

Identifying and Controlling Attributes Related to Potency for Cell and Gene Therapy Products

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CBER | U.S. Food & Drug Administration

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Learning Objectives

- Define *potency* and *comparability* as they relate to Cell and Gene Therapy (CGT) products
- Explain why controlling the potency of CGT products is challenging and summarize potency assay expectations at each phase of clinical development
- Explain why product characterization throughout product development is crucial to meeting challenges related to controlling potency and product comparability



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 obtained through the administration of the product in the manner intended, t

21 CFR § 610

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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

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§ 600.3(s) of

21 CFR § 610.1

“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.”

Controlling CGT Product Potency

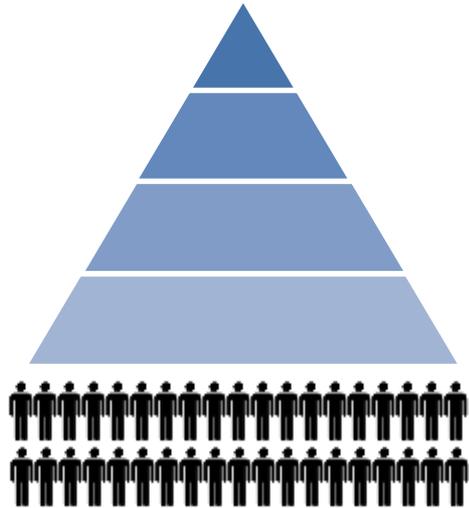
- Identifying attributes related to potency can be challenging:
 - Mechanisms of action (MOAs) may be complex or not fully characterized
 - Cell-based products are particularly complex and can have extensive lot-to-lot variability
- A loss of potency may not be immediately reflected in a change in physical 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

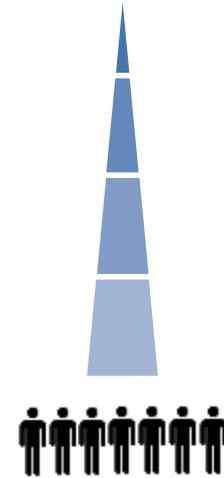
www.fda.gov

Cell & Gene Therapy Products

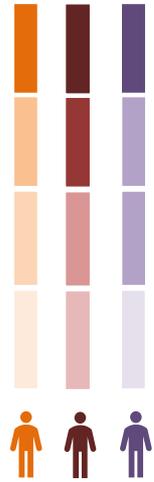
1 product lot

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>

Methods for Measuring Potency

Biological Assays (“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

Non-Biological 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

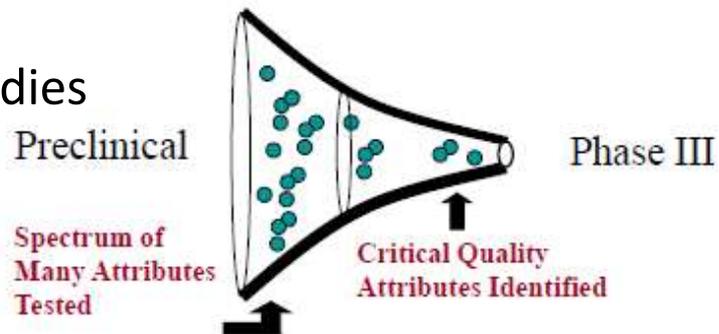
Scale-up
Test method validation
Process Validation
Justification of specification
Finalizing lot release plans
Facility inspection
Stability (for expiry dating, shipping)



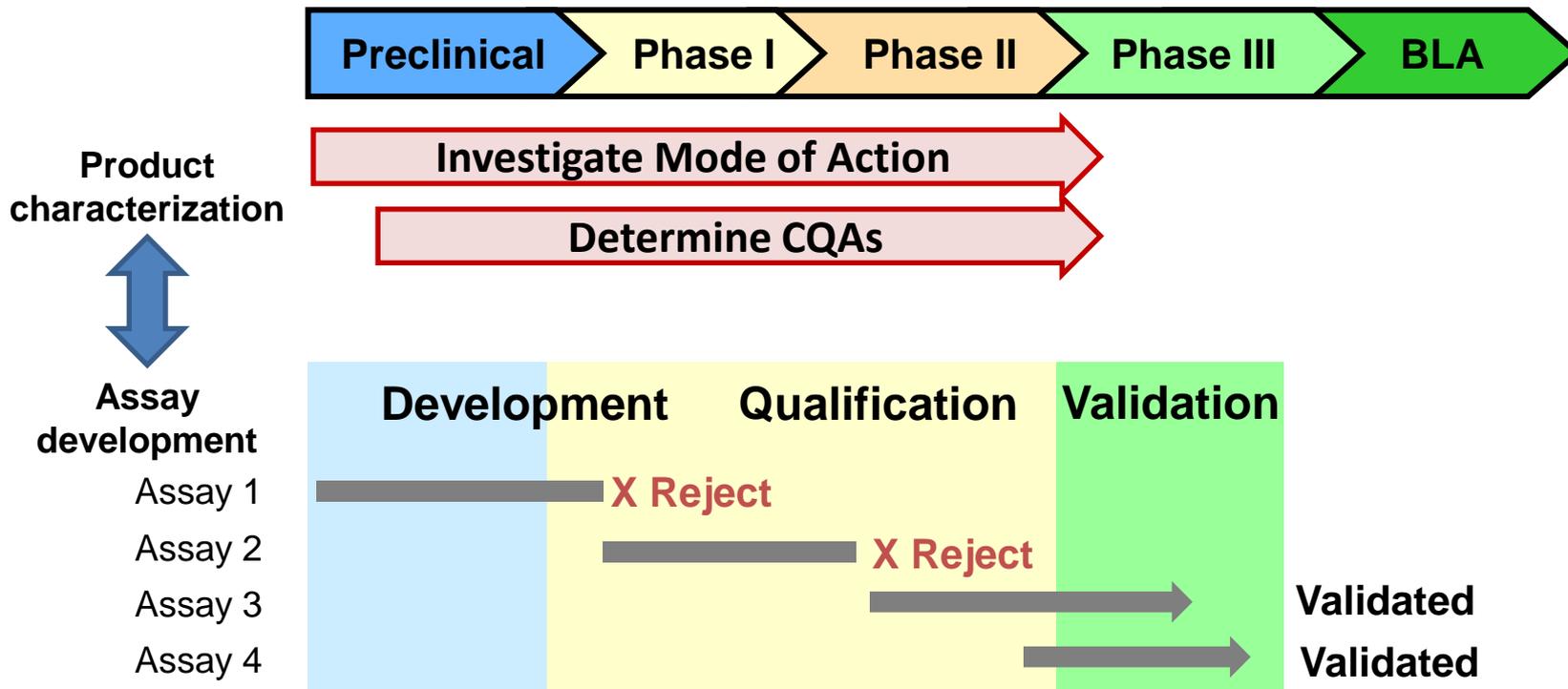
Product Characterization and Potency-Related CQAs

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)

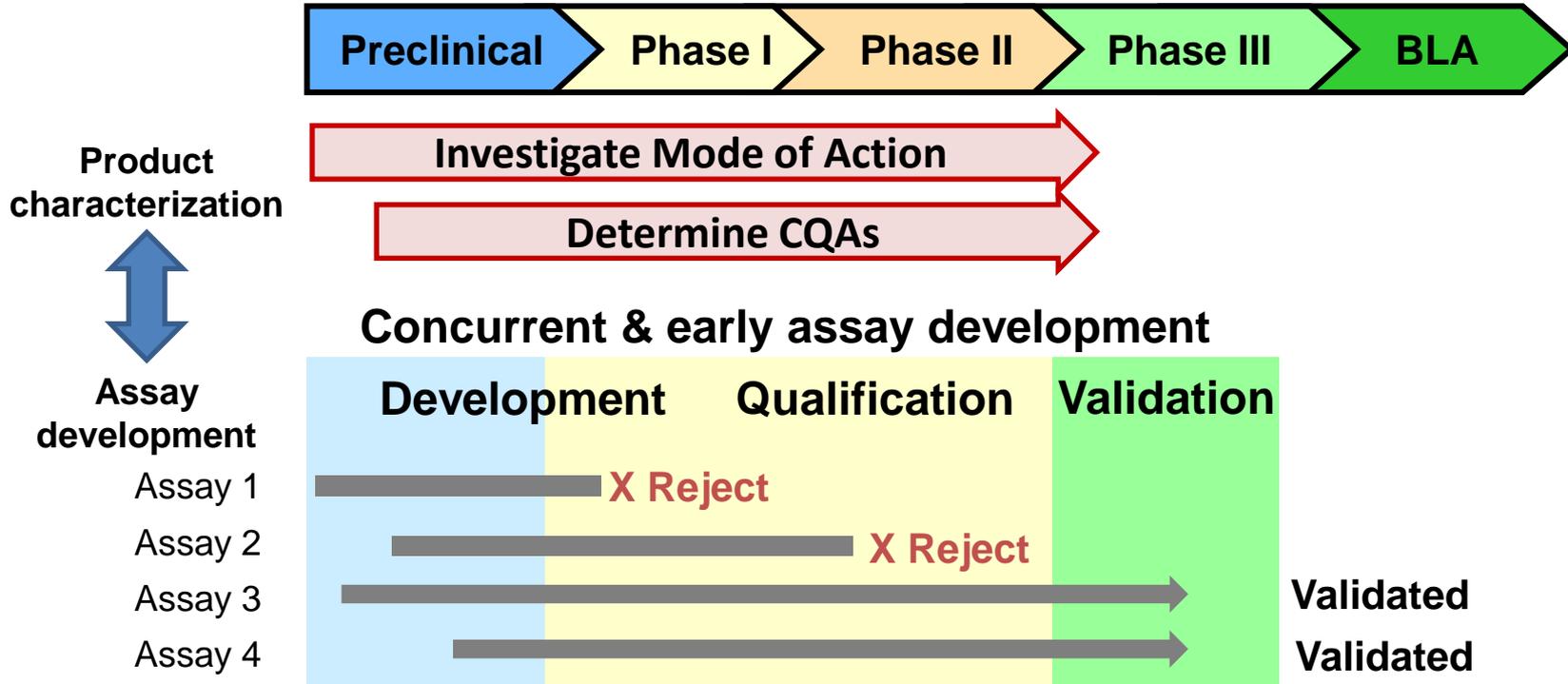
- Explore many CQAs during early development
 - Report results early in development
 - Choose relevant tests for later phase studies
- Evaluate multiple measures of CQAs (especially potency)
 - Matrix of assays
 - Orthogonal methods
 - Stability indicating



Assay Development Timeline



Assay Development Timeline



Product Characterization Throughout Development

The importance of understanding product attributes:

- Meeting certain specifications alone may not be adequate to detect a drop off in product quality – like driving a car without a functioning check engine light
- Potency Assay Development
 - Potency assays should measure a product attribute that is relevant to the product's mechanism of action or a relevant *in vivo* activity
 - An assay for product potency must be in place before initiating clinical studies intended to support a license application (e.g., Phase 3)
- Without well-characterized product attributes, it can be difficult to convincingly demonstrate by analytical means that manufacturing changes have not affected the clinical profile of the product
 - Process improvements, scale up/scale out
 - New manufacturing facilities or equipment
 - Change in source for critical reagents

What do we mean by Potency Matrix?



A ***Potency Assay Matrix*** usually refers to a collection of complementary assays that measure different product attributes **with acceptance criteria in place for lot release**

Product Characterization assays measure product attributes ***in addition to tests used for routine lot release*** and are generally exploratory

- The purpose of exploratory studies is to gain product information, which will help you to design meaningful and relevant potency assays. Assays used for product characterization early in development may be used for lot release later in development.
- While some of the assays you evaluate may not be practical for lot release, they may provide you with helpful information about product attributes related to biological activity or clinical effectiveness, or both.



Challenge Question #1

Which of the following statements regarding potency tests for CGT products is FALSE?

- A. FDA guidance recommends evaluating multiple potential potency tests during clinical development
- B. Federal regulations require that potency tests mimic the product's mechanism of action
- C. Tests for potency should be specifically designed for each product
- D. Each lot should be tested for potency prior to release

Product Comparability

Managing Manufacturing Changes

- Manufacturing changes are inevitable, but they need to be controlled and managed properly to avoid significant impact on product quality and delays in product development
- Manufacturing changes that fundamentally change the design or nature of the product-may require a new IND or BLA
- **Changes with a moderate or substantial potential to affect product safety or efficacy may require comparability studies**; however, the extent of product quality characterization in the comparability study may depend on the stage of development and type of change

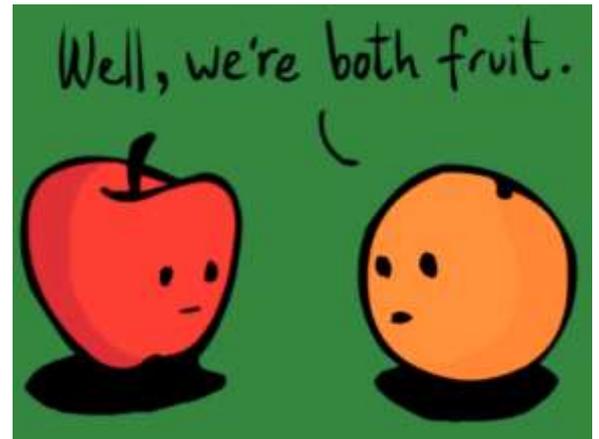
Challenges for CGT Product Comparability Assessments

- Limited manufacturing experience:
 - Not many lots produced
 - Not enough retention or test samples available
- Limited in-process testing: process variables and critical process parameters not known
- Limited product characterization: CQAs not known, product and process related impurities not well characterized
- Limited assay development (e.g., purity, potency)
 - Assays not qualified or not stability indicating
 - Reference standards not established or adequately characterized

What Are Comparable Products?

“...does not necessarily mean that the quality attributes of the **pre-change and post-change product** are identical, but that they are **highly similar and that the existing knowledge is sufficiently predictive to ensure** that any differences in quality attributes have **no adverse impact upon safety or efficacy of the drug product.**”

Refer to ICH Q5E and FDA Guidance for Industry Q5E
Comparability of Biotechnological/Biological Products
Subject to Changes in Their Manufacturing Process



Analytical Product Comparability

“Determinations of product comparability **can be based solely on quality considerations if the manufacturer can provide assurance of comparability through analytical studies [...]**. Additional evidence from nonclinical or clinical studies is considered appropriate when quality data are insufficient to establish comparability.”

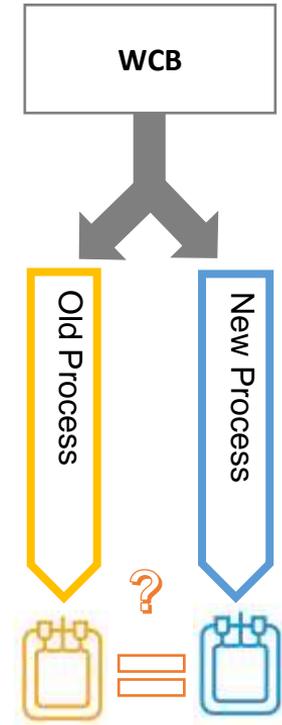
FDA (ICH) Guidance: Q5E Comparability of Biotechnological or Biological Products Subject to Changes in Their Manufacturing Process (2005)

Analytical Comparability Study Considerations

- Perform a risk assessment evaluating the impact of the change
- Assess attributes relevant to product quality and safety and most likely to be affected by the change
- Predefine acceptance criteria for comparability for each attribute being evaluated using appropriate, robust statistical methods
- Recommend making changes prior to initiating clinical studies intended to support efficacy for a marketing application (BLA)

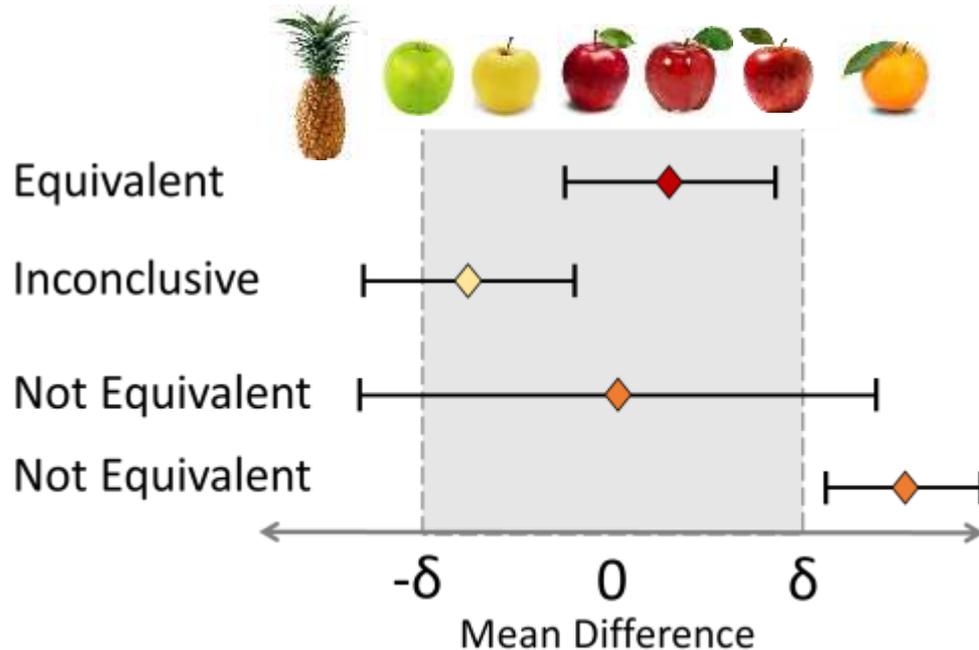
Analytical Comparability Study Considerations

- Side by side analysis with sufficient lots to do robust statistical analysis.
- If changes are introduced in late stages of development, the expected level of comparability demonstration will be significantly higher.
- If analytical comparability study data are not sufficient to establish comparability, additional pre-clinical and/or clinical studies may be required to demonstrate comparable safety and efficacy.
- Discuss with FDA prior to implementation



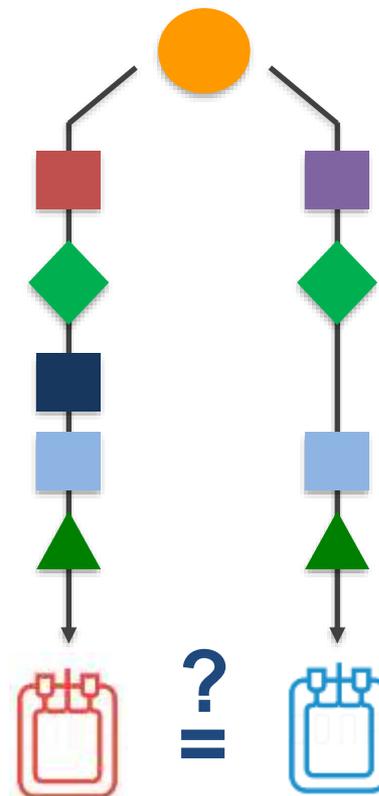
Analytical Comparability Analysis

- Predefine acceptance criteria for each attribute being evaluated
- Use appropriate robust statistical methods (e.g., equivalence testing)



Manufacturing Process Changes

- Change in reagent, process step, etc.
- Changes may be to improve an attribute or manufacturing process
 - Reduce culture time
 - Improve purity
- Comparability assessment requirements are affected by
 - Early vs. late stage of development
 - Minor vs. major change
 - Patient risk



Facility Changes

Comparability allows leveraging clinical data from pre- and post-change products



- Identify proposed commercial manufacturing site prior to Phase 3/registrational study
- Often associated with manufacturing process changes
- Depending on your product, comparison to historical experience may be insufficient

Multiple Manufacturing Facilities

Comparability supports clinical data analysis throughout study



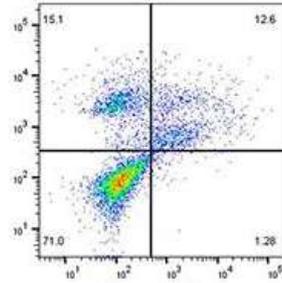
- Comparability study is necessary independent of stage of development
- Recommend comparison to a single “reference” site
- Recommend same SOPs, reagents, training programs, qualification requirements, and equipment are used across manufacturing facilities
- Defined acceptance criteria for product quality attributes will support production of comparable products across manufacturing sites

Analytical Testing Changes

Bridging study allows leveraging clinical data from products analyzed pre- and post-change



?



- Change in assay
 - Assessment of how the assays differ in what they measure
- Multiple testing sites or change in site
 - Demonstrate results are comparable between sites
- Side-by-side testing of the same material
- May impact stability studies



Challenge Question #2

According to ICH Q5E, what is the standard for establishing product comparability?

- A. The products are identical
- B. The products are nearly identical
- C. The products are highly similar

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 be helpful in identifying meaningful attributes that can be useful for controlling product quality and comparability assessments

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

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

- **CBER website:** www.fda.gov/BiologicsBloodVaccines/default.htm

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