The Office of Cellular, Tissue, and Gene Therapies
Web Seminar Series
presents:

Advanced Topics: Successful Development of Quality Cell and Gene Therapy Products

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Successful Product Development

- Demonstrate product to be safe, pure, potent, effective and stable
- Manufacturing control
  - product consistency
  - CGMP principles
  - ensure continued production of quality products
- Product testing and characterization
- Build quality into products

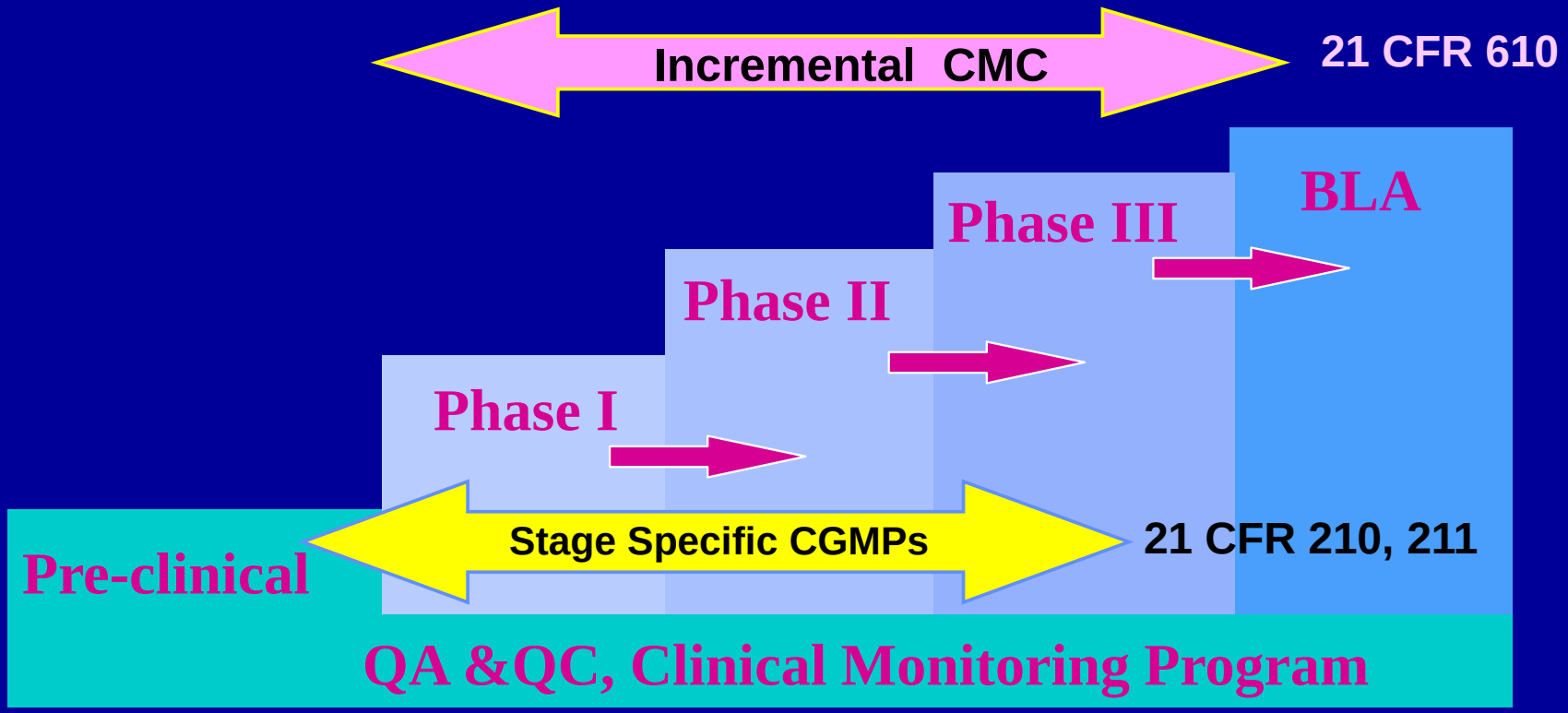
Product Quality Attributes

- Quality attribute: product characteristic selected for its ability to help indicate the suitability of the product for its intended use.
  - e.g. physical, molecular, biological property
- Collectively, the quality attributes define the safety, purity, potency, identity and stability of the product.

Why is Product Characterization Important?

- Biological products are complex, often heterogeneous mixtures, with complex mechanism(s) of action
- Determine product quality attributes
  - To demonstrate lot-to-lot consistency
  - To generate solid clinical data
- Determine relationship between product quality attributes and safety and efficacy
  - To support establishing specifications
  - To show comparability after manufacturing changes

Incremental Approach to CMC Development



Prior to Phase I : need product safety testing and basic characterization info

CMC Development-Phase I

- **Basic Product Characterization:**
  - Sterility
  - Endotoxin
  - Contaminating viruses
  - Dose (e.g. titer, mass, cell number)
  - Potentially unsafe impurities
    - Quality of raw materials
    - Process contaminants (e.g. column media, antibiotics)
  - Identity
    - Multi-product facilities
- OCTGT web seminars on “The chemistry, manufacturing and controls (CMC) section of a gene therapy IND” and “Cellular Therapy Products”

CMC Development: Product Characterization (1)

- Lifecycle expectations:
  - During early product development: data collection: product composition, biological activity, other product attributes
    - Stability
    - Comparability
    - In process evaluations: monitor process control
  - Compliance standards: subset may be used as basis for characterization assays (21 CFR 610)

CMC Development: Product Characterization (2)

- **Controlling product quality - CGMPs**
  - Process control and validation
  - Specifications and acceptance limits
  - Assay control and validation
- **CGMPs are defined as:**
  - A set of current, scientifically sound methods, practices or principles that are implemented and documented during product development and production to ensure consistent manufacture of safe, pure and potent products.

CGMP During Clinical Trials (1)

- Exemption from part 211 for Phase I studies
- General CGMP principles are applicable to phase I products
- CGMP principles for phase I:
  - sterility assurance
  - quality oversight and facility control
  - adequate documentation (traceability)
- Guidance for Industry CGMP for Phase 1 Investigational Drugs (July 2008).

CGMP During Clinical Trials (2)

- CGMPs apply to manufacturing process & facilities
- Expect control to increase as process development and clinical study progress
- Process control overlaps with product quality attribute characterization.
- FDA guidance on the “Preparation of Investigational New Drug Products (Human and Animal)” 1991 (reprinted November 1992).

CGMP During Clinical Trials (3)

- Examples of CGMPs that develop with clinical studies:
  - process validation
    - e.g. manufacturing
  - methods validation
  - process controls:
    - in-process testing
    - specifications
- Schedule a Type C meeting with CBER's Office of Compliance and Biologics Quality - Division of Manufacturing and Product Quality

Lot Release Specifications

- **Specifications:**
  - tests (e.g. analytical and biological) and acceptance criteria that confirm the quality of products and other materials used in the production of a product
- **Acceptance criteria:**
  - numerical limits, ranges, or other criteria for tests described in specifications
- **Incremental Approach**
  - Phase 1-2: safety, acceptance limits may have wider ranges
  - Phase 3-Pivotal studies: tests more refined and acceptance criteria more defined; established limits for release assays
  - BLA:
    - Specifications based on validated assays
    - Include statistical analyses
- **Guidance: ICH Q6B**

Methods Validation

- **The process of demonstrating that analytical procedures are suitable for their intended use**
  - Does the procedure do what it is intended to do?
  - Does it yields data to answer a question?
  - Does it provide confidence in the results?
- **Follow CGMPs**
- **FDA Guidance:**
  - FDA Guidance: Analytical Procedures and Methods Validation (08/2000)
  - ICH Q2(R1) Validation of Analytical Procedures: Text and Methodology (November 2005)
  - CBER review teams

Method Development: Licensed Biological Products

- 21 CFR 210, 211
  - Results available for lot release
  - Provide quantitative readout
  - Meet predefined acceptance and/or rejection criteria
  - Include appropriate reference material/controls
  - Validated for licensure
- Consult with a statistician
- Product quality standards (21 CFR 610)
  - Potency
  - Purity
  - identity

Potency

21 CFR 600.3 (s):

“The word potency is interpreted to mean the specific ability or capacity of the product…to effect a given result.”

21 CFR 610.10:

“Tests for potency shall consist of either in vitro or in vivo tests, or both, which have been specifically designed for each product so as to indicate its potency…”

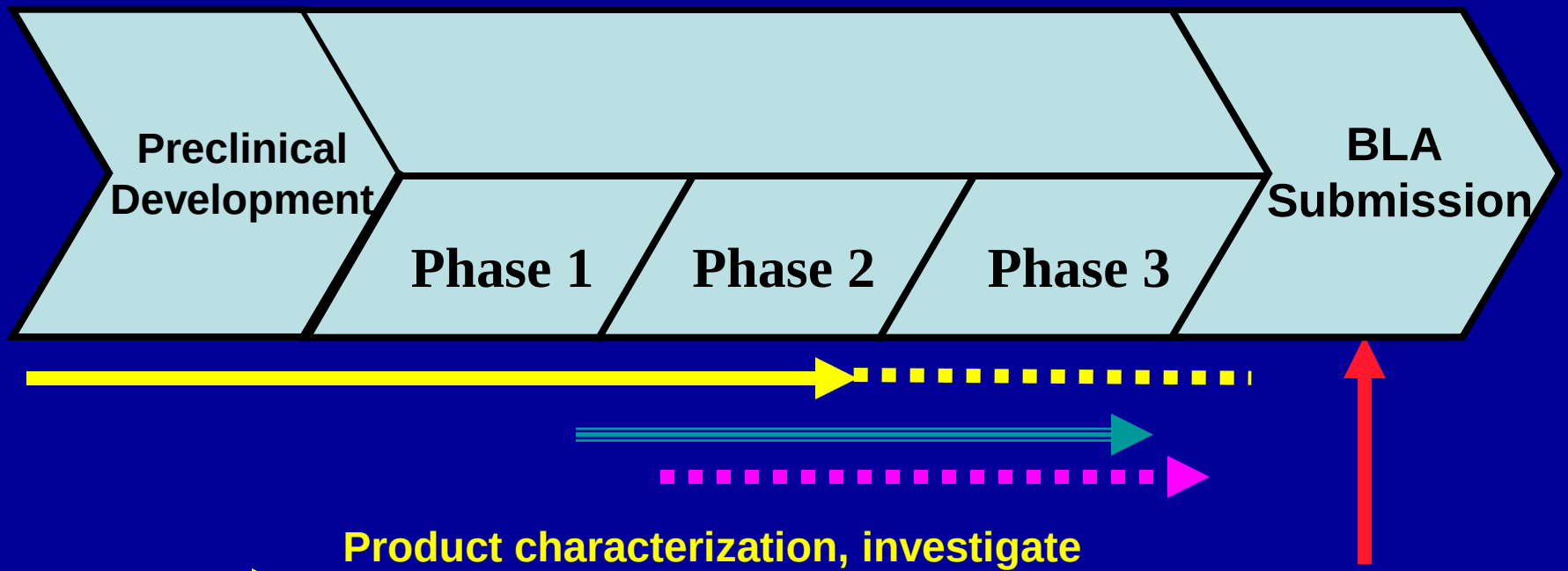
Potency Guidance

Draft Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products (October 2008)

Potency Assay Attributes: Licensed Biological Products

- Indicate biological activity (s) specific/relevant to the product
- Measure activity of all ingredients considered necessary for activity
- Indicate product stability

Incremental Approach: Potency



Product characterization, investigate mechanism of action to justify critical biological activity as target of potency assay development.

Potency assay (s) development, refinement and qualification.

Potency assay in place, ongoing validation studies.

Validated Potency Assay

Approaches for Potency Measurements

- **Direct Measurement of Biological Activity**
  - In vitro or in vivo biological assay methods (bioassay) based on product specific attributes
- **Indirect Measurement of Biological Activity (Surrogate measure)**
  - Non-bioassay analytical methods based on product attributes (e.g. : immunochemical, molecular, physical, biochemical properties) that are correlated to a relevant biological activity
- **Multiple Assay Approach (Assay Matrix)**
  - Combination of complementary assays based on product specific attributes (biological or analytical)

Surrogate Measure of Biological Activity

- Non-bioassay may be used if substantiated by correlation with results obtained from relevant biological assays
  - Sufficient, statistically sound data
  - e.g., by comparison to:
    - preclinical/proof of concept data
    - *In vivo* animal or clinical data
    - *in vitro* cellular or biochemical data
- Significant product characterization data may be required

Purity

- 21 CFR 610.13
  - Free of extraneous material
  - Unavoidable in the manufacturing process
  - Described in the approved biologics license application.
- Impurity profile
  - Description of process contaminants

CMC development- Purity

- During early CMC development possible contaminants or impurities should be tested for in the final product.
- As CMC development progresses your manufacturing process should be validated to either remove or not introduce process related contaminants.
- Contaminants should be removed or limits set based on data from lots shown to be safe in pre-clinical and/or clinical studies.

Purity testing - process validation

- **Characterize capacity of purification process to remove**
  - manufacturing components (e.g. cell culture media, helper virus, antibodies)
  - product isoforms (e.g. empty capsids, unintended cell populations)
- **Process controls in place**
  - Reagent qualification
  - Process development (in process testing)
  - Column regeneration (if applicable)
- **Risk from process contaminants**
  - CsCl or chromatography media

Identity

21 CFR 610.14

- The final container of each lot should be tested for identity after all labeling operations shall have been completed.
- The identity tests should be able to identify the product as designated on the final container, package label and circulars.
- The test should also be able to distinguish the product from any other product being processed in the same facility.

Identity Testing

- Evaluate multiple assays during product development
- Understand unique properties of product or process
- Demonstrate facility control for CGMP compliance
- Example gene therapy vector-
  - Can PCR assay for transgene distinguish product?
    - Components used to produce vector have transgene (e.g. plasmids, chimeric helper viruses, proviruses)
    - Other products have same transgene, but different backgrounds (e.g. multiple vector types with same gene)
    - Same virus genome, but multiple serotypes

CMC Development - Stability (1)

- Products under IND: 21 CFR 312.23
  - Required for all phases of IND
  - Demonstrate that the product is within acceptable quality limits for the duration of planned clinical study.
- Incremental approach for limits/ranges:
  - Phase 1: data from pre-clinical lots (same formulation, dilution, temperature, container)
  - Phase 2: refine limits/ranges based on Phase 1 data
  - Phase 3: Further refinement, data collection to support expiry date and storage conditions
  - BLA: data collected using validated assays

CMC Development- Stability (2)

- **Licensed Products: 21 CFR 211.165**
  - "Written testing program designed to assess the stability characteristics of drug products"
    - Determine storage conditions
    - Determine expiration dates
- Guidance documents:
  - ICH Q5C: Final Guidelines on Stability Testing of Biotechnological/Biological Products, July 1996.

Stability testing

- **Stability testing should encompass:**
  - **Stability during:**
    - **Planned storage conditions**
    - **Planned formulation**
    - **Manufacturing holding steps**
    - **Stressed conditions**

    - **Shipping / transport**
    - **Loading into delivery devices**

Change Is Inevitable

- Manufacturing or processing changes:
  - e.g. serum-containing medium → serum-free
  - e.g. purification: ultracentrifugation → chromatography
- Change in materials
  - e.g. cytokines, antibodies, media, closure/stoppers
- Scale-up
- Changes in manufacturing site
  - e.g. Larger capacity, GMP compliance
- Formulation/concentration changes
- Phasing in quality limits (e.g. cellular DNA levels)
- Change in analytical procedures

Assessing Manufacturing Changes

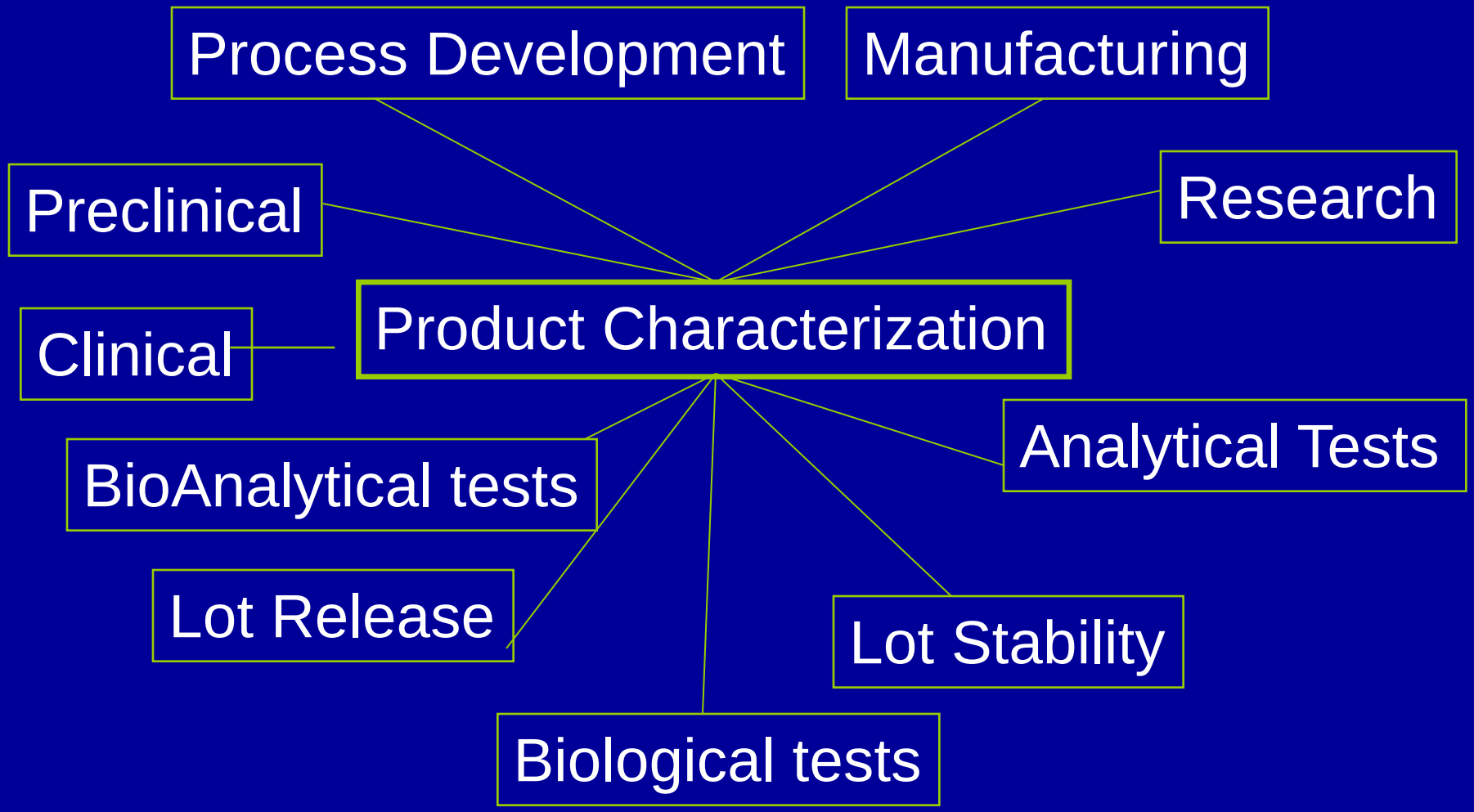
- Small changes in manufacturing might cause unpredictable changes in:
  - Safety
  - Efficacy
  - Antigenicity
  - Pharmacokinetics / biodistribution
  - Stability
- Minor components or contaminants might be important to safety and efficacy
- Need for product consistency
- Try to avoid major changes while in phase III

Comparability Guidance

- ICH Q5E - Comparability of Biotechnological/ Biological Products Subject to Changes in Their Manufacturing Process. (June 2005)

- Consult with your CBER review team prior to making major manufacturing changes

Product Development



Contact Information

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- For guidance document information:
  - http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm