U.S. FOOD & DRUG ADMINISTRATION

Developing Potency Assays for Cell Therapy Products

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Scope of Discussion

- Potency Assay Expectations Through the Product Development Lifecycle
- Developing Potency Assays for Cell Therapy Products
- Product Characterization vs. Potency Matrix

My comments are an informal communication and represent my own best judgement. These comments do not bind or obligate FDA

Definition and Regulatory Requirements

- **21 CFR 600.3(s) Definitions**
  *"…**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, **to effect a given result**."*

- **21 CFR 610.10 Potency**
  *"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** in a manner adequate to satisfy the interpretation of potency..."*

- **21 CFR 610.1 General Biological Product Standards**
  *"**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."*

Potency Testing Challenges for CGT Products

- Complex, variable products
- Mechanism of action may not be fully known
- Time constraints for release testing
- Limited material available for testing
- Limited availability of reference standards and controls

GUIDANCE DOCUMENT

Potency Tests for Cellular and Gene Therapy Products

Final Guidance for Industry:

JANUARY 2011

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

Developing a Potency Assay

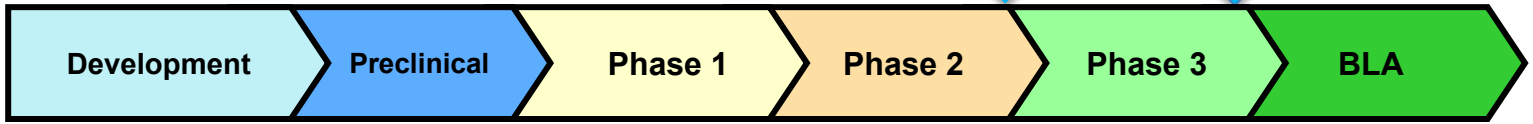
- Regulations are very flexible with regards to the kind of assay that can be used as long as it is measuring a meaningful biological parameter
- It is not a regulatory requirement to fully define the mechanism of action, nevertheless, it is useful to have an understanding of how the product is likely 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)



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

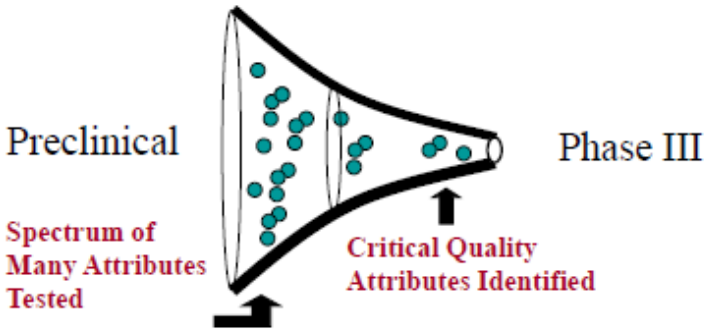
- May be composed of biological assays, analytical assays, or both
- Qualitative assays should be accompanied by one or more quantitative assays

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

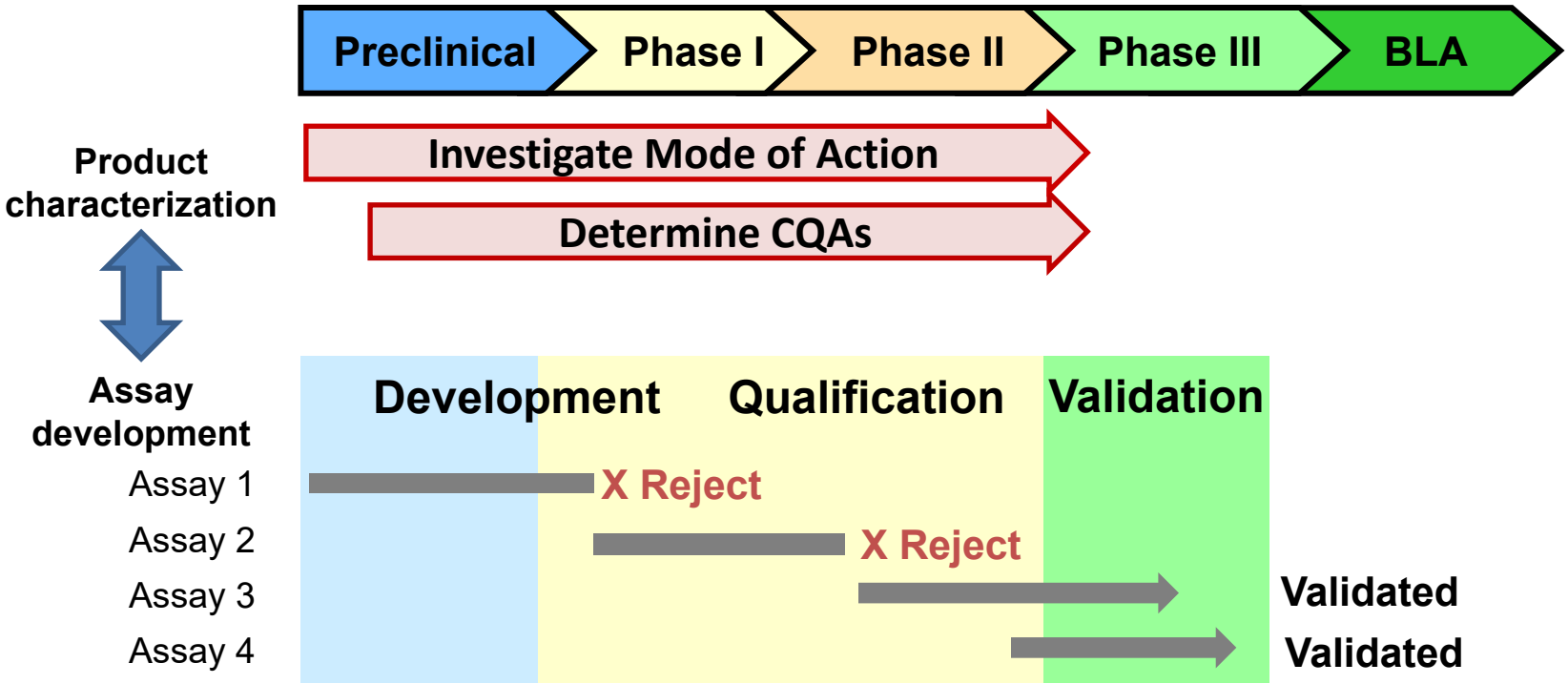
Product Characterization Throughout Development

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)*

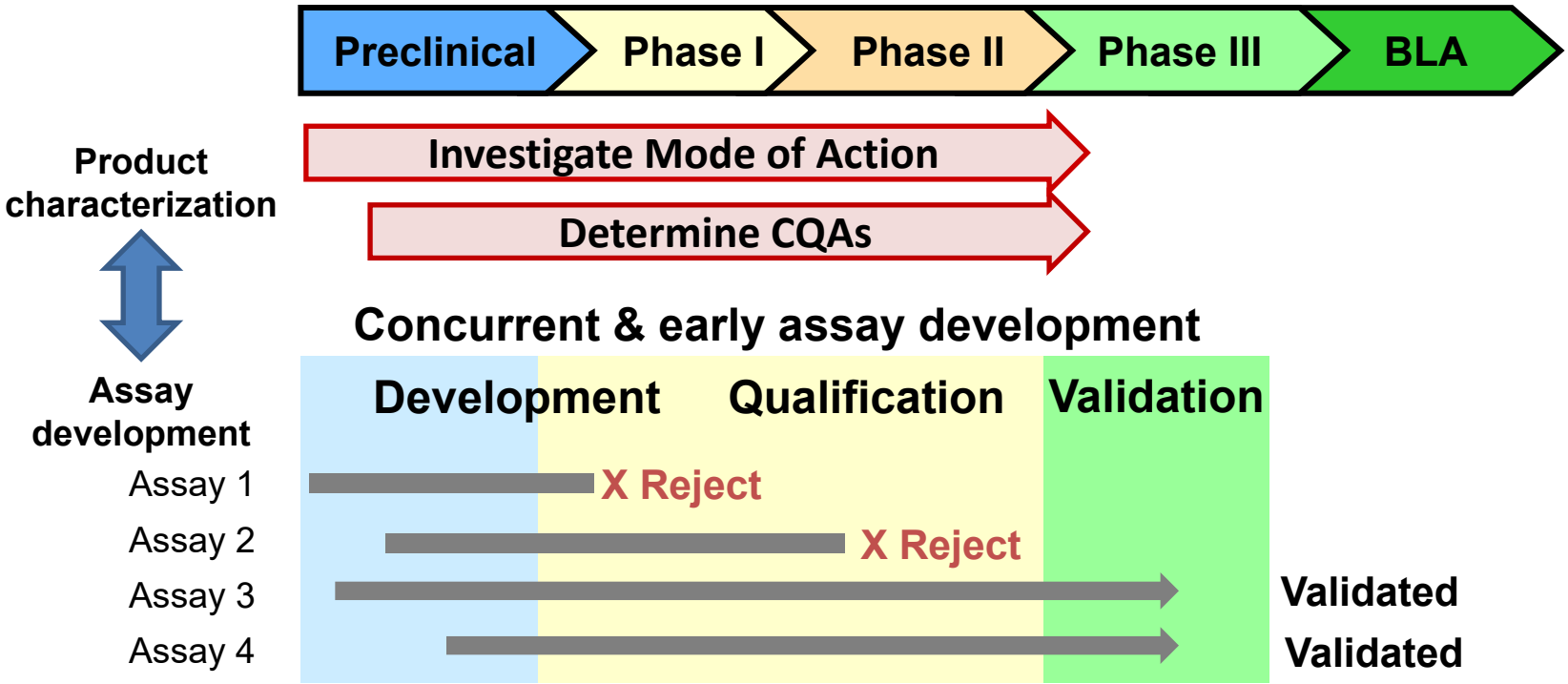
- Explore many CQAs during early development
  - Report results early in development
  - Choose relevant tests for later phase studies
- Evaluate multiple measures of CQAs (especially potency)
  - Matrix of assays
  - Orthogonal methods
  - Stability indicating



Assay Development Timeline



Assay Development Timeline



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.

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

Summary

- Regulations are very flexible with regards to the kind of assay that can be used for measuring potency as long as it reliably controls a meaningful product attribute
- For some products, a single potency assay may not be sufficient for assuring potency, and in these cases a potency assay matrix may be necessary for lot release
- We recommend that you start product characterization as early as is feasible to gain product information and help identify attributes relevant to product potency that can be measured reliably

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FDA Headquarters

- **OTAT Learn Webinar Series:**
  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm
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Links to Relevant FDA and ICH Guidance Documents*

Content and Review of CMC Information for Human Somatic Cell Therapy IND Applications (2008)	https://www.fda.gov/media/73624/download
CMC Information for Gene Therapy INDs (2020)	https://www.fda.gov/media/113760/download
Donor Eligibility for HCT/Ps (2007)	https://www.fda.gov/media/73072/download
cGMP for Phase 1 Investigational Drugs (2008)	https://www.fda.gov/media/70975/download
Formal Meetings Between FDA and Sponsors (2017)	https://www.fda.gov/media/109951/download
ICH Q8(R2) – Pharmaceutical Development	https://database.ich.org/sites/default/files/Q8%28R2%29%20Guideline.pdf
Potency Tests for Cellular and Gene Therapy Products (2011)	https://www.fda.gov/media/79856/download
Analytical Procedures and Methods Validation (2015)	https://www.fda.gov/media/87801/download
Process Validation: General Principles and Practices (2011)	https://www.fda.gov/media/71021/download
Comparability Protocols for Drugs and Biologics (2016)	https://www.fda.gov/media/97148/download

*Not a complete list. Go to https://www.fda.gov/regulatory-information/search-fda-guidance-documents to search all FDA guidance documents