

# Potency Bioassays for Cell and Gene Therapy Products

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# Scope of Discussion

- Why is potency testing so challenging for cell and gene therapy (CGT) products?
- How to develop *meaningful* potency assays for CGT products

**\*\*My comments are an informal communication and represent my own opinions and best judgement. They do not bind or otherwise obligate or commit the agency to the views expressed.\*\***

# CBER's Office of Therapeutic Products (OTP)

- CGT products were previously reviewed by CBER's Office of Tissues and Advanced Products (OTAT)
- In 2023, OTAT was reorganized into the **Office of Therapeutic Products (OTP)** – a newly established “super office” within CBER composed of six new offices:
  - Three CMC Offices: **Office of Gene Therapy (OGT)**, **Office of Cellular Therapy and Human Tissue (OCTHT)**, and Office of Plasma Protein Therapeutics (OPPT)
  - Office of Clinical Evaluation (OCE)
  - Office Pharmacology/Toxicology (OPT)
  - Office of Review Management and Regulatory Review (ORMRR)
- Reorganization aims to increase review capabilities and creates flexibility and capacity for future growth to meet hiring goals outlined in PDUFA VII

NOW WITH  
MORE  
REVIEWERS!

**Establishment of the Office of  
Therapeutic Products**

NEW LOOK!

SAME GREAT  
TASTE!

# Diversity of OTP-Regulated Products

- **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, adenovirus, vaccinia)
  - Microbial vectors (e.g., Listeria, Salmonella)
- **Stem cells/stem cell-derived**
  - Adult (e.g., hematopoietic, neural, cardiac, adipose, mesenchymal)
  - Perinatal (e.g., placental, umbilical cord blood)
  - Fetal (e.g., neural)
  - Embryonic
  - 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 active immunotherapies**
- **Blood- and Plasma-derived products**
  - Coagulation factors
  - Fibrin sealants
  - Fibrinogen
  - Thrombin
  - Plasminogen
  - Immune globulins
  - Anti-toxins
  - Venom antisera for scorpions, snakes, and spiders
- **Combination products**
  - Engineered tissues/organs
- **Devices**
- **Tissues**

# Defining “Potency” for Biologics



## 21 CFR § 600.3(s) – Definitions

“The word *potency* is interpreted to mean the specific ability or capacity of the **product**, as indicated by appropriate laboratory tests or by adequately controlled clinical data, in the manner intended for use.”

## 21 CFR § 610.1

“Tests for potency shall be conducted in a manner which has been shown to be valid, which shall be defined in a manner consistent with the definition in § 600.3(s).”

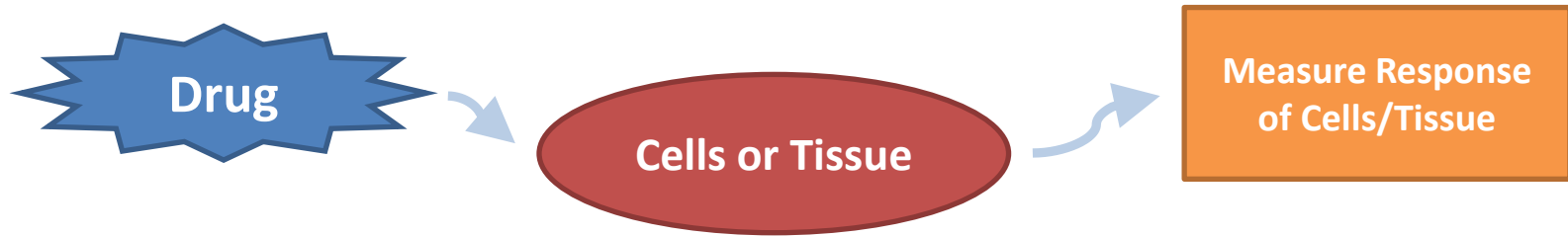
**Tests for Potency Should:**

- Test an attribute related to the product’s ability to mediate a clinical effect
- Be designed specifically for the product
- Be conducted on every lot prior to release

## 21 CFR § 610.1 - Release Requirements

“No lot of any licensed product shall be released by the manufacturer prior to the completion of tests for conformity with standards applicable to such product.”

# Traditional Bioassays



Bioassays of this design work well for measuring the potency of traditional drugs with well-characterized MOAs, but measuring potency of complex products can be more challenging

# Controlling CGT Product Potency

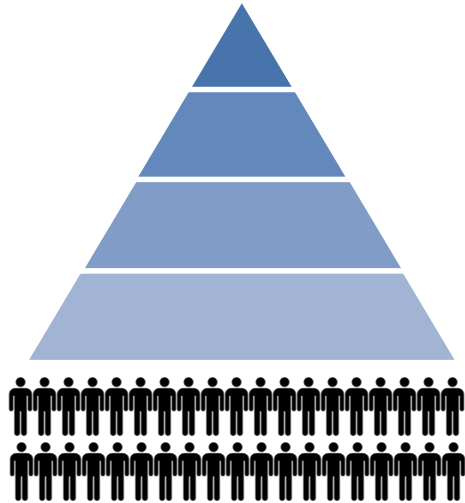
- Identifying attributes related to potency can be challenging:
  - Mechanisms of action (MOAs) may be complex or not fully characterized
  - Cell-based products are particularly complex and can have extensive lot-to-lot variability
- A loss of potency may not be immediately reflected in a change in physical attributes (e.g., viability, apoptotic markers)
- Some CGT products have very short shelf-lives, limiting the types of assays that can be completed before lot release
- Material available for testing may be limited due to smaller manufacturing scales
- Limited availability of reference standards and controls

# Different manufacturing paradigm



## Conventional Drug/Biologic

1 product lot



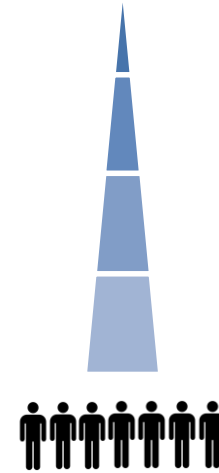
Many patients

## Cell & Gene Therapy Products

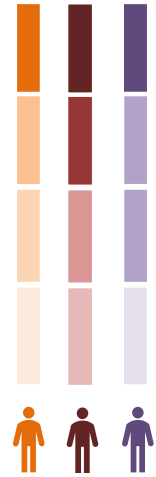
1 product lot

1 product lot

Raw materials  
CGMPs  
Advanced manufacturing  
In process and lot release testing  
Scale up/scale out  
Comparability  
Distribution  
Impact of manufacturing failure



Few patients



Single patient



GUIDANCE DOCUMENT

# Potency Tests for Cellular and Gene Therapy Products

*Final Guidance for Industry:*

JANUARY 2011

<https://www.fda.gov/media/79856/download>

# Bioassays for CGT Product Potency

*“The traditional approach for assessing the potency of biological products is to develop a quantitative biological assay (bioassay) that **measures the activity of the product related to its specific ability to effect a given result** [...]. Bioassays can provide **a measure of potency by evaluating a product’s active ingredient(s) within a living biological system** [such as] *in vivo* animal studies, *in vitro* organ, tissue or cell culture systems, or any combination of these.”*

## Methods for Measuring Potency of CGT Products:

### ▪ **Bioassays (Direct Measurement):**

- Evaluating a product’s active ingredient(s) **within** a living biological system
- Can be animal models, *in vitro* organ, or tissue or cell culture systems

### ▪ **Analytical Assays (Indirect Measurement):**

- Performed outside a living test system (e.g., immunochemical, biochemical, or molecular testing)
- Can be used to demonstrate potency if the surrogate measurements can be substantiated by correlation to a relevant product-specific activity

# Multiple Potency Assays (Assay Matrix)

## When might a single potency assay not be sufficient?

- Multiple active ingredients and/or multiple biological activities
- Complex and/or not fully characterized mechanism of action
- Biological assay is not quantitative, not sufficiently robust, or lacks precision
- Limited product stability

## If one assay is not sufficient, can use multiple complementary assays (an assay matrix) that measure different product attributes

- May be composed of biological assays, analytical assays, or both
- Qualitative assays should be accompanied by one or more quantitative assays

## If analytical methods are used, you should provide sufficient, scientifically sound data to establish a correlation between the surrogate measure and a biological activity related to the potency of the product

# Developing a Potency Assay

- Regulations are very flexible with regards to the kind of assay that can be used as long as it is measuring a meaningful biological parameter
- It is not a regulatory requirement to fully define the mechanism of action, nevertheless, it is useful to have an understanding of how the product is likely to work
- FDA recommends developing an assay early and evaluating multiple potential measures of potency
- At least one quantitative potency assay should be in place before initiation of a clinical study(s) intended to provide evidence of effectiveness to support a marketing application



# Later Phase Potency Assay Expectations



*If product manufacturing and controls are not adequate, FDA may not permit Phase 3 studies or file a BLA*

## By end of Phase 2:

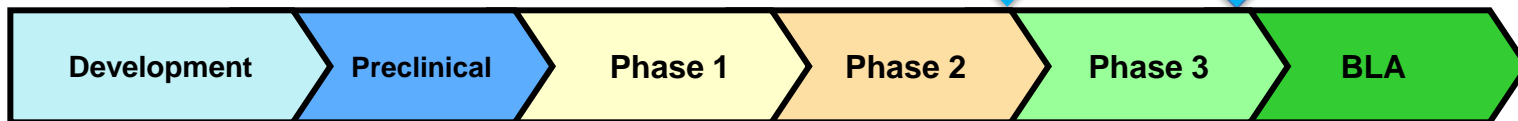
Manufacturing process consistency, control variables  
Product stability  
Adequacy of product characterization

**Potency assay** must be in place for Phase 3

## By end of Phase 3 /Pre-BLA:

### Comparability

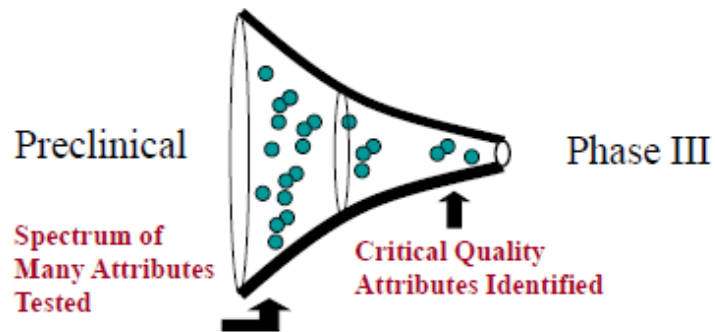
Scale-up  
Test method validation  
Process Validation  
Justification of specification  
Finalizing lot release plans  
Facility inspection  
Stability (for expiry dating, shipping)



# Product Characterization and Potency-Related CQAs

***A Critical Quality Attribute (CQA) is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. - ICH Q8 (R2)***

- Explore many CQAs during early development
  - Report results early in development
  - Choose relevant tests for later phase studies
- Evaluate multiple measures of CQAs (especially potency)
  - Matrix of assays
  - Orthogonal methods
  - Stability indicating



## Summary

- CGT products present many challenges to potency assay development, but regulations allow for considerable flexibility in how potency is measured so long as the method reliably controls a meaningful product attribute related to potency
- Potency-related CQAs for some CGT products may not be well established, so starting product characterization early in development can help identify attributes relevant to product potency that can be measured reliably

# Contact information

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- **Regulatory Questions:**

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Email: [OTPRPMS@fda.hhs.gov](mailto:OTPRPMS@fda.hhs.gov)

- **OTAT (OTP) Learn Webinar Series:**

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

- **CBER website:** [www.fda.gov/BiologicsBloodVaccines/default.htm](http://www.fda.gov/BiologicsBloodVaccines/default.htm)

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

- **Consumer Affairs Branch:** [ocod@fda.hhs.gov](mailto:ocod@fda.hhs.gov)

- **Manufacturers Assistance and Technical Training Branch:** [industry.biologics@fda.gov](mailto:industry.biologics@fda.gov)

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