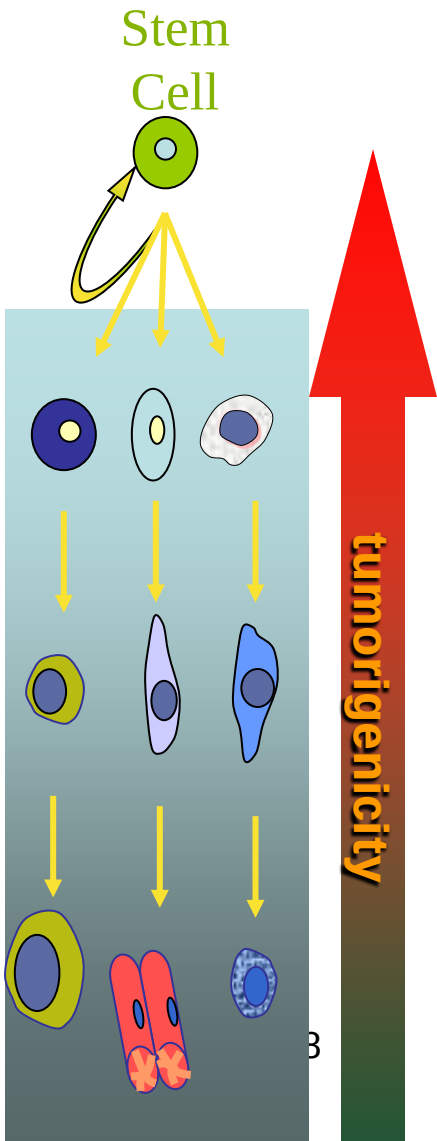
# Challenges for testing regenerative medicine products

- Small lot size/limited sample volume
- Limited shelf life (due to cell viability)
- Limited availability of starting material for process, product, and test method development
- Lack of reference standards
- Patient to patient variability and cellular heterogeneity
- Multiple potential mechanisms of action



# Cell-based Products: Considerations for Safety Evaluation

- **Properties of stem cell products**
  - Heterogeneous mixture
  - Persistence
- **Safety Evaluation**
  - Pluripotency
  - Inappropriate differentiation
    - Tumorigenicity
    - Ectopic tissue formation
  - Migration
- **Anatomic constraints**
  - Enclosed space (eg IC vs. IV administration)



# Preclinical Assessment- Provide data to support:

- Scientific rationale/POC for conducting clinical trial
- Starting dose, dosing schedule and dose escalation schemes
- Parameters for monitoring in the clinical protocol (e.g., safety, duration of follow-up, etc.)
- Patient eligibility criteria
- Preliminary risk/benefit assessment
- Discern mechanism of action/toxicity

# Questions to ask before designing experiments

- What cellular material will be used clinically?
  - What cellular material will be used for POC?
- What is the intended delivery method/ route of administration?
  - ...implanted alone… with a scaffold… encapsulated? … at single or multiple implantation sites? ..by single or multiple administrations?
- Is short-term or long-term cell survival desired?
- Will cells proliferate, differentiate, or migrate to non-target sites following *in vivo* administration?
- Can cell trafficking be monitored by non-terminal modalities?
- Will immunosuppressive agents be needed?
- What are the relevant animal model(s) for assessment of POC, toxicology/safety, cell trafficking and tumorigenicity?

# Preclinical Studies

- Assess pharmacology/POC/cell fate in relevant animal model(s) of disease/injury
- Assess the safety/toxicology (T)/cell fate in healthy animals
- Hybrid pharmacology-toxicology study design – POC + T + cell fate in an animal model of disease/injury

# Major considerations for early stem cell clinical trials

- Very strong proof of concept evidence may be required
- The dose of cells administered to humans should be below the minimum number of cells observed to form tumors in animal models
- First in man clinical applications should be picked carefully due to inherent risks
- Long term follow up recommended due to perceived risk

# Trends in Cell Therapy

- Novel sources of adult stem cells
  - Placental and amniotic membrane, adipose derived
- New Methods of iPS induction
  - Episomal plasmids
  - Chemical reprogramming
- Cell products to induce immune tolerance
- Cells encapsulated in a biomaterial
- Tissue engineering constructs
- Cells administered using a Device

# CBER/FDA International Engagements for Cell and/or Gene Therapies

- **Regulatory exchanges**
  http://www.fda.gov/InternationalPrograms/Agreements/ConfidentialityCommitments/default.htm
- **FDA-EMA ATMP "Cluster"**
  http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000294.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800241e0
- **ICH**
  http://www.ich.org/cache/compo/276-254-1.html
- **Asian-Pacific Economic Communities Life Sciences Innovation Forum**
- **Global Regulators Forum**

# OCTGT Regulatory Exchanges

- **Hosting of international regulatory colleagues**
  - **EMA**
  - **Japan Pharmaceutical and Medical Device Agency (PMDA)**
  - **Singapore Health Sciences Authority**
  - **Swiss Medic**
- **Respond to foreign regulatory inquiries**
  - **Non-public information is not shared with foreign regulatory authorities that do not have confidentiality agreements with FDA**

# FDA-EMA Interactions

- **Formal cooperation and confidentiality arrangement between FDA and European Medicines Agency (EMA) for pharmaceuticals (2003-extended indefinitely)**
- **"Clusters"**
  - **Pediatrics, Oncology, etc**
- **Advanced Therapy Medicinal Products (ATMP) Cluster, initiated 2008**
  - **Regular teleconferences to share thinking on regulatory approaches, both general and specific issues**
  - **Information sharing on draft documents**
  - **Engage reciprocally in workshops and advisory committees, working parties**

# FDA's Goals for International Harmonization

- To safeguard global public health
- To assure that consumer protection standards and requirements are met
- To facilitate the availability of safe and effective products
- To develop and utilize product standards and other requirements more effectively
- To minimize or eliminate inconsistent standards internationally

# Summary

- Manufacturing, pre-clinical testing, and clinical trial design are all inter-related
- Safety is the primary concern, including reagents, cell banks, and devices
- Source control has stood the test of time to ensure safety
- Call us if you have a question- it may save you time and money
- FDA actively engages international regulatory partners

# CBER/OCTGT Regulatory Resources

- Webcast of Pluripotent Stem Cells in Translation:Early Decisions (March 21-22, 2011) http://videocast.nih.gov/PastEvents.asp
- OCTGT Learn Webinar Series: http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm
- References for the Regulatory Process for the Office of Cellular, Tissue, and Gene Therapies (OCTGT) http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/ucm094338.htm
- OCTGT Regulatory Questions: CBEROCTGTRMS@fda.hhs.gov or Patrick.Riggins@fda.hhs.gov

*Thank you for your attention*