Regulatory Considerations for the Development of Potency Assays during CAR T Cell Development

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2022 USP Biologics Stakeholder Forum
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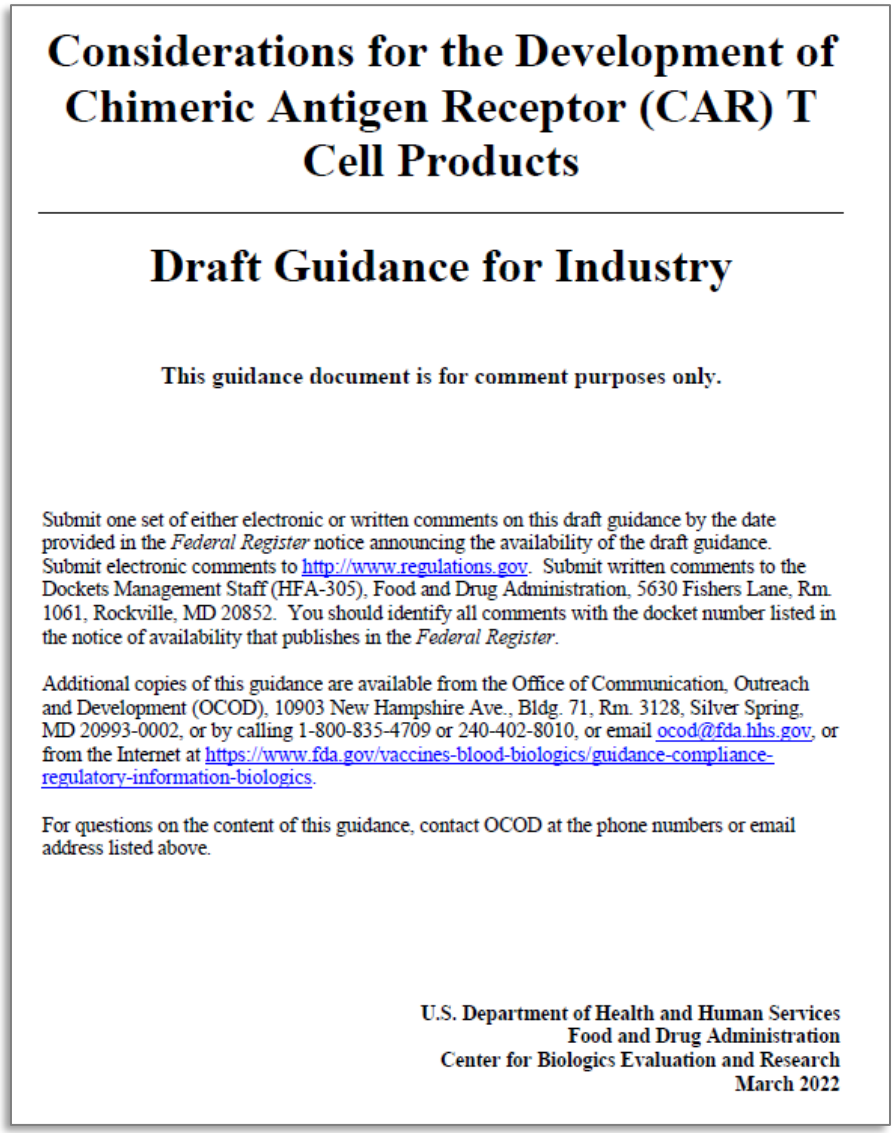
CMC Considerations for CAR T Cell Development

- Overview of relevant guidance documents
- Challenges and expectations during CAR T cell development
- Regulatory Definitions of Potency
  - Importance of early product characterization
- Avoiding CMC Headaches
  - Concurrent assay development

Relevant Gene Therapy Guidance Documents

- Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products; Draft Guidance for Industry
  3/2022
- Human Gene Therapy Products Incorporating Human Genome Editing; Draft Guidance for Industry
  3/2022
- Studying Multiple Versions of a Cellular or Gene Therapy Product in an Early-Phase Clinical Trial; Draft Guidance for Industry
  9/2021
- Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)
  1/2020

DRAFT CAR T cell Guidance



Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell 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Draft Guidance for Industry

This guidance document is for comment purposes only.

Submit one set of either electronic or written comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance.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 http://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*.

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics.

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
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- CMC, preclinical, and clinical
- Recommendations specific to autologous or allogeneic CAR T cell products are noted
- Generally applicable to other genetically modified lymphocyte products, such as CAR Natural Killer (NK) cells or T cell receptor (TCR)-modified T cells
- Additional considerations would depend upon the specific product and manufacturing process

CMC Challenges for CAR T Development

- Limited manufacturing experience:
  - Not many lots produced
  - Multiple rounds of process changes
- Limited in-process testing:
  - Process variables and CPPs not well understood
- Limited product characterization:
  - Critical Quality Attributes (CQAs) poorly defined
  - Limited knowledge of product- and process-related impurities
- Limited product stability data
- Limited assay development (potency)
  - Assays not qualified

CMC Expectations for Late-Stage CAR T Cell Development

- Have a controlled manufacturing process
  - Sufficient knowledge of the manufacturing process to determine Critical Process Parameters (CPP)
  - Sufficient knowledge to set in-process quality criteria: Action Limits and Rejection Limits
  - Sufficient knowledge to plan for future production scale up/scale out
- Have well developed and qualified/validated analytical assays
  - Have a biologically relevant potency assay in place
- Have sufficient manufacturing experience to narrow product acceptance criteria

Potency: Regulatory Definitions

- Regulatory Definition of Potency
  - 21 CFR 600.3(s): 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, 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 in a manner adequate to satisfy the interpretation of potency given by the definition in §600.3(s) of this chapter.

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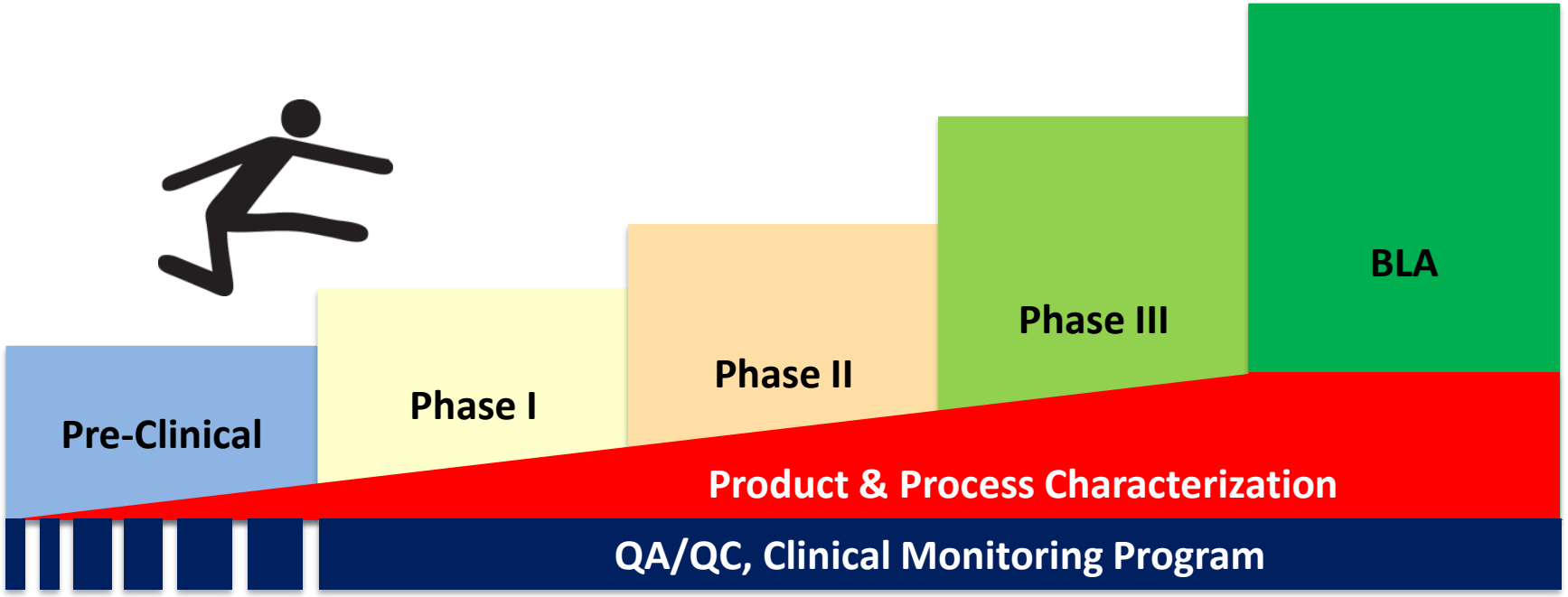
Potency Testing Challenges

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

Lifecycle approach to Potency measurements

- Stepwise assay development
  - Investigation of biological activity
  - Development of relevant potency assay



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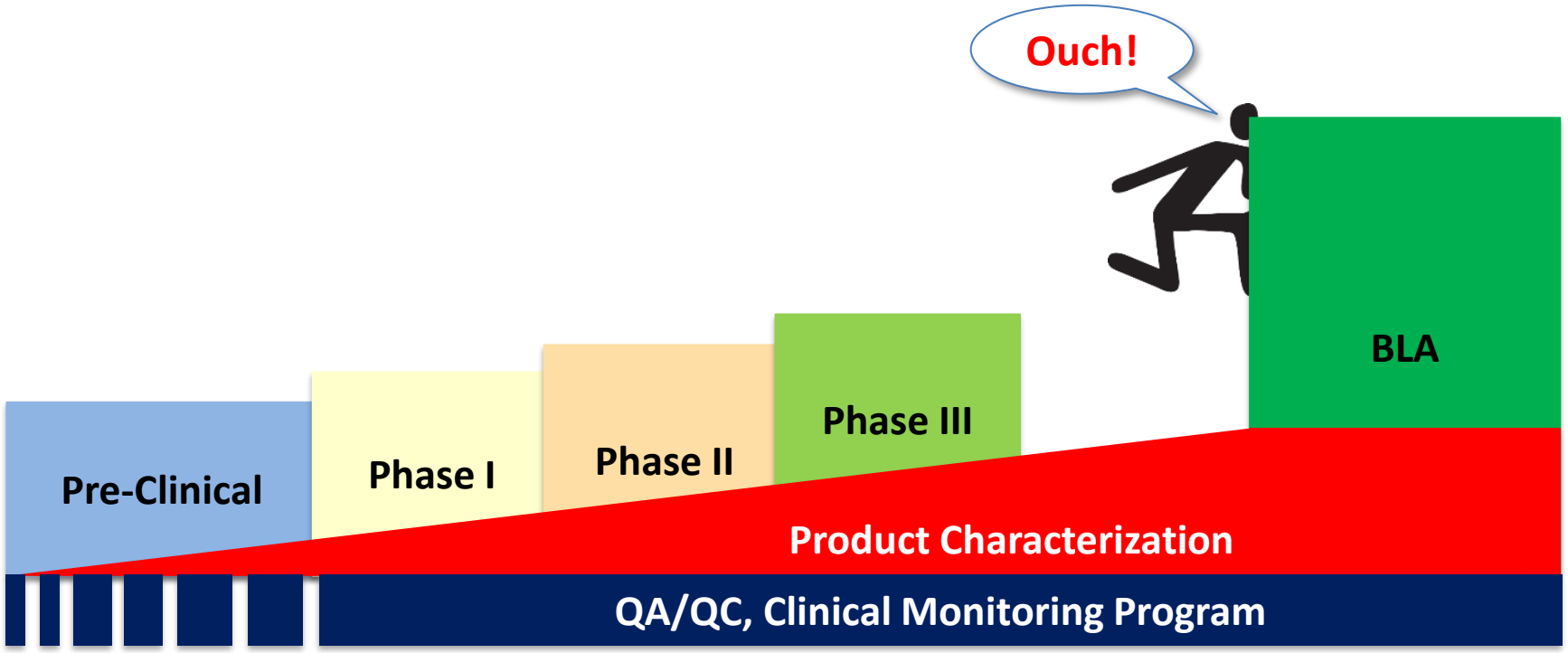


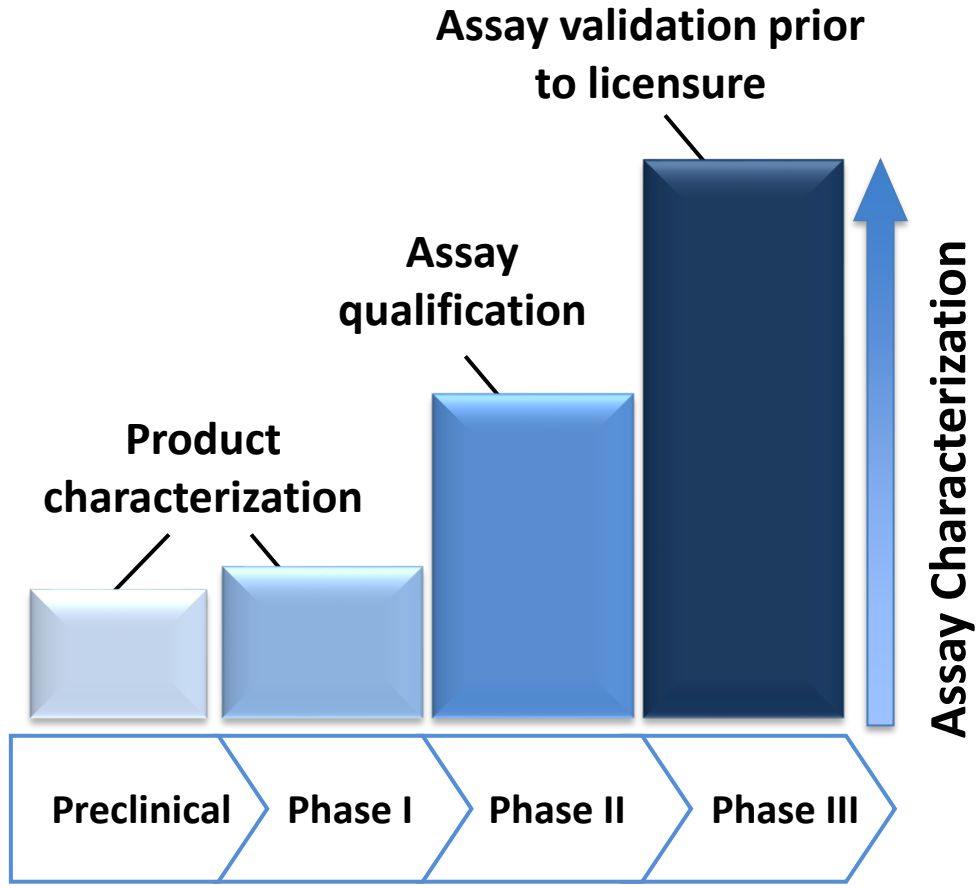
Encourage Early Product Characterization

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 assay(s) for late phase studies
- Evaluate multiple measures of CQAs, especially potency
  - Matrix of assays
  - Orthogonal methods
- Support comparability studies

CAR T Cell Characterization Testing

- Perform a range of characterization assays throughout development
- Evaluate multiple measures of potency
- Identify additional product attributes that reflect product performance
  - Cellular impurities (e.g., non-T cells)
  - Other process impurities
- Characterization studies are important for any process, either manual or automated
- Characterization studies may support comparability study design



Concurrent & Early Assay Development

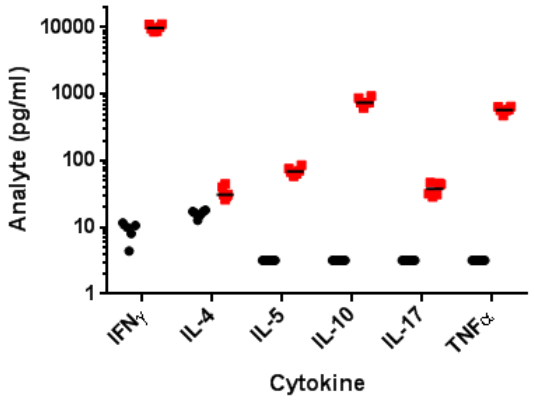
Example: CAR T cell therapy

Product attribute: Potency

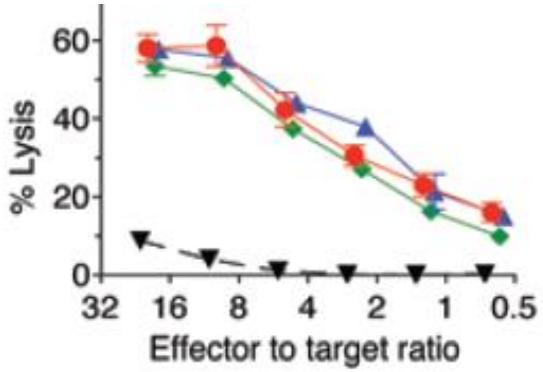
Evaluating a variety of methods during development supports:

- Product characterization and stability
- Understanding effects of manufacturing changes
- Choice of potency assay that represents the best fit for late-stage studies or licensure

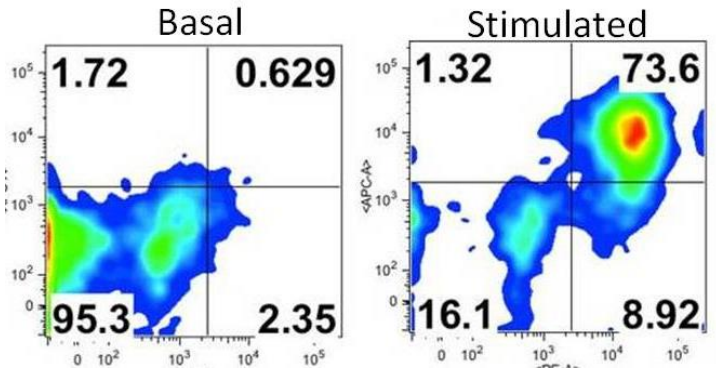
Cytokine profile



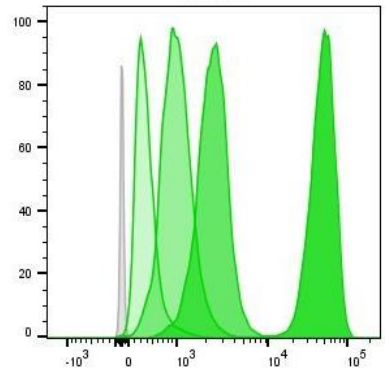
Cell Killing assay



T cell activation marker

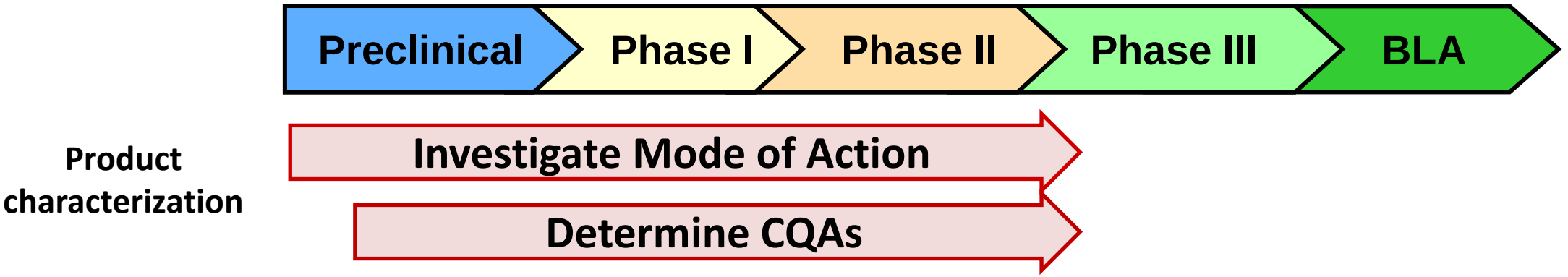


Antigen-specific T cell expansion



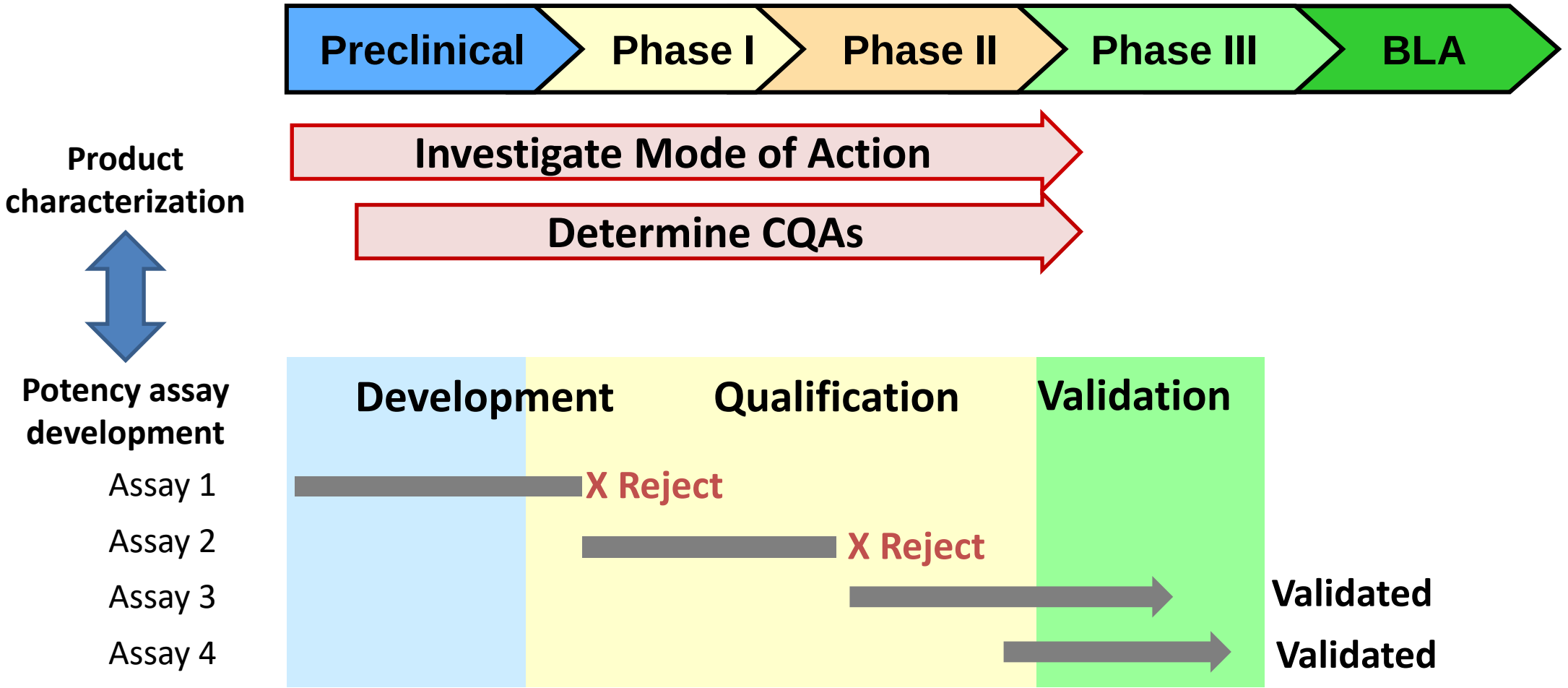
Assay Development Timeline

Product characterization supports potency assay development



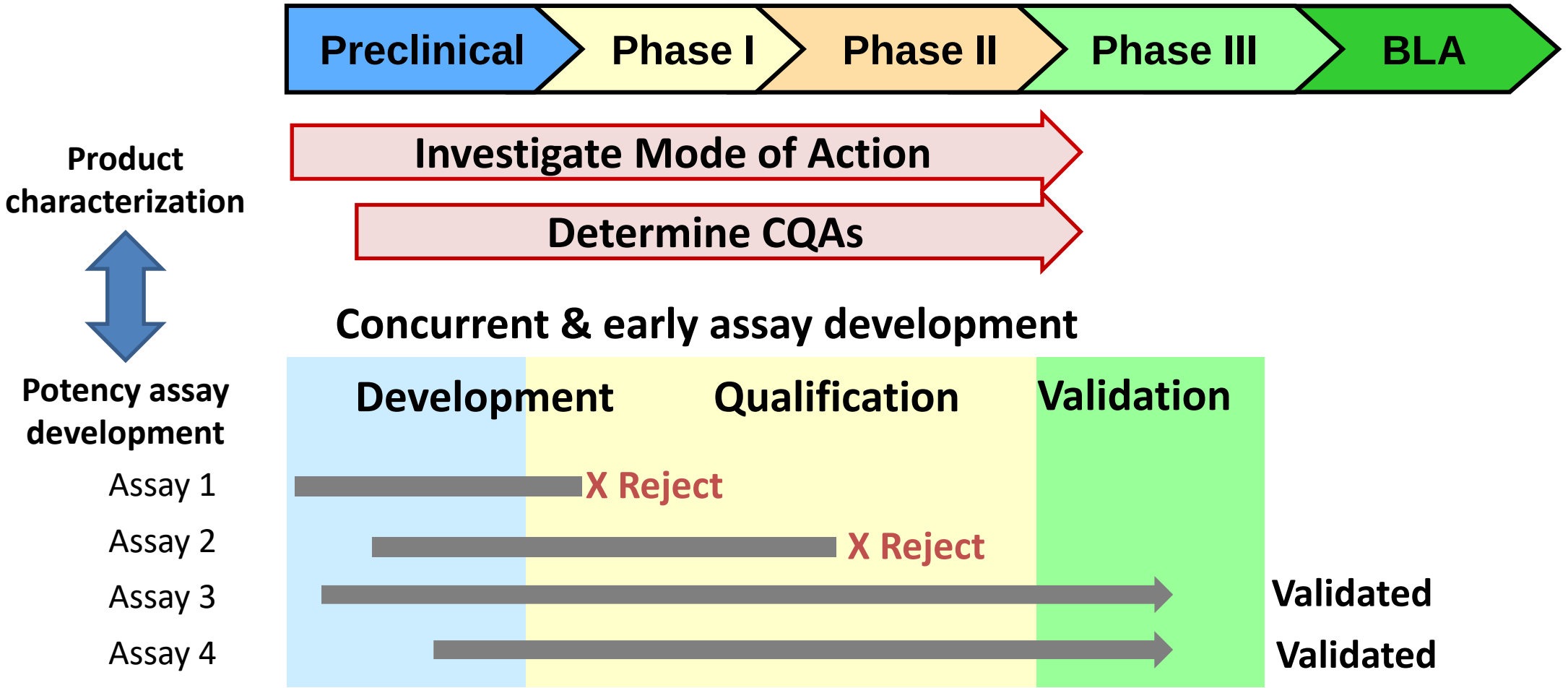
Assay Development Timeline

Poorly designed example



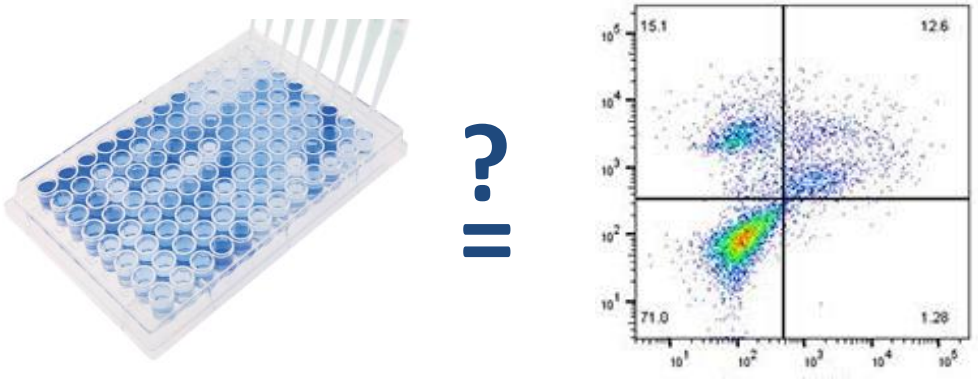
Assay Development Timeline

Well designed example



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

Contact Information

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- **OTAT Learn Webinar Series:**

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