U.S. FOOD & DRUG ADMINISTRATION

Potency Assurance for Cellular and Gene Therapy Products

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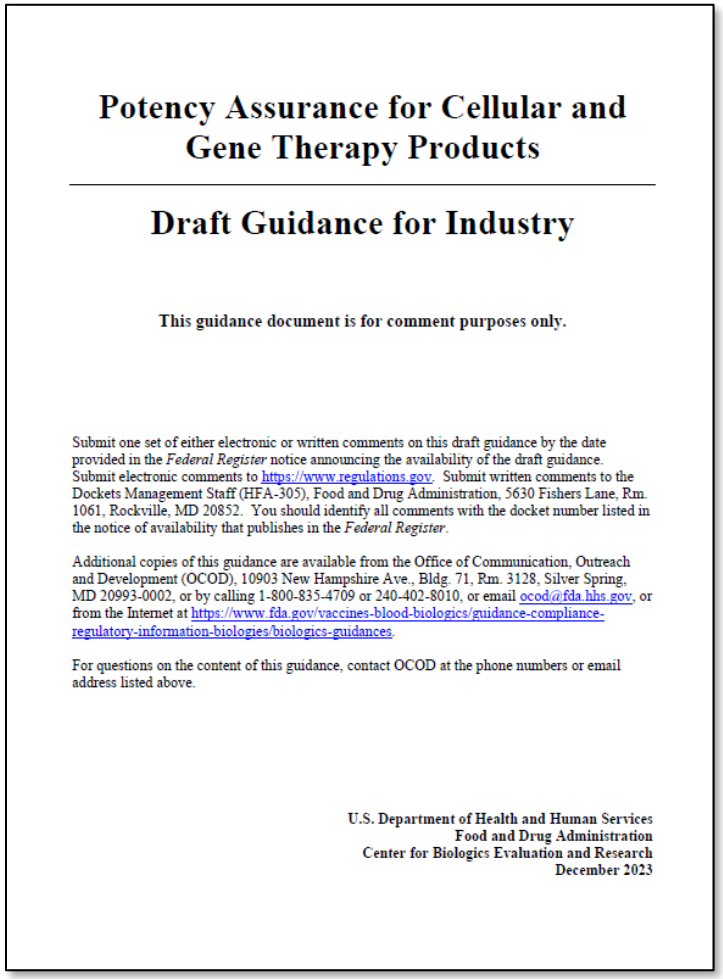
Goals of the draft guidance document



Potency Assurance for Cellular and Gene Therapy Products

Draft Guidance for Industry

This guidance document is for comment purposes only.

Submit one set of either electronic or written comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
December 2023

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You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations

Update our 2011 guidance: *Potency Tests for Cellular and Gene Therapy Products*

- Provide more options without imposing new burdens
- Scope covers all cellular and gene therapies, including genome-editing products and tissue-engineered medical products

Covers all aspects of potency, not just potency assays

Incorporates quality risk management approach and ICH terminology

- From Q8, Q9, Q10 and Q14

Gives industry and regulators a science-based and risk-based framework for discussing potency

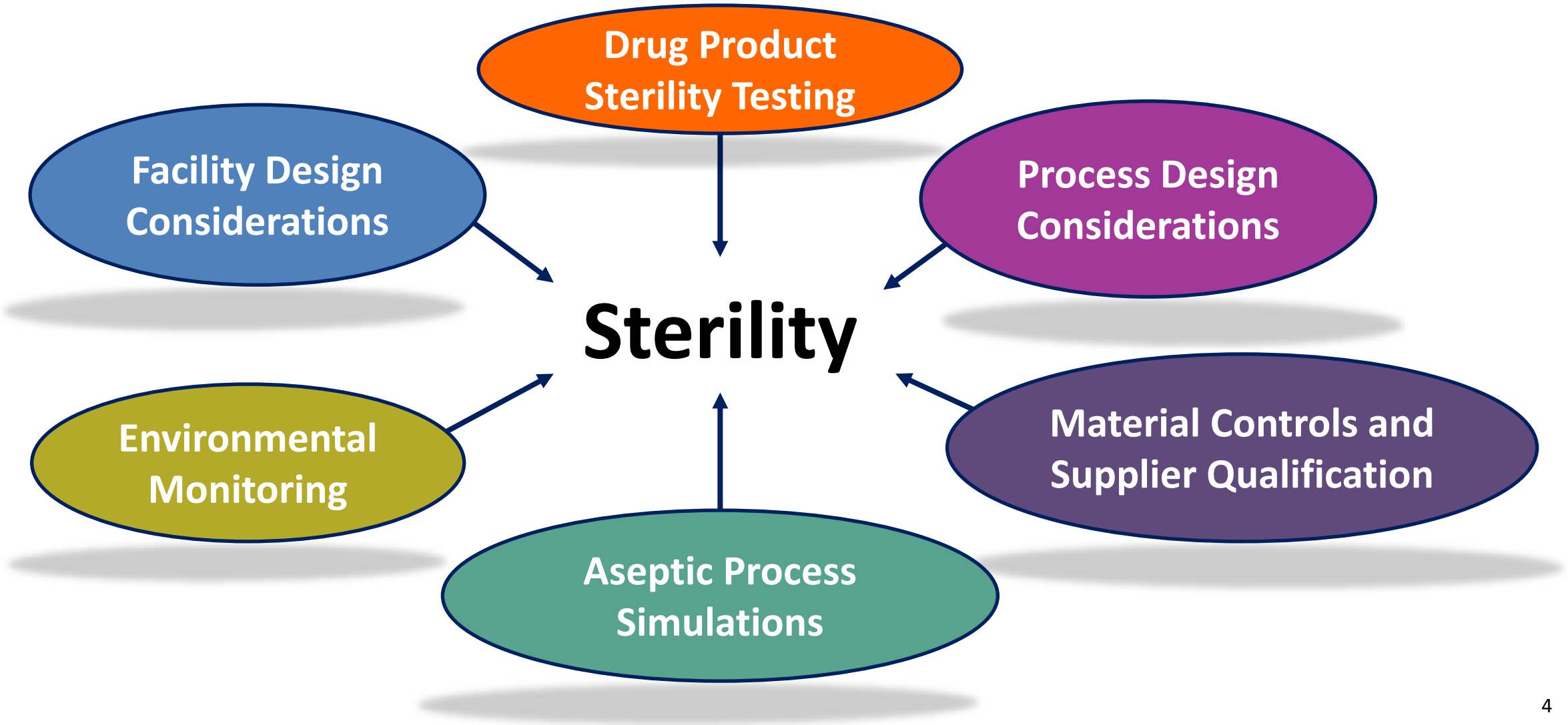
- Additional advice on communicating with CBER about potency

Continues to allow progressive implementation of potency assays during clinical development

What is a potency assurance strategy?

"A comprehensive approach to help ensure that every lot of a product will have the potency necessary to achieve the intended therapeutic effect."

Sterility assurance



From the first paragraph of the guidance

A potency assurance strategy is a multifaceted approach that reduces risks to the potency of a product through manufacturing process design, manufacturing process control, material control, in-process testing, and potency lot release assays. The goal of a potency assurance strategy is to ensure that every lot of a product released will have the specific ability or capacity to achieve the intended therapeutic effect.

Risk assessment and risk reduction

1. Identify what might go wrong during manufacturing to harm potency – assess likelihood and severity of the risks
2. If risk is high, reduce risk by improving the manufacturing process and/or the controls

Manufacturing process design

The manufacturing process should be designed to consistently produce a potent product

Control strategy

Potency release assays are just the final check – they are not the entire control strategy

Product lots should have the ability or capacity to be therapeutic

Key aspects of potency assurance strategies

Understand the potency-related characteristics of your product

Develop a quality target product profile (QTPP)

Identify *potency-related critical quality attributes (CQAs)* that are important for achieving the intended therapeutic effect

Conduct a risk assessment for each potency-related CQA

Identify risks to product potency

Evaluate the significance of these risks by analyzing their probability and severity

Example:
Potency-related CQAs for a viral gene therapy vector

Viral vector: A vector particle (capsid) that contains nucleic acids

Vector particles – typical potency-related CQAs:

- Structural integrity
- Ability to deliver nucleic acids to cells

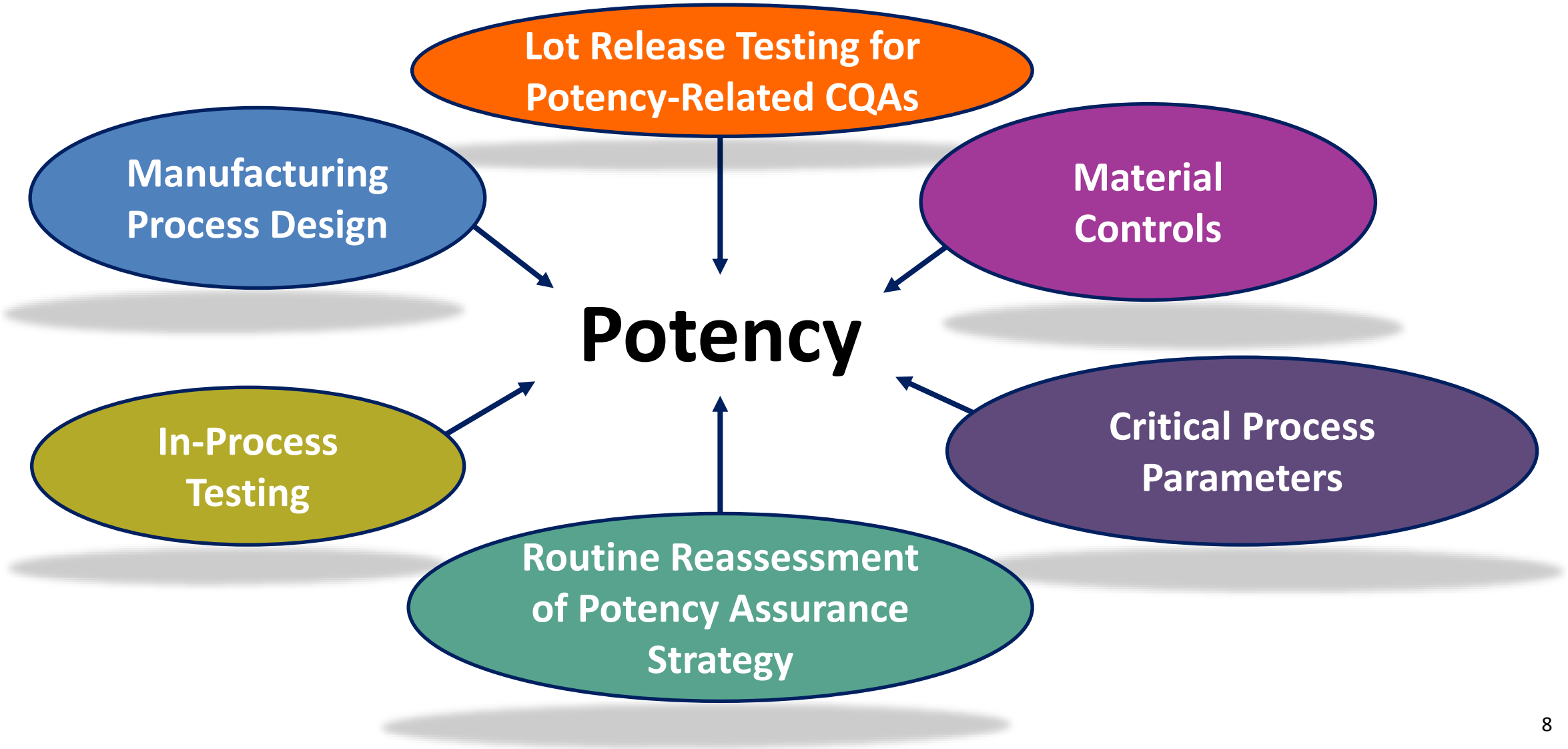
Nucleic acids – typical potency-related CQAs:

- Length
- Sequence
- Activity

If risks to these potency-related CQAs cannot be adequately mitigated by the manufacturing process design or control strategy…

…then implement potency assays for these CQAs, along with quantitative acceptance criteria

Potency assurance



Key aspects of potency assurance strategies

Take a multi-faceted approach to mitigate risks to potency-related CQAs

- Design your manufacturing process to consistently produce potent product lots
- Control critical material attributes and manufacturing process parameters that may affect product potency
- Implement potency tests with appropriate acceptance criteria for in-process and lot release testing

Reassess and refine your potency assurance strategy as you increase your understanding of your product and manufacturing process

Potency assays and acceptance criteria

Potency release assays and their acceptance criteria are essential elements of a potency assurance strategy

- May include physicochemical assays or bioassays
- Should have suitable precision, accuracy, specificity, and robustness
- Should quantitate a potency-related CQA *that is at risk*

Potency assurance strategies should typically include multiple release assays, including at least one bioassay that measures a relevant biological activity of the product

Minimize assay redundancy

Avoid redundant assays that measure multiple steps of a biological cascade

- A bioassay at a later step of a cascade can often ensure the biological activities at the earlier steps of the cascade
  - **Gene therapy vector**: transduction → transgene mRNA expression → protein expression → protein activity → effect on cell physiology → effect on disease
- Potency assays should be focused on potency-related CQAs that are at risk
  - The purpose of a potency assay is to confirm that a potency-related CQA is within an acceptable range
- It is not essential for a potency bioassay to mimic the product's mechanism of action
  - Mechanism of action drives selection of potency-related CQAs

Progressive Implementation of a Potency Assurance Strategy

Your potency assurance strategy may not be fully mature during early development stages, but you should still have a defined potency assurance strategy that includes:

- Identification of initial potency-related CQAs for your product
- An assessment of risks to potency-related CQAs and measures to mitigate these risks

Include the following information in your initial IND submission:

- Your product's mechanism of action and QTPP, a list of initial potency-related CQAs and an explanation of how potency-related CQAs were identified
- A description and justification of your potency assurance strategy
- General descriptions of your plans for further strengthening your potency assurance strategy during product development
  - e.g., plans for product characterization and potency assay development

Progressive Implementation of a Potency Assurance Strategy

By later stages of clinical development, you should have developed a comprehensive potency assurance strategy:

- Manufacturing process and control strategy should provide phase-appropriate assurance of consistent product potency
- Control strategy includes at least one assay measuring a potency-related CQA with appropriate acceptance criteria
- Assays measuring potency-related CQAs are qualified to demonstrate they have adequate performance to confirm that CQAs are within acceptable limits
- Potency-related CQAs are stable during storage and preparation of the product for administration

Before submitting a BLA, you should use all available product quality and clinical data to reassess and refine your potency assurance strategy

Ensuring adequate potency of investigational products

Inadequate potency assurance may lead to a clinical hold:

For clinical investigations involving significant risk of illness or injury, if the potency of the product is not adequately assured it may be unreasonable to expose subjects to these risks

If potency is not adequately assured in a Phase 2 or 3 investigation, the investigation may be considered deficient in design for the following reasons:

- Reduced statistical power to detect an effect of the product if not all lots have the capacity to achieve the intended therapeutic effect
- Investigations using lots with unknown or inadequately-controlled potency may not provide sufficient product data to justify specifications of the commercial product

Post-release testing

Some products have short shelf lives – no time to perform a bioassay for drug product release

- Example: Non-cryopreserved “fresh” cell therapies

Potential solution: Release DP based on physicochemical potency assays, then perform a potency bioassay post-release

- Physicochemical assays for potency-related CQAs may include viability, flow cytometry
- Perform bioassay after release, and compare the results to an acceptance criterion
  - If out of specification, perform an investigation
  - If needed, implement corrective and preventive actions

Advantages

- Problems with potency become visible
- Fixing these problems can reduce risks to the potency of subsequent lots
- Data gained from bioassays are useful for risk assessment and comparability
- For a licensed product, post-release testing may be part of continued process verification

Other topics in the draft potency assurance guidance

Recommendations for requesting advice from FDA about your potency assurance strategy

General advice for identifying potency-related CQAs and developing a potency assurance strategy throughout the product development lifecycle

Detailed recommendations on the use and development of potency assays and acceptance criteria

Examples of recommended approaches to potency assay selection and design for some CGT product classes

Advice on assay control, qualification/validation, reference materials, and change management

Summary
Potency assurance

Potency tests are an important aspect of potency assurance, but assuring potency requires a broader approach

Develop a potency assurance strategy for your CGT product

Define your product's QTPP and identify potency-related CQAs

Conduct a risk assessment for each potency-related CQA

Use a multi-faceted approach to reduce risks to potency-related CQAs, including tests for at-risk potency-related CQAs

Take a lifecycle approach to potency assurance - reassess and refine your potency assurance strategy as you gain knowledge during development

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