

Donor Eligibility and Testing of iPSCs and hESCs For Therapeutic Use

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Food and Drug Administration
Office of Cellular, Tissue, and Gene Therapies

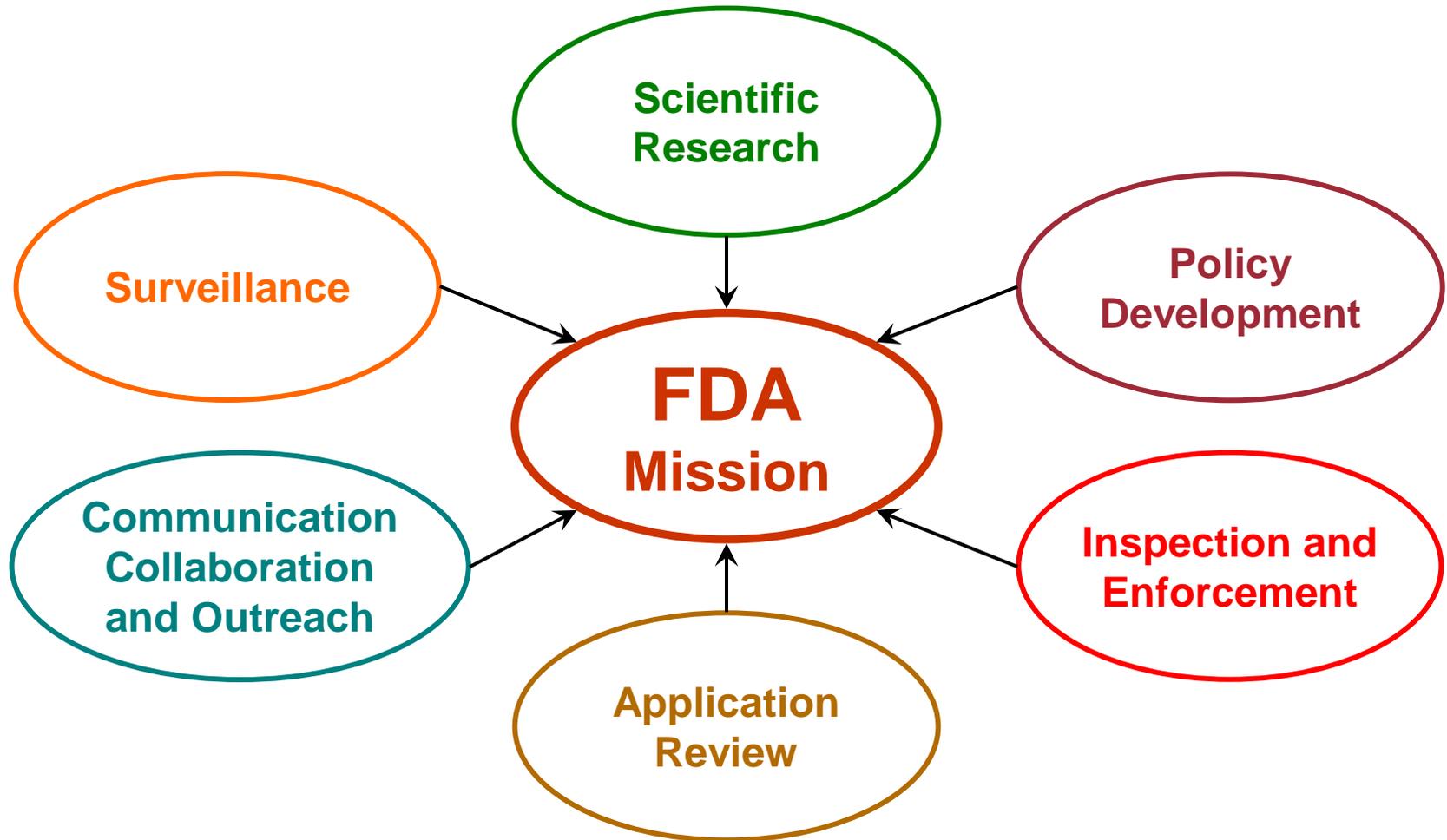
FDA Overview



FDA Mission Statement

- The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.
- The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.

Key Functions of FDA



FDA

Center For **Devices** and Radiological Health

Center for **Drug** Evaluation and Research

National Center for Toxicological Research

Office of the Commissioner

Center for **Veterinary** Medicine

Center for **Food** Safety and Applied Nutrition

Center for **Biologics** Evaluation and Research

Office of Chief Counsel

Office of Regulatory Affairs

Center for **Tobacco** Products

Office of Compliance and Biologics Quality

Office of Management

Office of Biostatistics and Epidemiology

Office of **Blood** Research and Review

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

Office of **Vaccines** Research and Review

Office of Information Technology

Division of Clinical Evaluation and Pharm/Tox

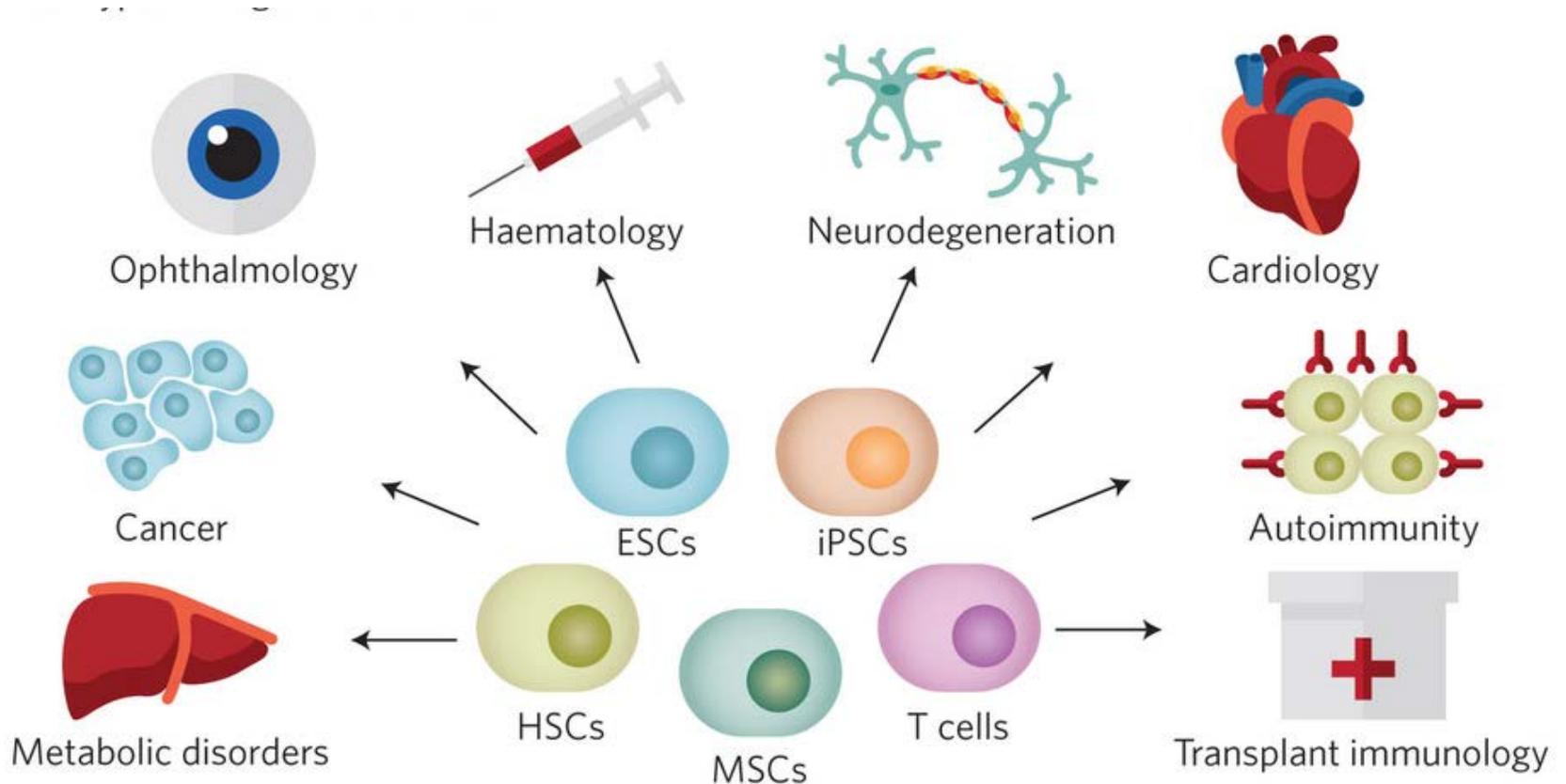
Division of **Cellular and Gene Therapies**

Division of Human Tissues

Office of Communication, Outreach, and Development



Examples of Cellular Therapy



Regulatory Expectations

Regulatory Framework: 3-Tiered System

- **Statutes (Laws):**

Passed by Congress and signed by the President

- Food, Drug & Cosmetic Act (FD&C Act)
- Public Health Service Act (PHS Act)

- **Regulations (details of the law):**

Written by FDA and approved by the Executive Branch

- 21 CFR (Code of Federal Regulations)

- **Guidance (the FDA's interpretation of the Regulations):**

Written and approved within FDA

- Advice non-binding on FDA or sponsor

Definitions

- Human Cells, Tissues, and Cellular and Tissue Based Products (HCT/Ps; 21 CFR 1271.3 (d)): Articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer to a human recipient
- Biologic (42 USC 351(i)) - Virus, Therapeutic Serum, Toxin or Antitoxin, Vaccine, Blood, Blood Component or Derivative, Allergenic Product , Protein (except any chemically synthesized polypeptide), or Analogous Product, ... applicable to the prevention, treatment, or cure of a disease or condition of human beings
- Drug (21 USC 201(g)) - Articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and...to affect the structure or any function of the body of man or other animals

Drug and Biologics Marketing Regulations for Cell Therapies

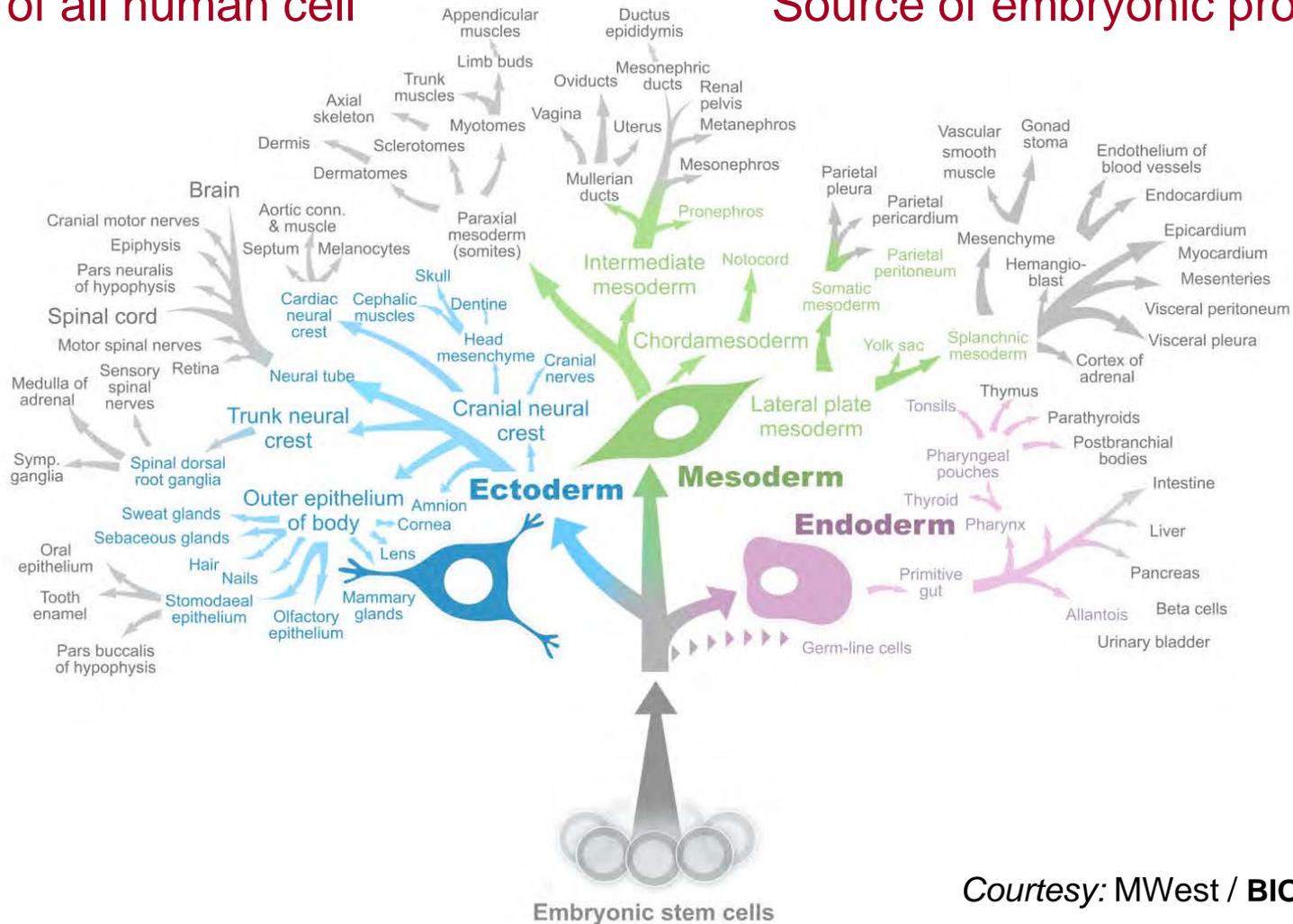
- 21 CFR parts 210, 211, 225, & 226
 - Good manufacturing practices for drugs and biologics
- 21 CFR parts 600, 601, & 610
 - Biological products regulations
- 21 CFR parts 201, 202, 203, 314
 - Prescription drug regulations
- 21 CFR part 1271
 - Registration, Donor Eligibility, Good Tissue Practices
- 21 CFR part 25
 - Environmental impact considerations

Pluripotent Stem Cells

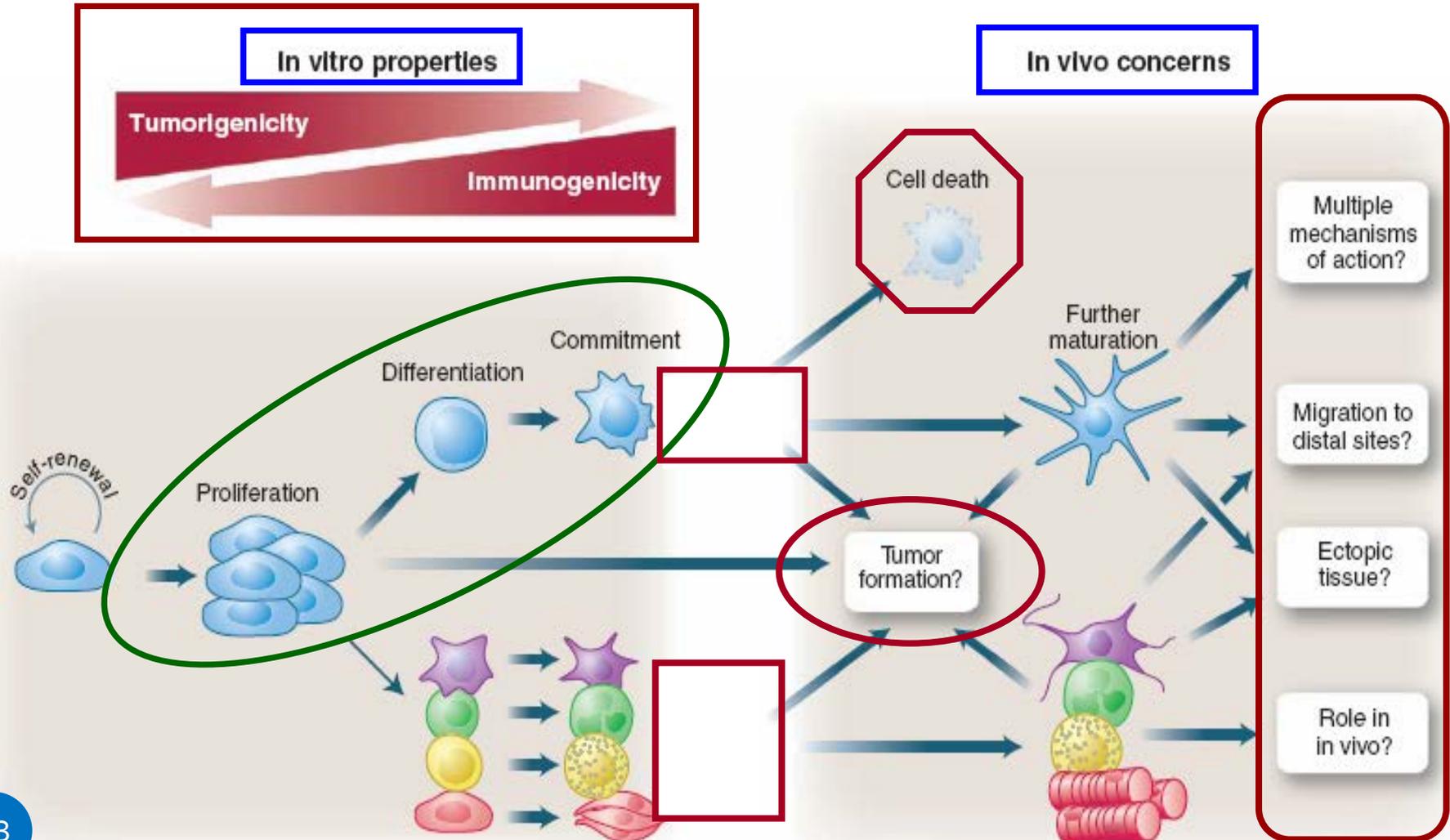
Pluripotency Provides:

Source of all human cell types

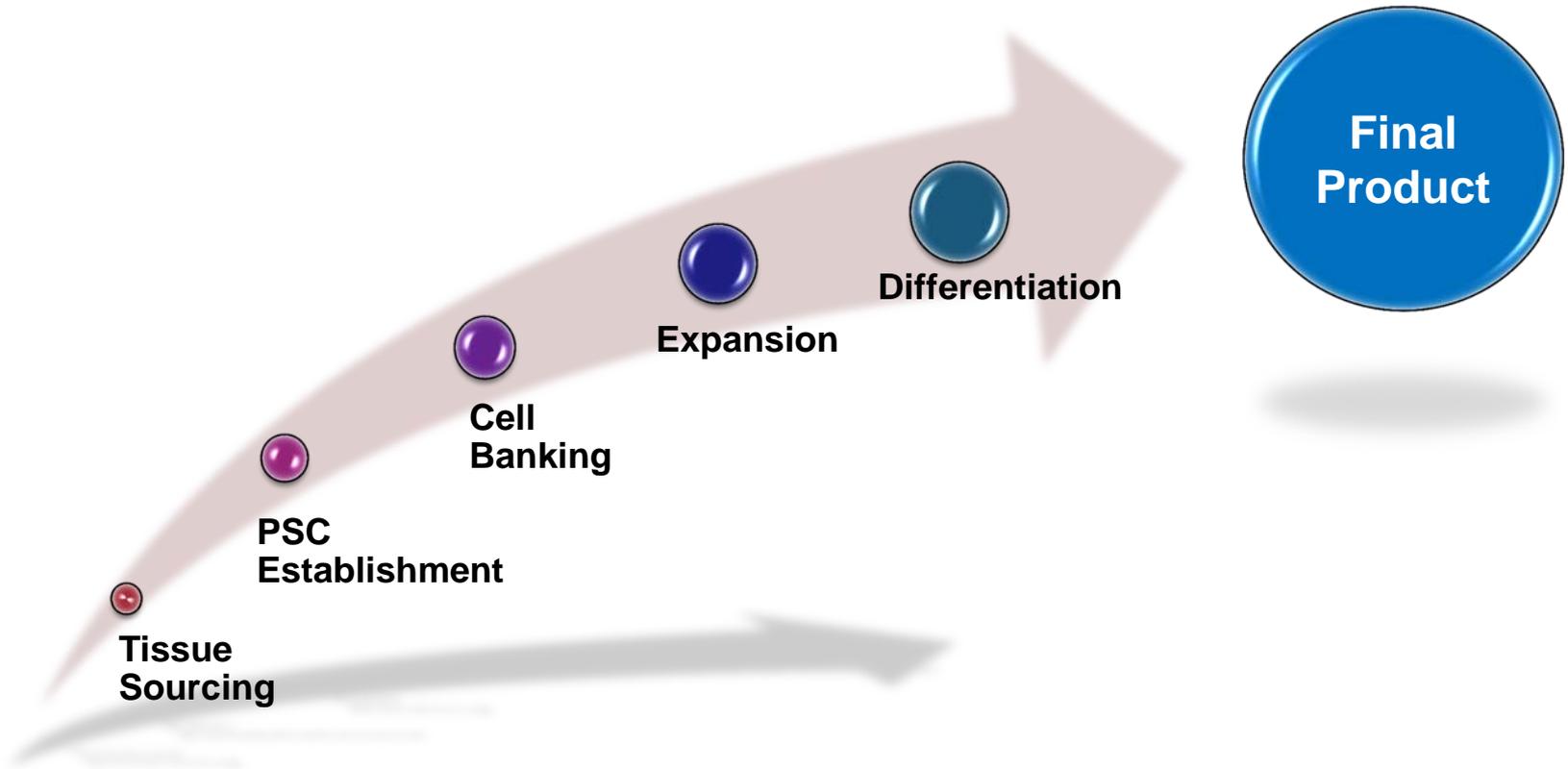
Source of embryonic progenitors



Potential Risks Posed by Stem Cell Biology



Pluripotent Stem Cell Product Development

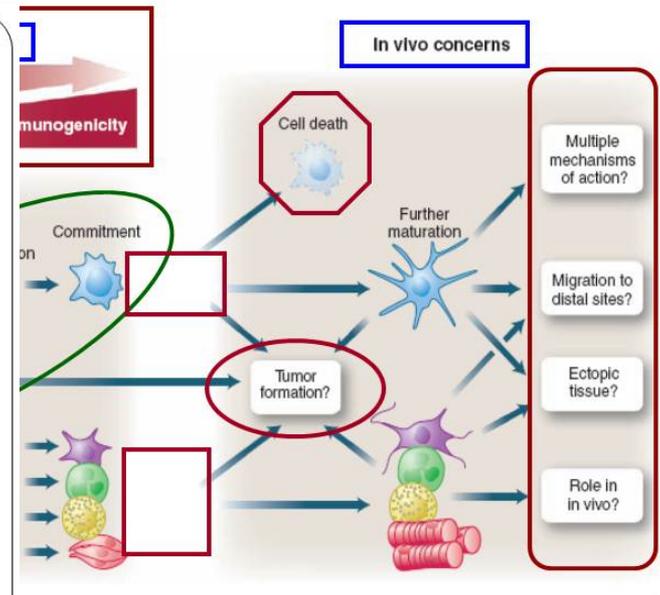


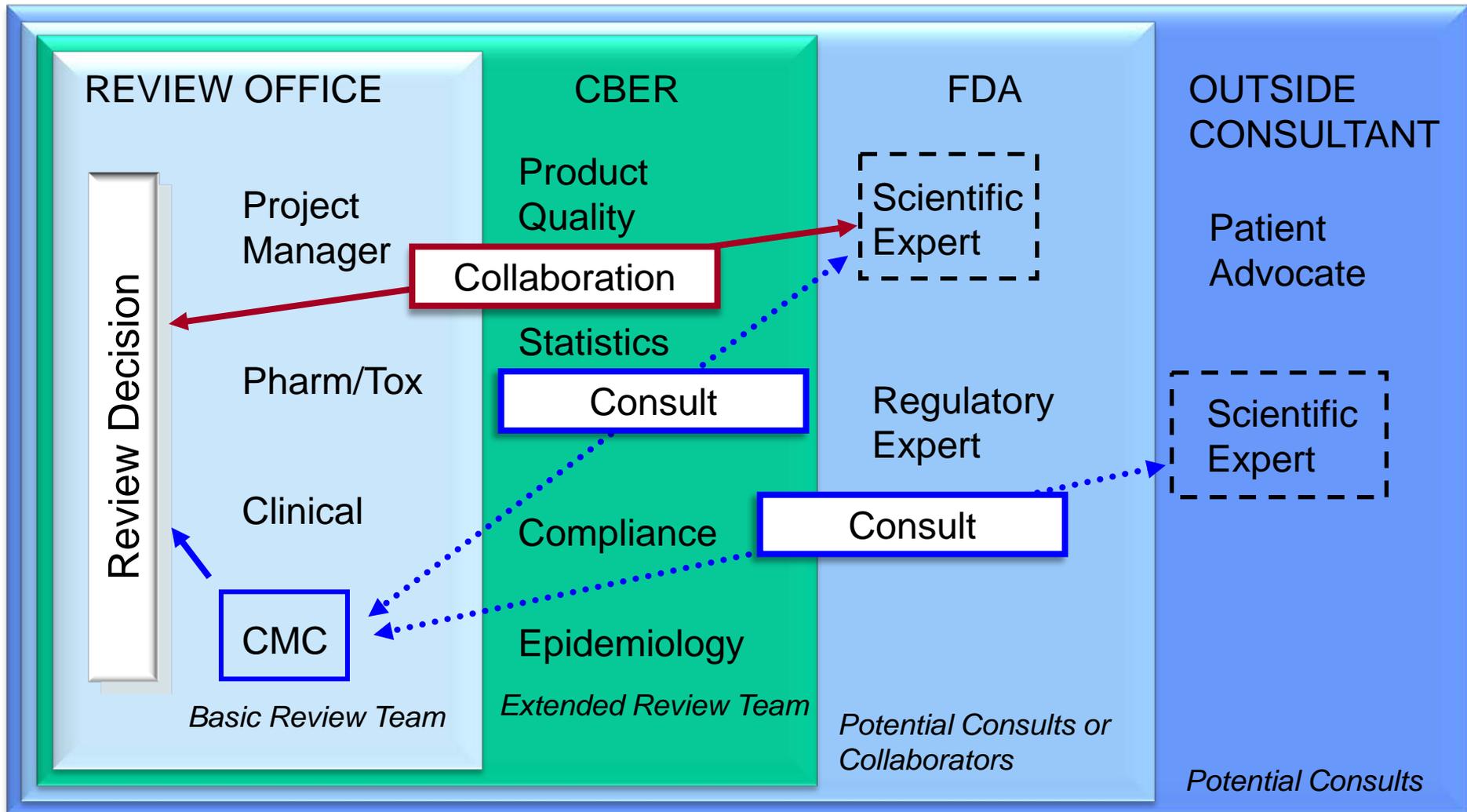
Addressing scientific concerns and regulatory requirements during the review process

Potential Risks Posed by Stem Cell Biology

Drug and Biologics Marketing Regulations for Cell Therapies

- 21 CFR parts 210, 211, 225, & 226
 - Good manufacturing practices for drugs and biologics
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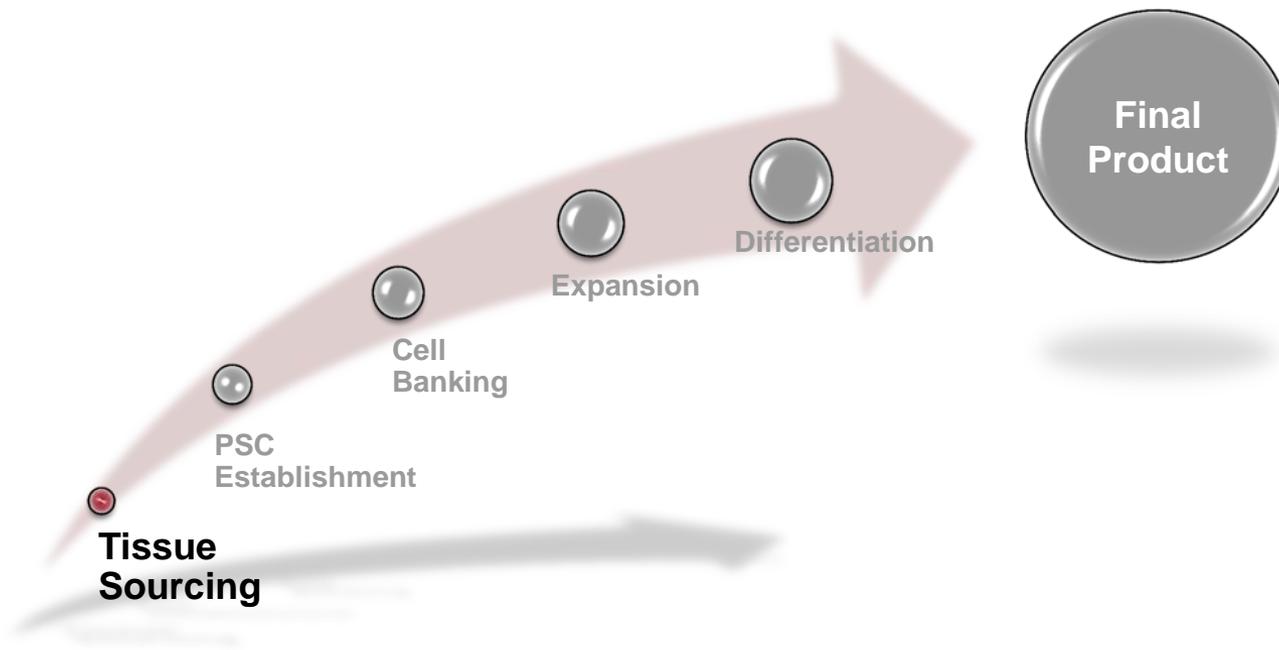




FDA Review Team



Tissue Sourcing



The “Tissue Rules”

(21 CFR 1271, Effective May 25, 2005)

Tissue Rule	Issues Addressed
Establishment Registration and Listing	Applicability: types and uses of products that will be regulated by these rules; requirements for registering and listing products
Donor Eligibility	Requirements for donor screening and testing for “relevant communicable disease agents and diseases”
Current Good Tissue Practice (CGTP)	Manufacturing to ensure that HCT/Ps do not contain communicable disease agents; reporting; inspections

What is a donor-eligibility determination?

- A donor-eligibility determination is a conclusion that a donor is either eligible or ineligible to donate cells or tissues
- Based on:
 - Donor Screening (1271.75)
 - Donor Testing (1271.80 and 1271.85)for relevant communicable disease agents or diseases (RCDAD)

Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products [August 2007](#)

Donor Screening

- Review of relevant medical records
 - Medical history and relevant social behavior interview (questionnaire)
 - Available medical records
 - Physical exam
- For Risk Factors or Clinical evidence of:
 - Relevant communicable disease agents and diseases
 - Risks associated with xenotransplantation

Donor Testing

- Testing for RCDAD
 - Collect specimen within 7 days of recovery, except for PBSC, BM, oocytes may be up to 30 days before recovery
 - Test for all required RCDAD
 - Use FDA-licensed, approved, or cleared donor screening test kits in accordance with manufacturer's instructions
 - In CLIA certified lab (or CMS equivalent)

Agent	Required for	Screening	Testing*
HIV-1 and -2	All	X	X
Hepatitis B	All	X	X
Hepatitis C	All	X	X
Syphilis	All	X	X
TSE	All	X	
WNV	All	X	
Sepsis	All	X	
Vaccinia (recent smallpox vaccination)	All	X	
HTLV-I and II	Viable, Leukocyte-rich	X	X
CMV**	Viable, Leukocyte-rich		X
<i>Chlamydia trachomatis</i>	Reproductive	X	X
<i>Neisseria gonorrhoea</i>	Reproductive	X	X

* More than one test may be necessary to adequately and appropriately test for a single RCDAD (e.g. anti-HCV and HCV NAT for Hepatitis C)

** CMV is not a RCDAD; donors of viable leukocyte-rich HCT/Ps must be tested for CMV and positive test results must be communicated to the responsible physician



Testing for donors who are 1 month of age or younger

- Screening
 - Review medical records of the infant donor
 - Screen the birth mother
 - Medical history interview, review other relevant medical records, etc.
- Testing
 - Test a specimen from the birth mother instead of the donor
 - Specimens must be collected within 7 days of the donation

When is a donor eligible?

(21 CFR 1271.50)

- Screening shows that the donor is free from risk factors or clinical evidence of RCDADs and risks associated with xenotransplantation
- Test results for relevant communicable disease agents or diseases are negative or nonreactive
 - Exception 1271.80(d)(1)

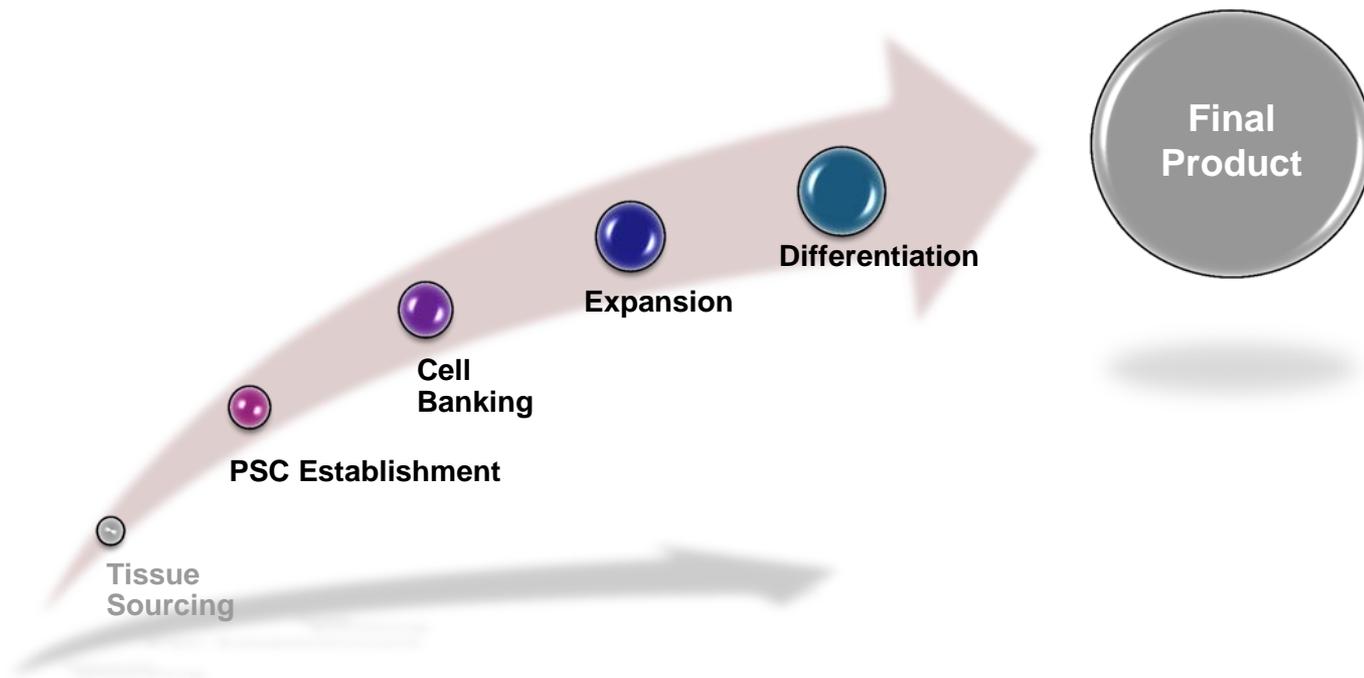
Pooling of cells from multiple donors is not allowed

- Tissue Rules do not allow pooling of donors-
 - 21 CFR 1271.220 (b): “Human cells or tissue from 2 or more donors must not be pooled (placed in physical contact or mixed in a single receptacle) during manufacturing.”

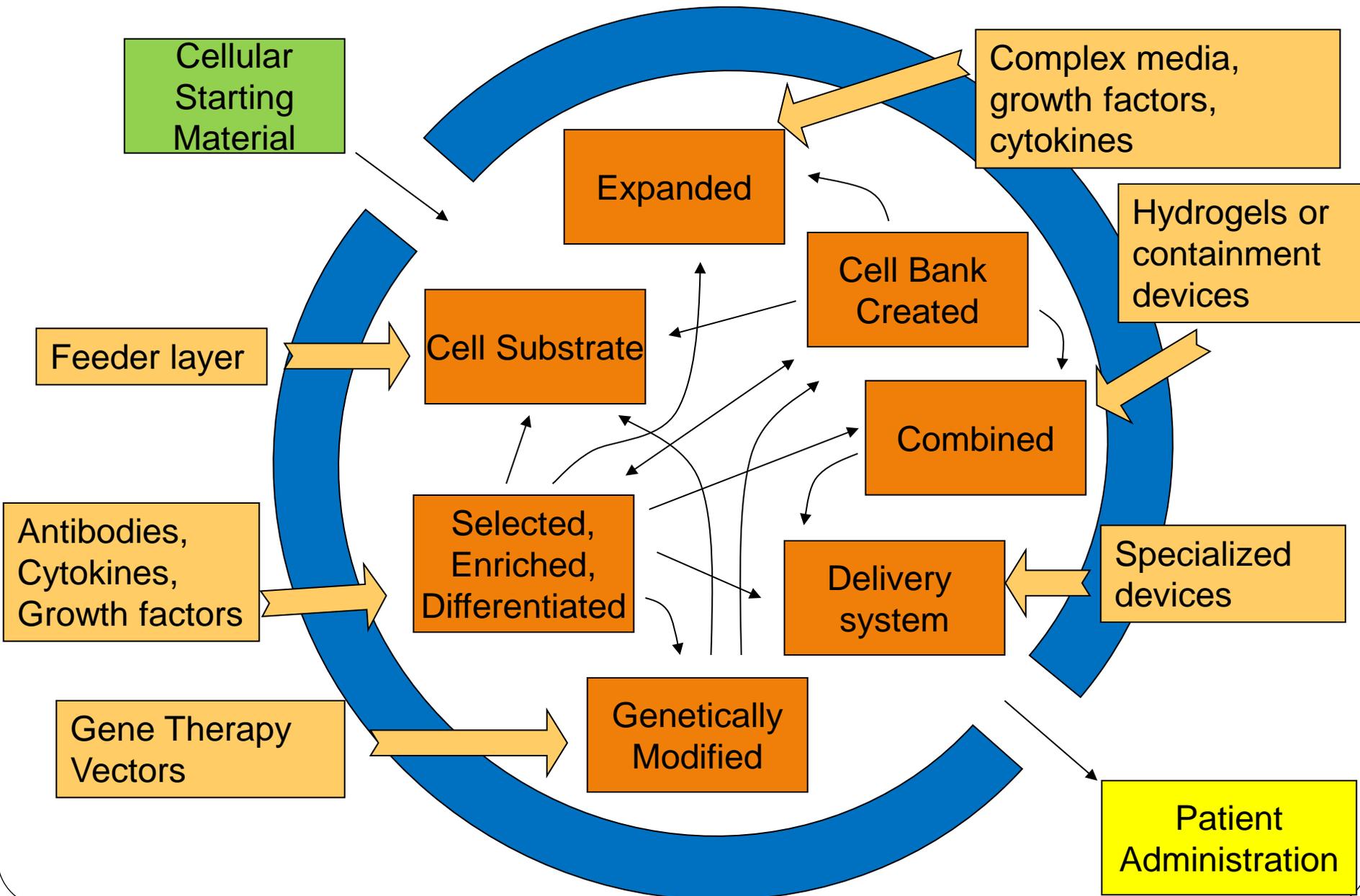
Exemptions

- May apply for an exemption or alternative under provisions of 21 CFR 1271.155
- Request must be accompanied by supporting documentation, including all relevant valid scientific data, and information justifying the requested exemption
 - Consider including information such as:
 - Risk information and mitigation related to the donor, the tissue of origin, the screening and testing, impact of the processing, subsequent testing, intended clinical use, etc.

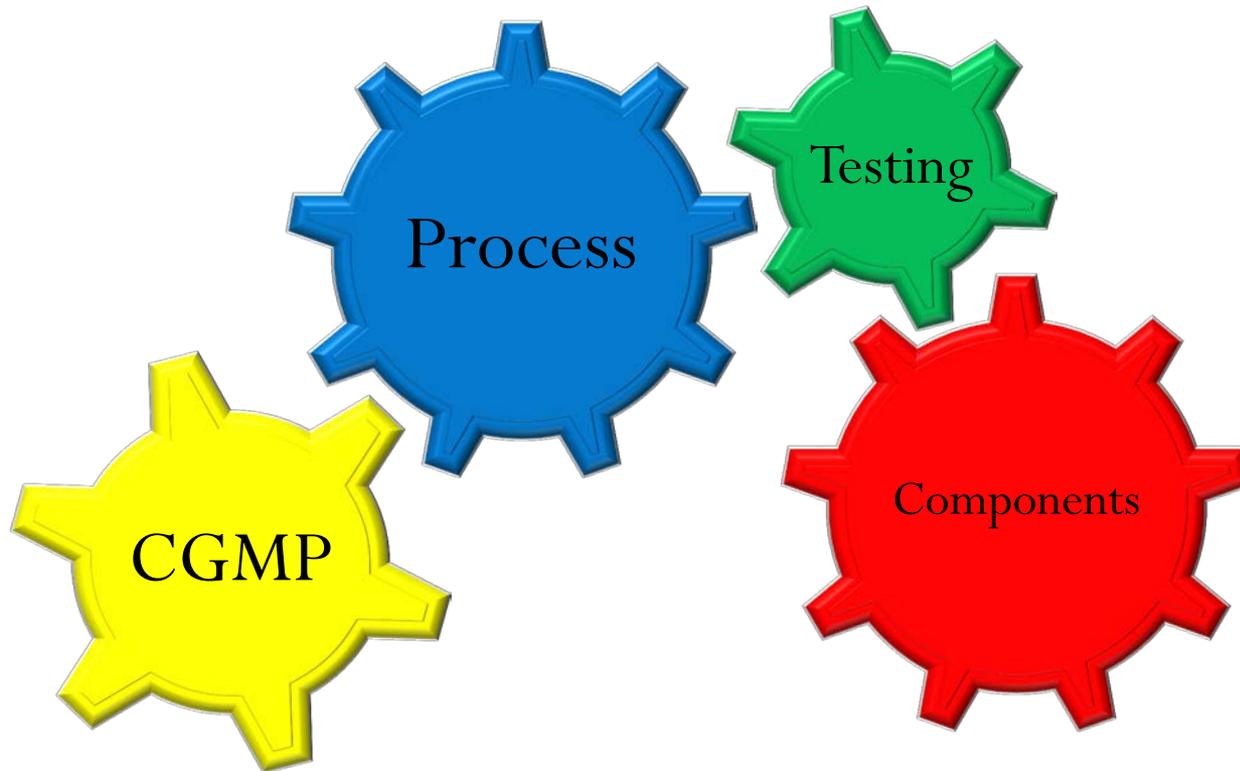
Cell bank establishment and product manufacture



Stem Cell Manufacturing Can Be Complex



Many factors contribute to product quality



Process

Tissue sourcing

PSC generation

Cell banking

Expansion

Differentiation

Final formulation

Testing

Donor Eligibility

Cell bank testing

Immunogenicity

Tumorigenicity

Karyotypic stability

Characterization

In-process testing

Lot release testing

Components

Gene vectors

Feeder layers

Growth factors

Cytokines

Antibodies

Scaffolds

Delivery devices

CGMP

Equipment

SOPs

Record keeping

Validation

Facility

Personnel

Tracking

Shipping

Master Cell Bank Testing

- Safety Testing
 - Sterility
 - Mycoplasma
 - Endogenous and Adventitious virus testing – in vivo and in vitro
 - Human pathogen testing
 - Retroviral testing when required
- Characterization
 - Isoenzyme/Identity test
 - Karyotype
 - Viability
 - Product specific assays

Working Cell Bank Testing

- Sterility
- Mycoplasma
- In vitro adventitious virus tests
- Product specific assays

Tumorigenicity testing

- Needed for cells with tumorigenic potential
 - This is a major safety concern associated with products derived from cell lines, tumors, or stem cells
- Cells need to be tested using conditions that resemble their intended use

Reagent Controls

- Qualification program for source materials, reagents, ingredients, excipients and components used throughout the manufacturing process.
- Careful evaluation of all reagents for safety concerns

Special care should be taken when certain types of reagents are used

- Growth factors and cytokines
- Tissue culture media or supplements containing a complex mix of ingredients
- Feeder cells
- Poorly-defined biological substances
- Scaffolds, encapsulation reagents

These reagents may contain, or have come in contact with animal derived materials

Manufacturing Process Controls

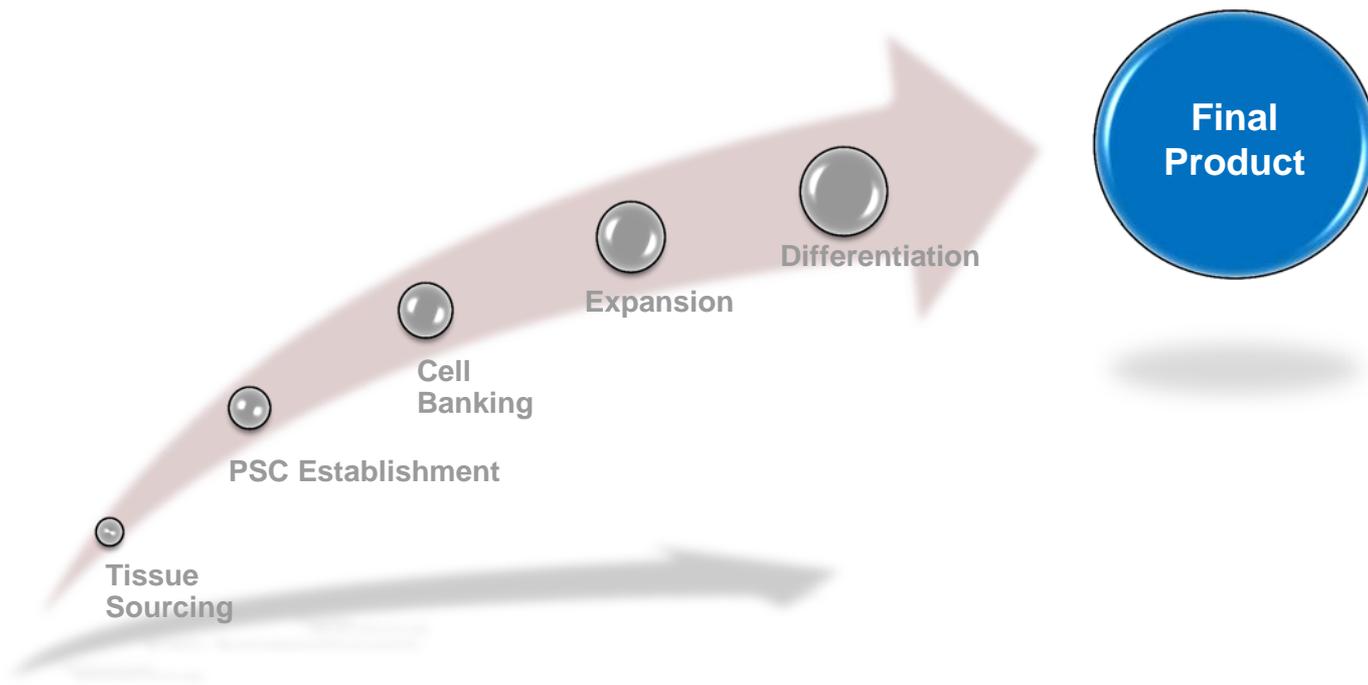
- Well-controlled manufacturing process including isolation, differentiation, cryopreservation, shipping, and other procedures
- Development of critical process and product parameters
 - Controlling purity and impurities profiles of the final cellular product.
 - Establish parameters to ensure product integrity.
 - Identify characteristics that anticipate adverse events: assess during preclinical testing.
 - Develop analytical test methods to evaluate proposed acceptance criteria for in-process intermediates and final product, demonstrate stability.

Basic Principles of CGMP

- Well-defined, written procedures
- Adequately controlled equipment and manufacturing environment
- Accurately and consistently recorded data from manufacturing (including testing)
- Appropriate product tracking and segregation procedures throughout the manufacturing process

*See guidance for application of CGMP in phase 1 clinical trials

Cell Product Testing



Developing Final Product Specifications

- Final product characterization and development of acceptance criteria.
 - Controlling purity and impurities profiles of the final cellular product.
 - Establish parameters to ensure product integrity.
 - Identify characteristics that anticipate effectiveness and adverse events: assess during preclinical testing.
 - Develop analytical test methods to evaluate proposed acceptance criteria for in-process intermediates and final product, demonstrate stability.

Cell Therapy Lot Release Testing

Test	Test Method	Reference
Sterility	Determined by sponsor ^{†*}	21 CFR 610.12
Mycoplasma	Specified by regulation ^{**}	21 CFR 610.30
Purity (pyrogenicity)	Specified by regulation	21 CFR 610.13
Identity	Determined by sponsor [*]	21 CFR 610.14
Potency	Determined by sponsor [*]	21 CFR 610.10
Others as needed (ex: viability, stability, phenotypes)	Determined by sponsor [*]	Guidance

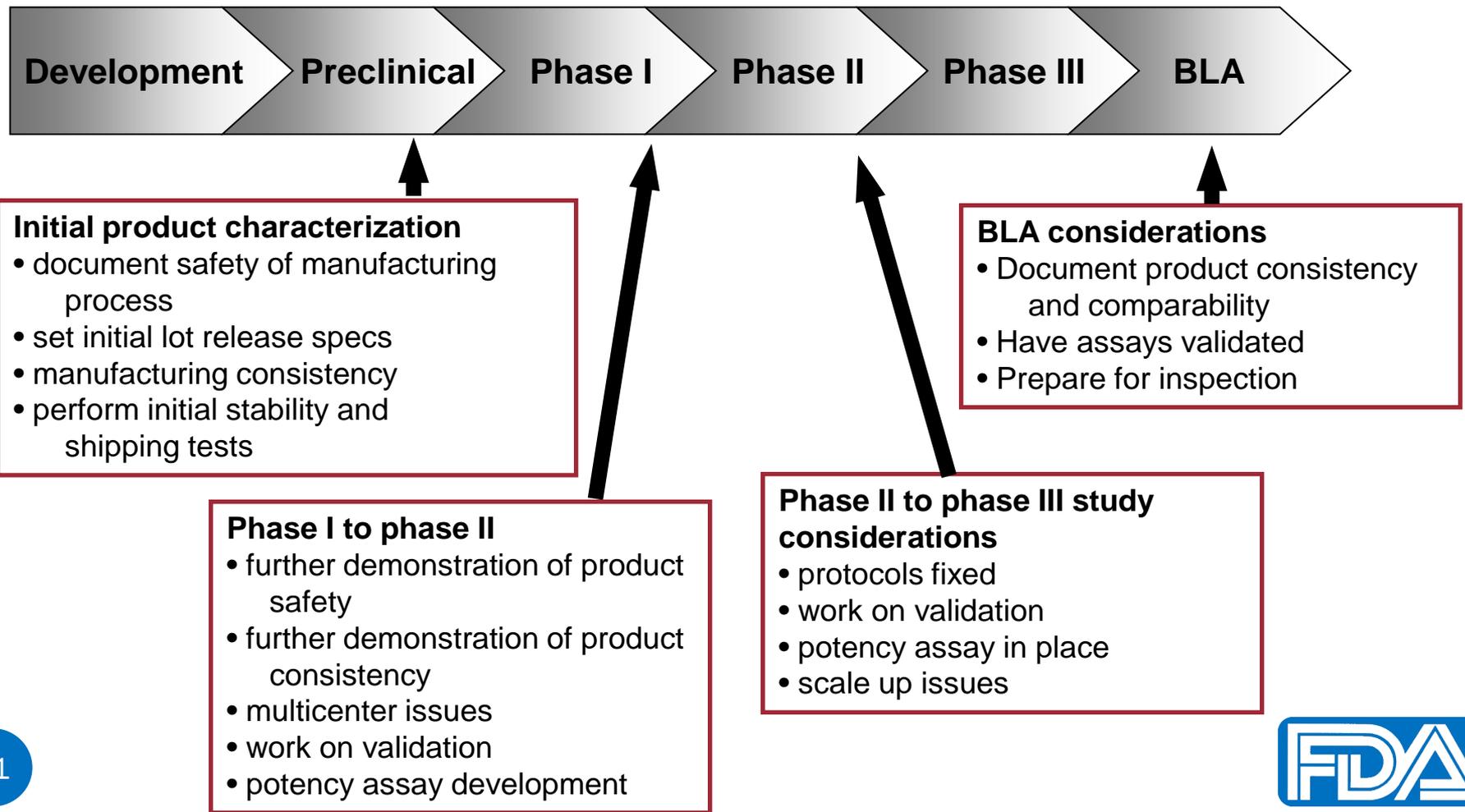
† Recent regulation change allows flexibility in methodology

*To be developed by product manufacturer

** Recommend testing at cell harvest. Refer to 1993 PTC.

Product development cycles: key points

The further along in product development the more product manufacturing should become fixed and the specifications carefully refined



Additional Resources

- Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products [August 2007](#)
- Guidance of Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products [November 2013](#)
- Final Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products [January 2011](#)
- Draft Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products [August 2013](#)
- Guidance for Industry: Current Good Manufacturing Practice for Phase 1 Investigational Drugs [July 2008](#)
- Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs) [April 2008](#)
- Guidance for Industry: Q5A Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin [September 1998](#)
- Draft Guidance for Industry: Use of Nucleic Acid Tests to Reduce the Risk of Transmission of West Nile Virus from Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) [October 2013](#)

Careful planning can overcome regulatory hurdles

The Novice



1. Selection of source material and reagents used in product manufacture is vital to meeting safety requirements.
2. Product testing for cell-based products is often characterized by technological challenges. Identify potential problems and try to address them early in development

Guidance Access

Reference documents and contact information for the Office of Cellular, Tissue and Gene Therapies (OCTGT) can be found at:

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/ucm094338.htm>

Additional CBER regulatory and guidance documents are available at:

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

OCTGT Contact Information

Cellular product manufacturing questions

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(240) 402-8371

Regulatory Questions:

Contact the Regulatory Management Staff in OCTGT at

CBEROCTGTRMS@fda.hhs.gov

or Lori.Tull@fda.hhs.gov

or by calling (240) 402-8361

OCTGT Learn Webinar Series:

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

Public Access to CBER

CBER website:

<http://www.fda.gov/BiologicsBloodVaccines/default.htm>

Phone: 1-800-835-4709 or 240-402-8010

Consumer Affairs Branch (CAB)

Email: ocod@fda.hhs.gov

Manufacturers Assistance and Technical Training Branch (MATTB)

Email: industry.biologics@fda.gov

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