Food and Drug Administration
Center for Biologics Evaluation and Research

CMC Considerations for Stem Cell-based Products

Donald W. Fink, Jr., Ph.D.

Phone: (301) 827-5153

E-Mail: donald.fink@fda.hhs.gov

Office of Cellular, Tissue and Gene Therapies
Division of Cellular and Gene Therapies / FDA

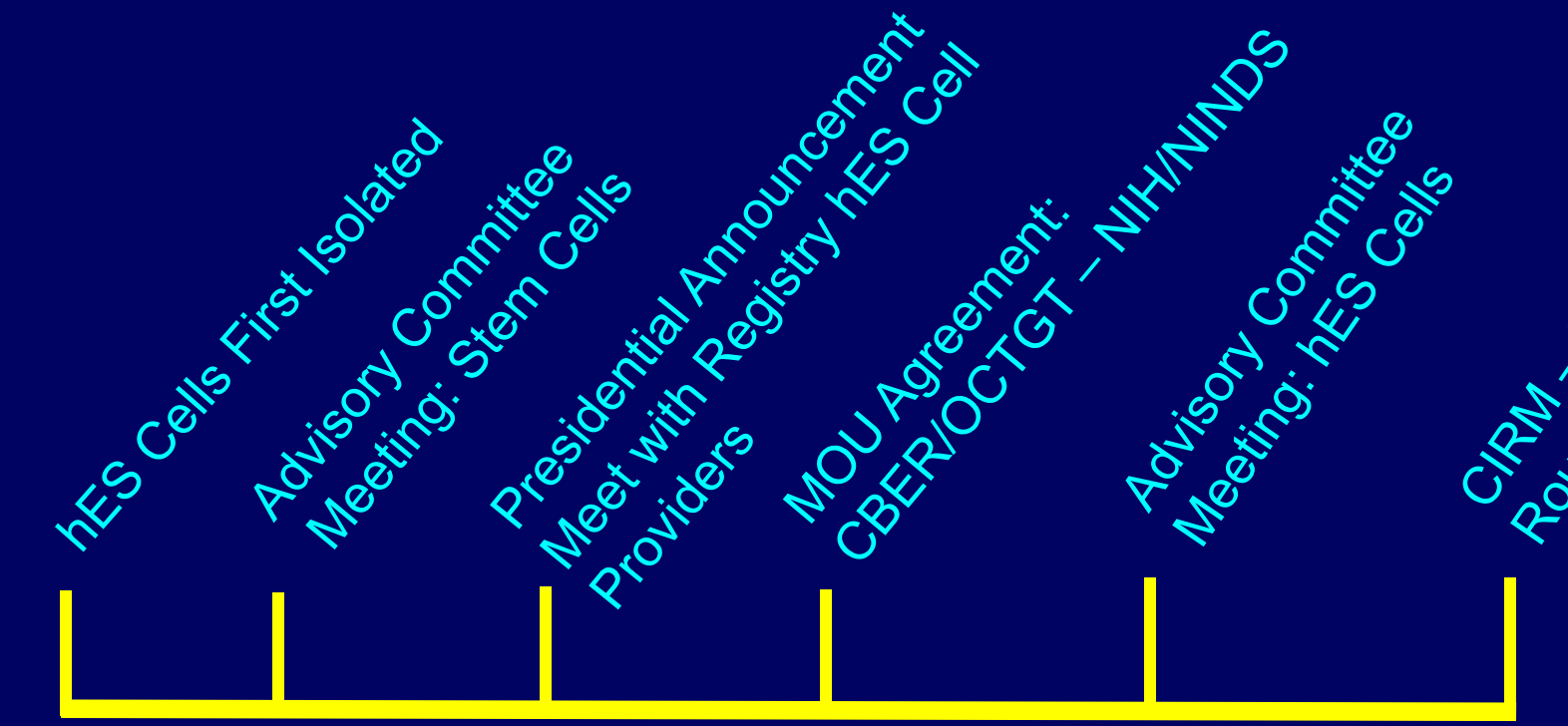
CIRM Regenerative Medicine Consortium
and FDA Roundtable

November 5, 2009

Presentation Overview

- Timeline FDA Activities – Pluripotent Stem Cells
- Stem Cell Biology Poses Regulatory Challenges
- General Regulatory Approach
- Key CMC Issues: Source Controls, Raw Materials, Cell Banking, Process Controls, Product Characterization
- Early FDA Interaction: Pre-IND Meeting

FDA Activities Timeline



CBER RESEARCH PROGRAM

OUTREACH: NIH Stem Cell Task Force / NAS / ISSCR / CIRM / ISCF / US-UK Stem Cell Banks / Presentations / Book Chapters

Internal Human Embryonic Stem Cell Working Group

MOU Agreements: NINDS (2002) / NHLBI (2008)

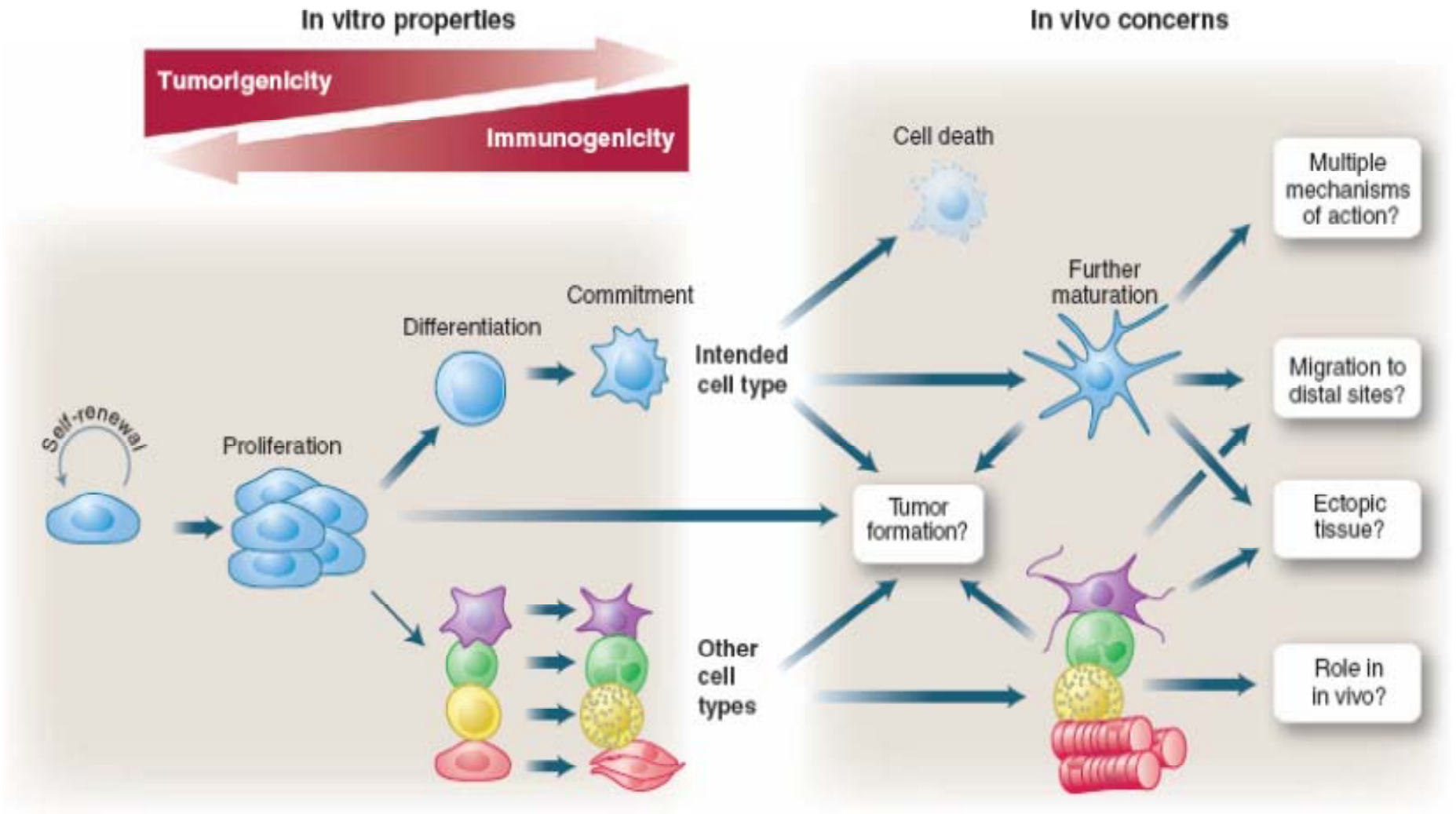
Challenges Posed by Stem Cell Biology

Unique Properties of Stem Cells

- Capable of self-renewing proliferation
- Stem cells may be entirely unspecialized or possess restricted specialization potential, do not have tissue-specific structures or perform specialized functions.
- Unspecialized stem cells give rise to specialized cells through differentiation.

All of the Above Pose Challenges

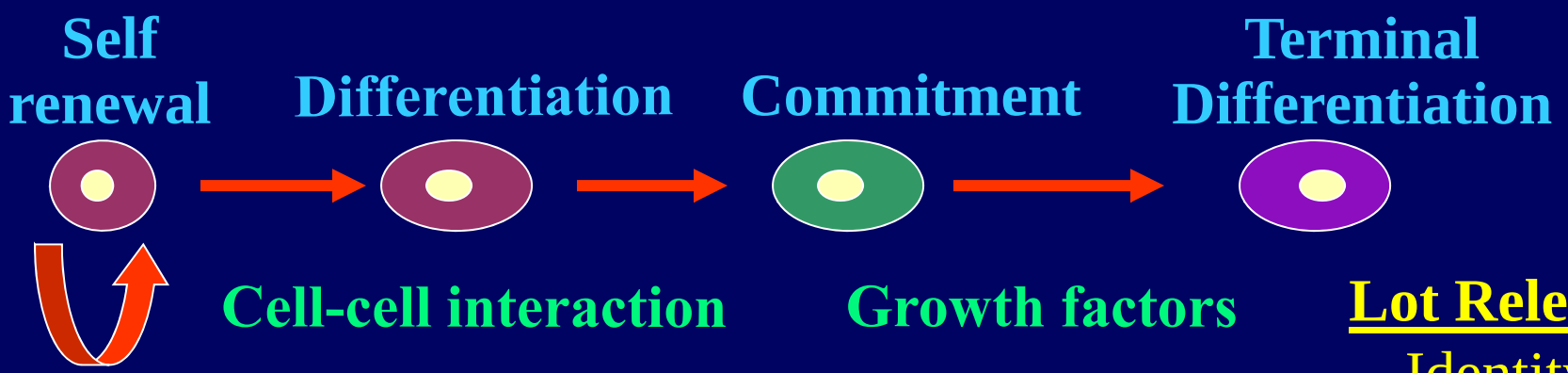
Potential Product Risks Posed by Stem Cell Biology



Characterization

Gene expression profile,
Antibodies, Enzymes,
In vitro differentiation

Developmental Stages
Exogenous Influences
Manufacturing Concerns



Lot Release

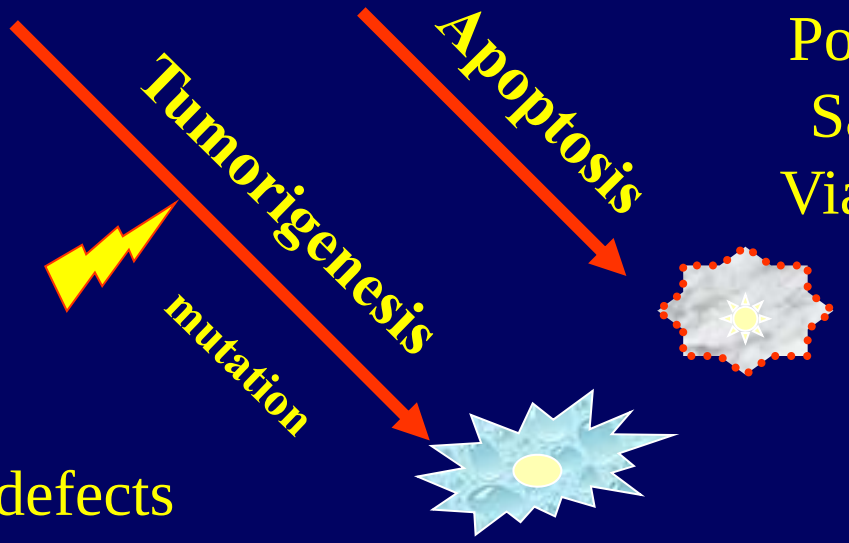
Identity
Potency
Safety
Viability

Manufacturing

Cell Banks
Feeder Layers
Growth Factors
Cell Characterization

Screening

Donors, Viruses, Genetic defects



General Regulatory Approach

Regulation of Cellular and Tissue-Based Products

- A tiered regulatory framework with the level of regulation proportional to the degree of risk
- Provides greater flexibility intended to encourage innovation in the field of cellular therapies
- Risk determines level of regulation

✓**Lower Risk** – Premarket approval not required; for Control of Communicable Disease the Tissue Regulations Apply: Section 361, PHS Act, 21 CFR Part 1271- *Human Cells, Tissue and Cellular and Tissue-Based Products*

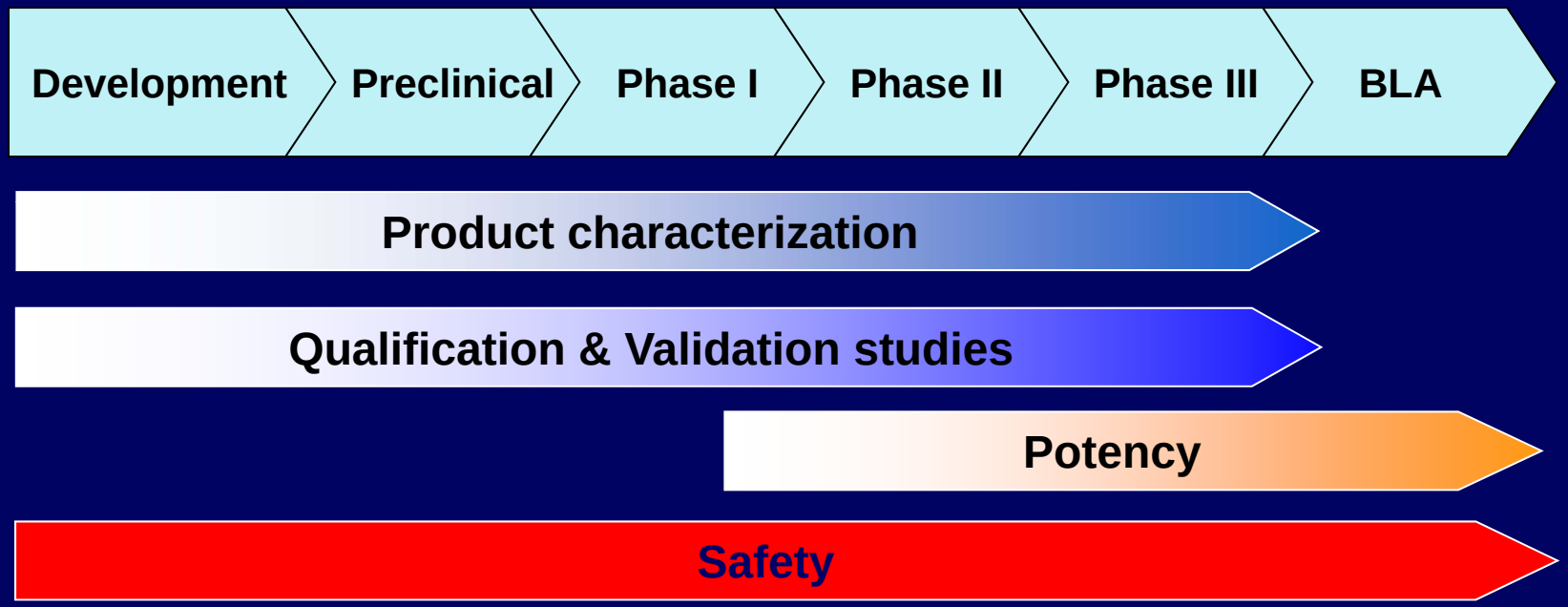
✓**Higher Risk** – Preapproval Required to demonstrate Safety and Efficacy: Section 351, PHS Act (Biologic); Section 505 Food, Drug and Cosmetic Act (Drug), Investigational New Drug Requirements – 21 CFR Part 312; Investigational Device Exemptions – 21 CFR Part 812.

Regulatory Framework: Goals

- ✓ Prevent unwitting use of contaminated tissues with the potential for transmitting infectious disease
- ✓ Prevent improper handling or processing that might contaminate or damage tissues
- ✓ Ensure that clinical safety and effectiveness is demonstrated for cells and tissues that are highly processed, used for purposes other than direct re-placement, are combined with non-tissue components, or that have systemic effects.

Key CMC Issues

Product Development Stage and Review Issues



Stage of product development serves to determine key review issues, with safety being a primary focus during all stages of development/clinical testing.

Developing Stem Cell-Based Product: *Source Controls*

- Evaluating Human Stem Cell Sources
  - Donor Eligibility Determination (DE): screening / testing of donors for relevant communicable disease - 21 CFR 1271, Subpart C: Donor Eligibility Final Rule
    - ✓ EFFECTIVE DATE: May 25, 2005 (Tissue Rules Finalized)
    - ✓ Anonymous/Directed gamete donors must have DE determination performed based on screening/testing.
    - ✓ DONOR SCREENING: review of relevant medical records (history/exam) for risk factors, clinical evidence of relevant communicable disease agents
    - ✓ DONOR TESTING: required for evidence of relevant communicable disease infection, collection of test specimens within 7-days ± recovery of gametes.

NOTE: NIH Guidelines on Human Stem Cell Research do not require DE Determination

Developing Stem Cell-Based Product: *Source Controls (cont)*

- Evaluating Human Stem Cell Sources

  - Assess whether intrinsic safety concerns exist based on their biological status as stem cells.
  - Develop standardized criteria for accepting donor source materials to initiate production of a stem cell-based product.
  - Segregation and Tracking: traceability throughout the entire manufacturing process from donor source to final cell preparation given to patients

Chemistry, Manufacturing and Controls (CMC) Objectives for Cellular Products

- Demonstrate capability of manufacturing process to reproducibly generate an investigational cellular product of defined quality intended for commercial distribution:
  - ☑ Within and Between Clinical Trials
  - ☑ Throughout the entirety of clinical/product development

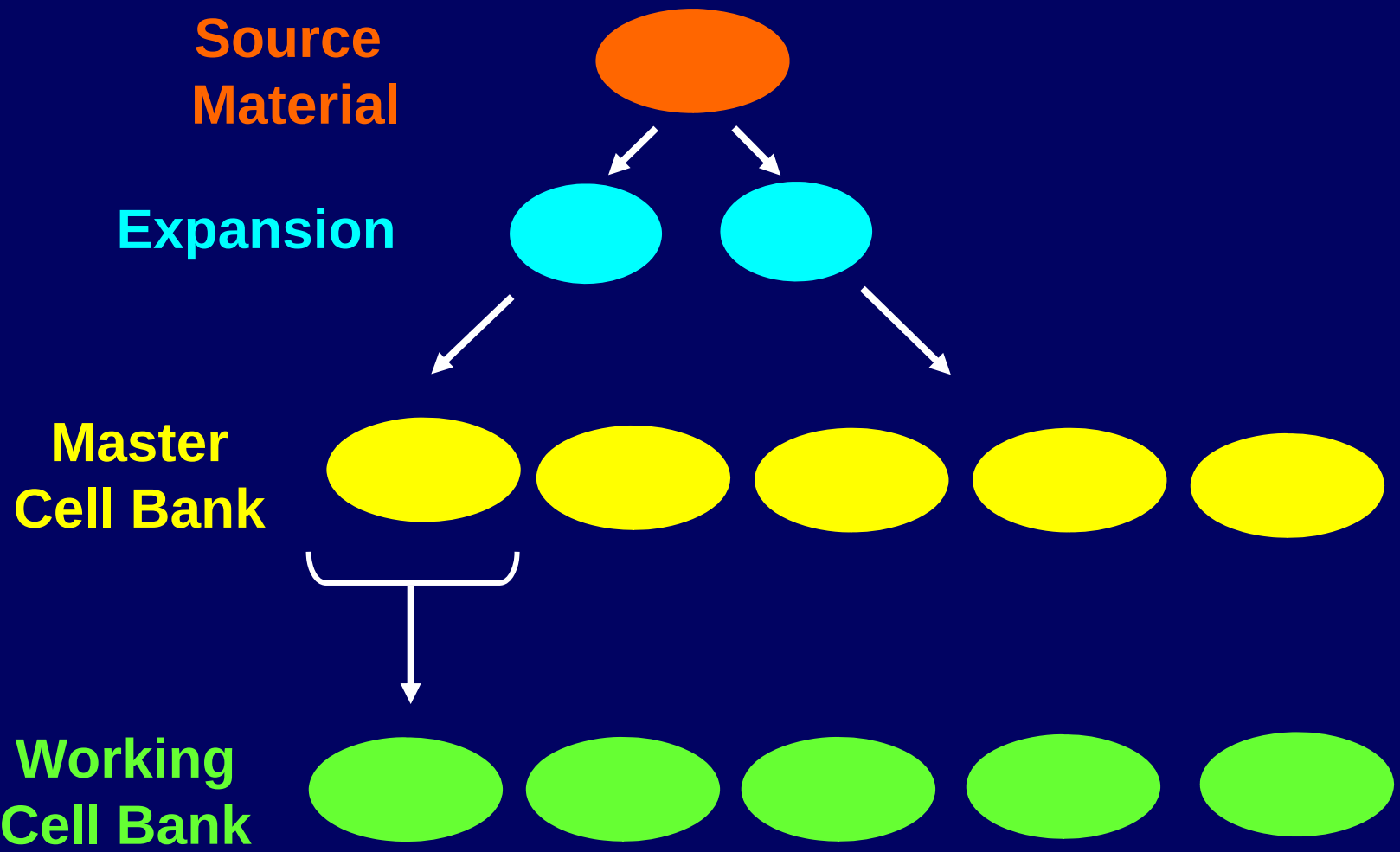
Achieving CMC Objectives: *Control of Raw Materials Quality*

- Manufacture of a cellular product of defined quality relies on thorough description, characterization, and testing beginning with:

  (1) Source Materials
  (2) Reagents
  (3) Ingredients
  (4) Components used throughout the manufacturing process.

- Contingent upon developing a qualification program implemented during product development: applies to raw materials used to manufacture product.

Cell Banking System Considerations



Same level of testing not required for all stages of a multi-tiered cell bank.

Developing Stem Cell-Based Products: *Manufacturing Process Controls*

Critical Manufacturing Process Controls

- Standardization/optimization of reagents/processing procedures, including *in vitro* differentiation protocols
- In-process/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.

Developing Stem Cell-Based Product: *Detailed Characterization*

- Multi-Parametric Approach: Examples of Analytical Tests
  - ✓ Morphologic evaluation / adherence
  - ✓ Detection of phenotype-specific cell surface antigens (tool for performing enrichment)
  - ✓ Unique molecular / biochemical markers
  - ✓ Gene and protein expression analysis (microarray / proteomics – useful for stability / identity)

Developing Stem Cell-Based Product: *Detailed Characterization*

- Multi-Parametric Approach: Examples of Analytical Tests (cont)
  - ✓ Cellular phenotype profile assessment (target / non-target cell types)
  - ✓ Biologic activity assay ≈potency
  - ✓ MHC/HLA expression- predicting immunologic compatibility / anticipating immunogenicity

Interacting with FDA

Developing a Stem Cell-Based Therapy: *Early FDA Interaction*

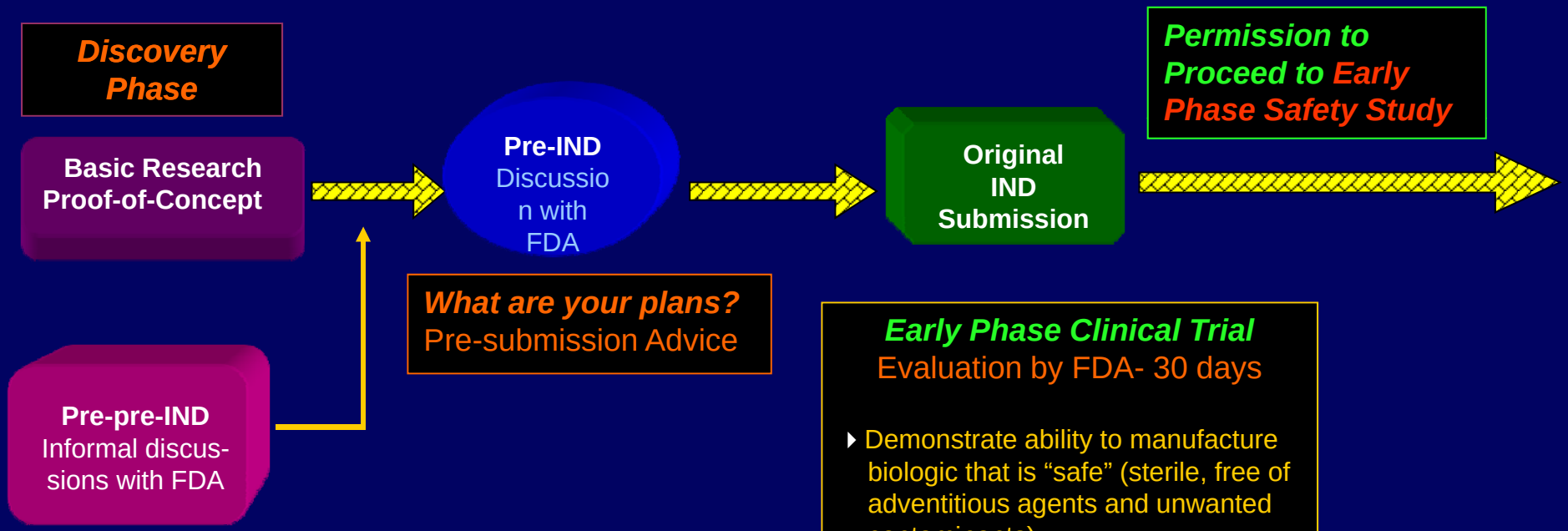
- Informal – Pre-pre IND Discussion: Generally CMC and Preclinical Topics
- Pre-IND / Type B – Formal Meeting
  - Sponsors and CBER/FDA staff discuss product development activities prior to submission of an Investigational New Drug application (IND): may touch on CMC, Preclinical and Clinical.
  - Represents a key juncture in the regulatory process.
  - *Rule of Thumb:* Generally grant one Type B / pre-IND meeting prior to the submission of an IND: Exceptions do occur when circumstances dictate. Follow-up communication/interaction is not uncommon.

When is the “Right Time” to Request a Pre-IND Meeting: CMC Perspective

- Directly correlated with the maturity of your cellular product development efforts.
- Should have developed standard procedures that allow for reproducible product manufacturing: adequate cellular product characterization.

When is the "Right Time" to Request a Pre-IND Meeting

Regulatory Roadmap: Early Phase Clinical Trials



Pre-IND Meeting : Examples of CMC Topics

- Sourcing of Cellular Material - Adequate Donor Testing/ Screening
- Qualification of Raw Materials - Reagents: use of animal-derived reagents.
- Establishing Cell Banks to Support Product Manufacturing: adventitious agent testing.
- Adequate Characterization of Investigational Cellular Product: multi-parametric analytical testing, identity and impurities profile, stability.

Pre-IND Meeting : Examples of CMC Topics (cont)

- In-Process and Final Formulated Product Testing: acceptance criteria and release testing (sterility, endotoxin, mycoplasma, identity, potency).
- Catheter / needle injection systems-reliably and reproducibly deliver targeted number of viable cells.
- Biocompatible cell scaffolds and matrices: tissue constructs
- Encapsulation methodologies that prevent immunologic rejection while permitting release of bioactive materials from encapsulated cells (i.e. β-islets, insulin)

Tips for a Productive Pre-IND Meeting

- Be Prepared: Draft responses to questions in informational package communicated to sponsor prior to meeting (within 24-hrs)
- Focus on the questions requiring additional discussion.
- Avoid expending an excessive amount of time on any one topic/issue when there is a difference of opinion
- Seek additional clarification and explanation when there is uncertainty / request follow-up interaction if necessary.

SUMMARY

- Unique biological attributes of stem cells pose significant regulatory challenges.
- A tiered, risk-based regulatory framework is used for evaluation of investigational stem cell-based products.
- Source controls, raw material quality, manufacturing process controls, and detailed product characterization are pivotal to stem cell-based product development.
- Early interaction with FDA encouraged.

SELECTED GUIDANCES

- Guidance for FDA Reviewers and Sponsors: “Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy IND Applications”

http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Xenotransplantation/ucm092705.pdf

- Guidance for Industry: “Q5A Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin”

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073454.pdf

- Guidance for Industry: “cGMP for Phase 1 Investigational Drugs”

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070273.pdf

- Guidance for Industry: Formal Meetings with Sponsors and Applicants for PDUFA Products”

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079744.pdf

REFERENCES

- Fink Jr, DW. "FDA Regulation of Stem Cell-Based Products." *SCIENCE,* **324:**1662-1663, 2009.
- Moos Jr, M. "Stem Cell-Derived Products: an FDA Update." *Trends in Pharmacological Sciences,* **29**:591-593, 2008.
- DW Fink, Jr., and Bauer, SR**.** "Stem Cell-based Therapies: FDA Product and Preclinical Considerations." In The Essentials of Stem Cell Biology (Second Edition). Ed. R Lanza, J Gearhart, B Hogan, D Melton, R Pedersen, J Thomson, E Thomas and I Wilmut; Elsevier Academic Press: Burlington, MA, pp. 619-630, 2009.
- CBER/FDA Cellular, Tissue and Gene Therapies Advisory Committee Meeting: "Cellular Therapies Derived from Human Embryonic Stem Cells Scientific Considerations for Pre-Clinical Safety Testing." (April 10-11, 2008). Transcript Available at:

http://www.fda.gov/ohrms/dockets/ac/cber08.html#CellularTissueGeneTherapies

Contacting the Center for Biologics

CBER CONTACT INFORMATION

- PHONE: 1-800-835-4709 (Within U.S.)
  301-827-1800 (Local or Outside U.S.)
- INTERNET: http://www.fda.gov/BiologicsBloodVaccines/default.htm
- Send e-mail to: OCOD@fda.hhs.gov
- CBER Regulatory and Guidance Documents on the Internet at:

http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm