CMC Challenges during Accelerated Development of Human Cell & Gene Therapy Products

A CBER Perspective

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CASSS Cell and Gene Therapy Products: Manufacturing, Quality and Regulatory Considerations
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Diversity of Cell & Gene Therapy (CGT) Products

Gene Therapy Products (GTPs)

- Ex vivo modified genetically engineered cells: stem cells, immune cells (CAR-Ts, NKT)
- Genome-edited T cells or stem cells
- Microbial Vectors; e.g., Listeria
- Viral Vectors; e.g., AAV, Ad
- Oncolytic viruses
- Tumor vaccines: peptides (tumor derived or synthetic),
- Plasmids, mRNA

Cell Therapy Products (CTPs)

- Stem cells: HSCs, MSCs, cord blood-derived etc.
- Cell products derived from pluripotent stem cells (iPSCs, ESCs)
- Pancreatic Islets
- Chondrocytes
- Keratinocytes
- Hepatocytes
- Xenotransplantation products

CGT products encompass a wide spectrum of products, each with its own concerns

Autologous single product lot

Large scale allogeneic cell bank-based product

Common concerns

Mechanism of action, material qualification, challenges establishing specifications, manufacturing facility, product shipping/handling, major manufacturing changes

Specific concerns

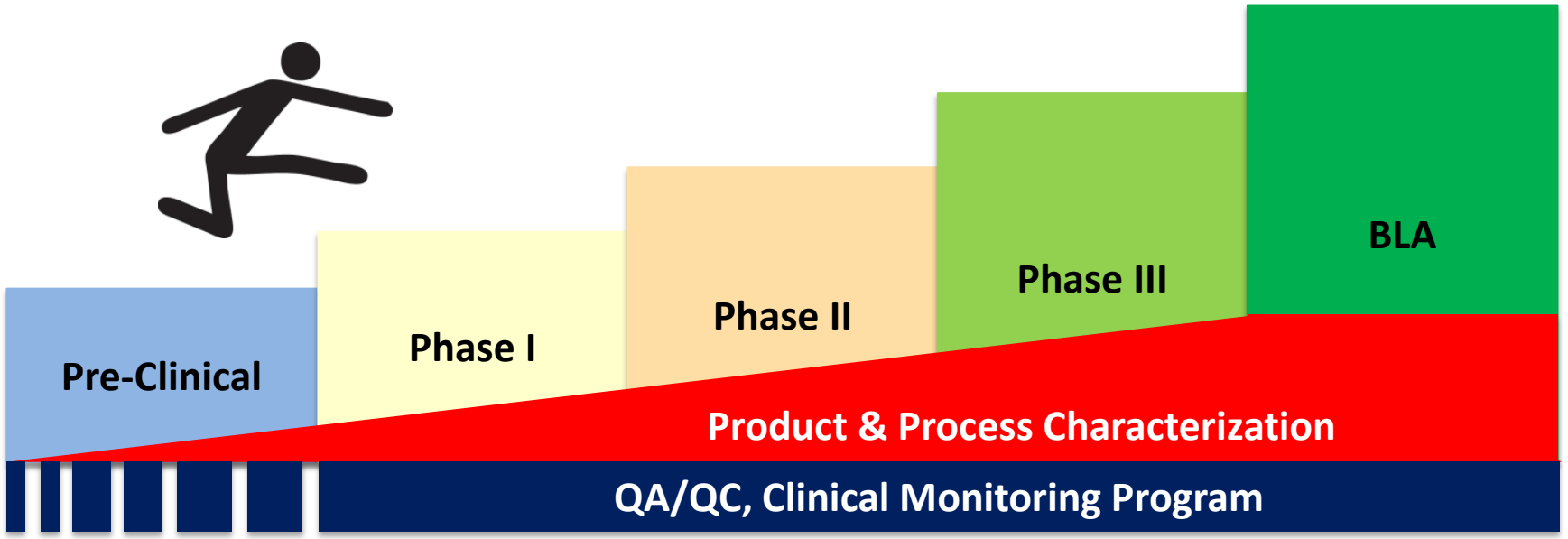
- Product tracking and segregation
- High product variability
- Limited material or time for testing
- Short shelf life
- Manufacturing logistics
- Scale-out

- Donor eligibility
- Qualification of cell banks
- Reproducibility of replacement bank
- Stability of cell banks and intermediates
- Scale up

Lifecycle Approach to Product Development

Assurance of product quality increases with clinical development

- Implementation of complete cGMPs
- Process and assay qualification and validation
- Establishment of appropriate release criteria



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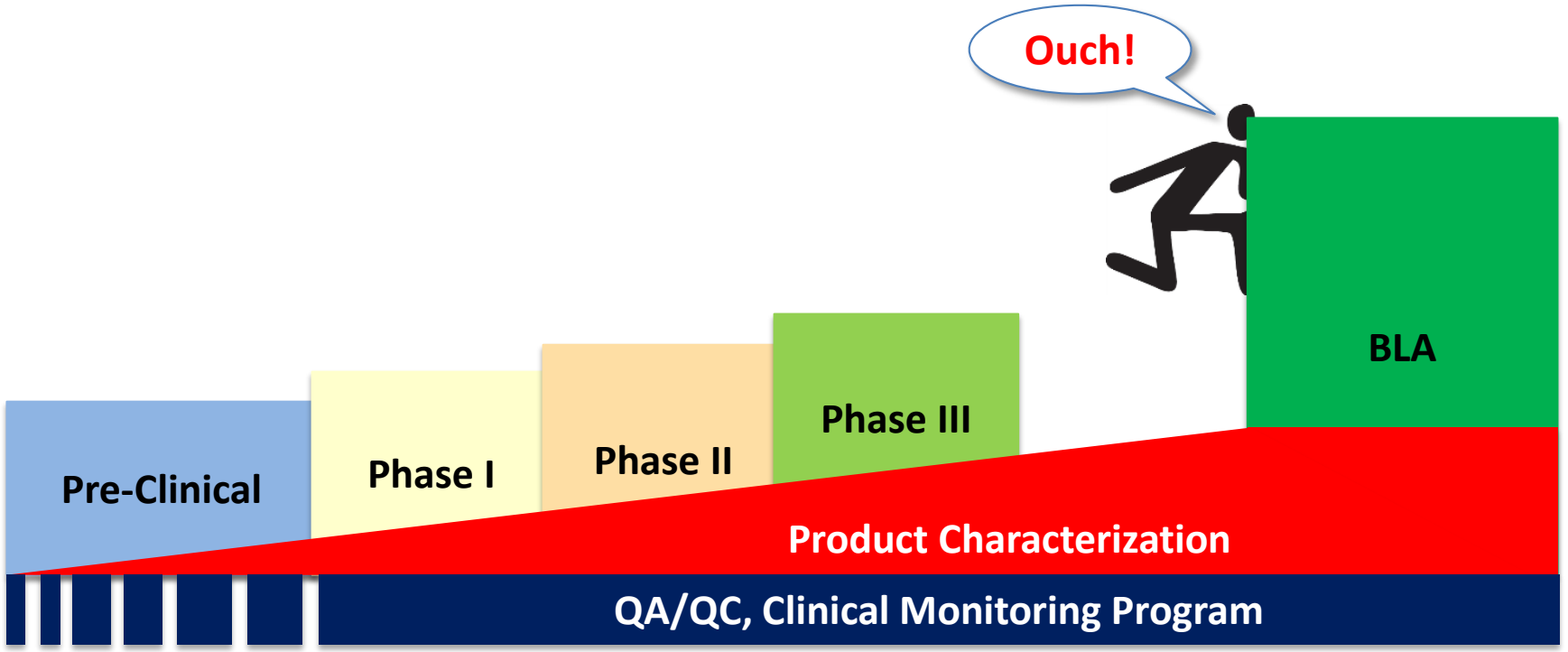


Challenges for accelerated development of CGT Products

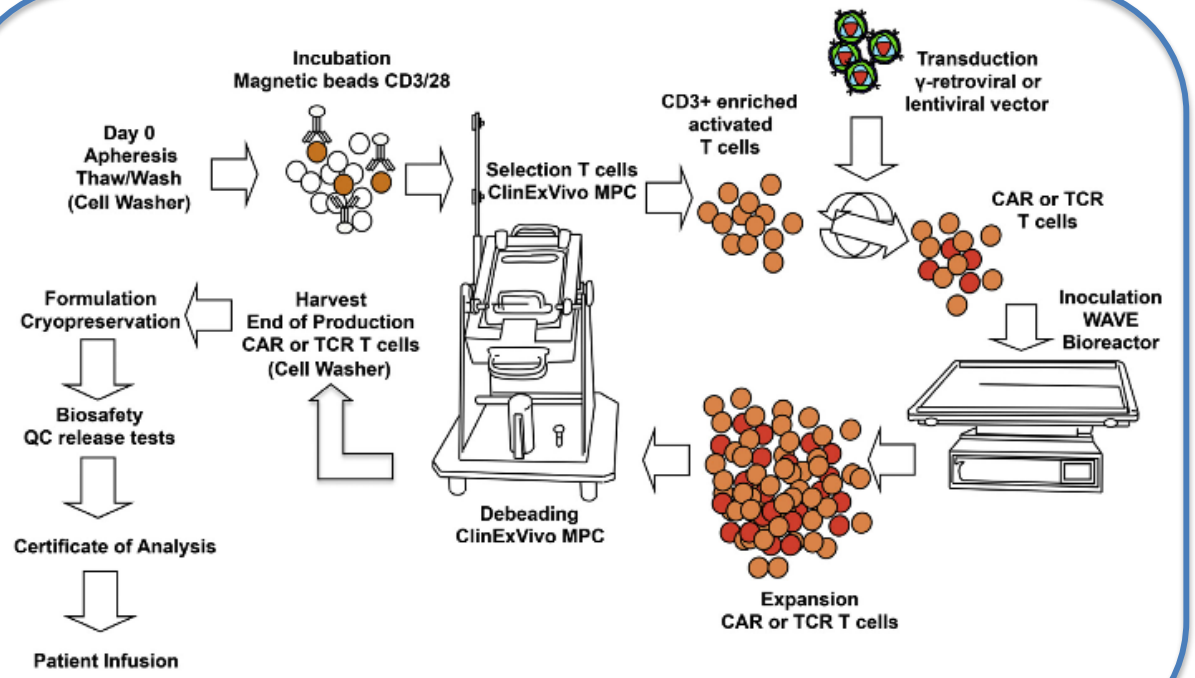
- When a clinical program advances rapidly the timelines from early to late product development may be compressed
- Planning for product commercialization, including when comparability studies may be needed, should be conducted early
- Expedited development does not change regulatory requirements

CMC challenges for accelerated development of CGT Products

- Limited manufacturing experience:
  - Not many lots produced
  - Multiple rounds of process changes
- Limited in-process testing:
  - Process variables and critical process parameters (CPP) not known
- Limited product characterization:
  - Critical Quality Attributes (CQAs) not known
  - Limited knowledge of product- and process-related impurities
- Limited assay development (potency, purity)
- Limited product stability data collected

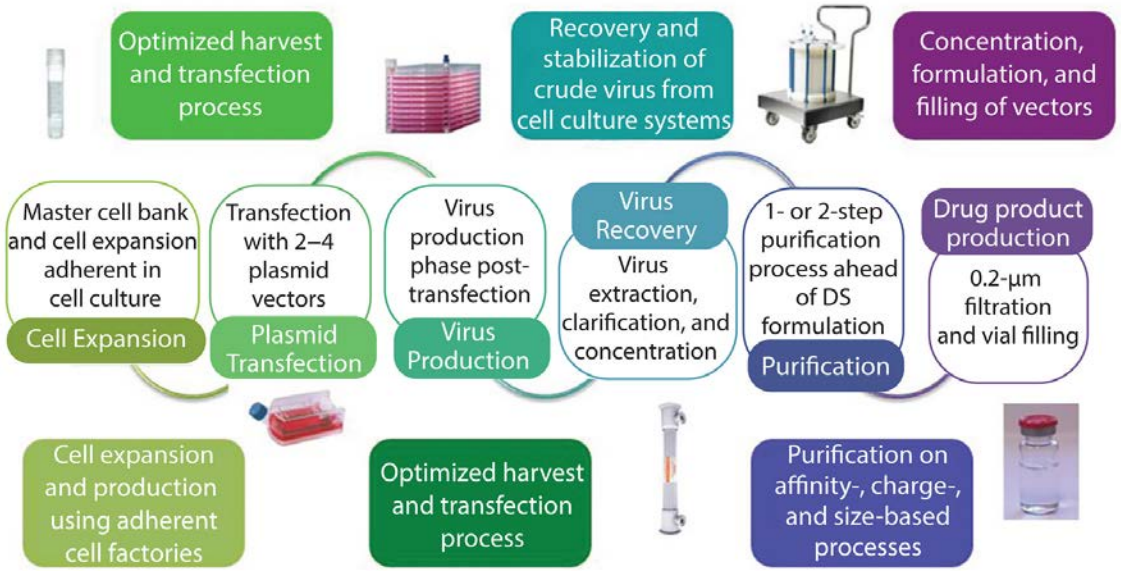
CGT Product Manufacturing is Complex

Autologous engineered T cell manufacturing



Themeli et al., 2015

AAV vector manufacturing

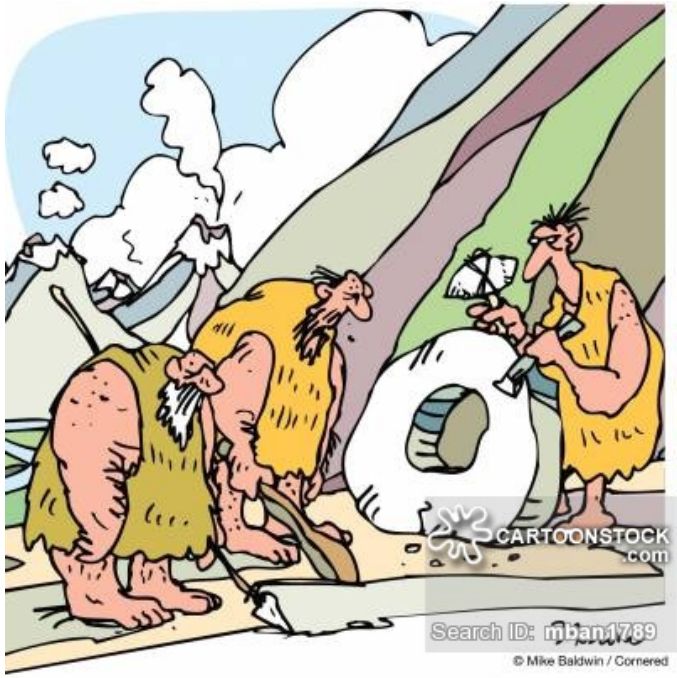


Hitchcock et al., 2017

- There is often a need for significant in-process characterization.

Manufacturing changes are inevitable

- React to a manufacturing problem or contamination
- Reagent or material is no longer available or in short supply
- Cell bank has expired or been exhausted
- Improve product quality based on new scientific or clinical information
- Switch to a more modern, more efficient or streamlined process
- Reduce costs



"What's with kids nowadays? Walking upright's not good enough for you?"

- Change can occur at any point in the product lifecycle, but you need to ensure that the change does not negatively impact product quality

Possible Changes During CGT Product Development

- Reagents, starting materials, components, manufacturing equipment
- Manufacturing processes
  - Change to suspension cultures
  - Change to stimulation method
  - Change to purification procedures
- Scale of manufacturing
- Manufacturing site
- Formulation
  - Buffer (cryopreservation, lyophilization)
  - Concentration
- Change in analytical testing procedures

Product Comparability

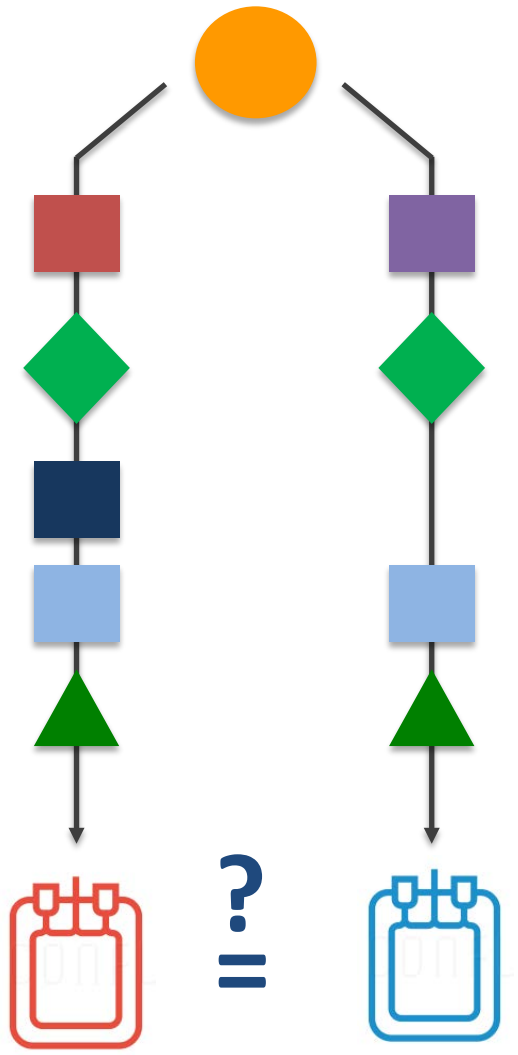
FDA (ICH) Guidance: Q5E Comparability of Biotechnological or Biological Products Subject to Changes in Their Manufacturing Process (2005)

- When changes are made to the manufacturing process, **the sponsor generally evaluates the relevant quality attributes of the product to demonstrate that modifications did not occur that would adversely impact the safety and efficacy of the drug product.**

- 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.

Analytical Comparability Study Considerations

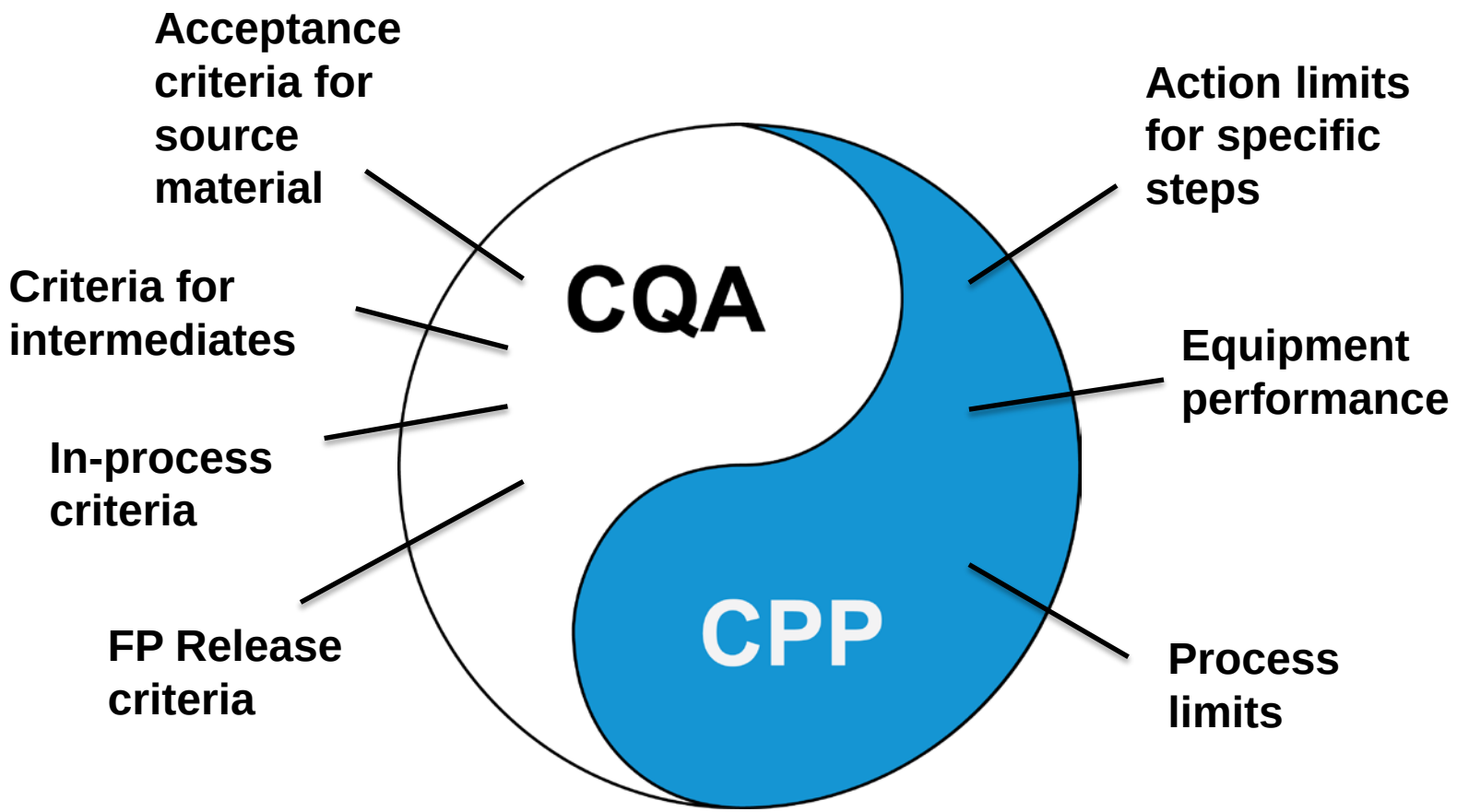
- Perform a risk assessment evaluating the impact of the change
- Assess attributes relevant to product quality and safety and most likely to be affected by the change
- Predefine acceptance criteria for comparability for each attribute being evaluated using appropriate, robust statistical methods
-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



Challenges for Establishing CGT Product Comparability

- Limited manufacturing experience:
  - Not many lots produced
  - Not enough retention or test samples available
- Limited in-process testing: process variables and CPPs 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

CQAs and CPPs are used together to help ensure quality and manufacturing consistency

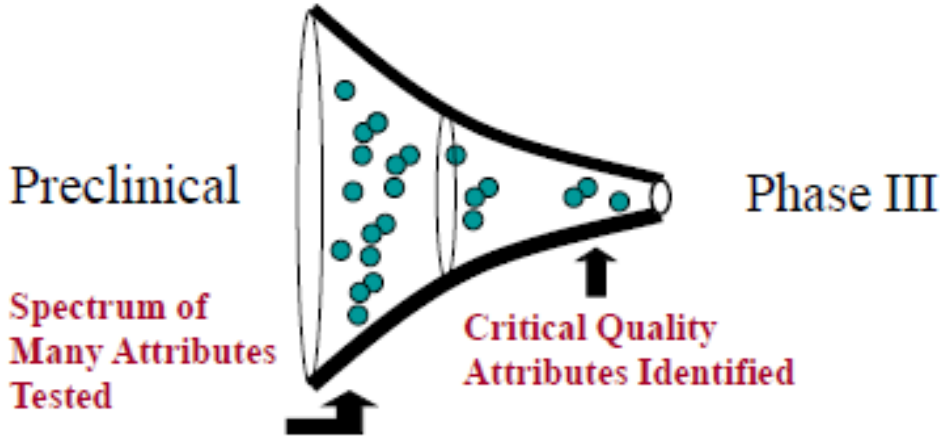


CGT Product CQAs

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

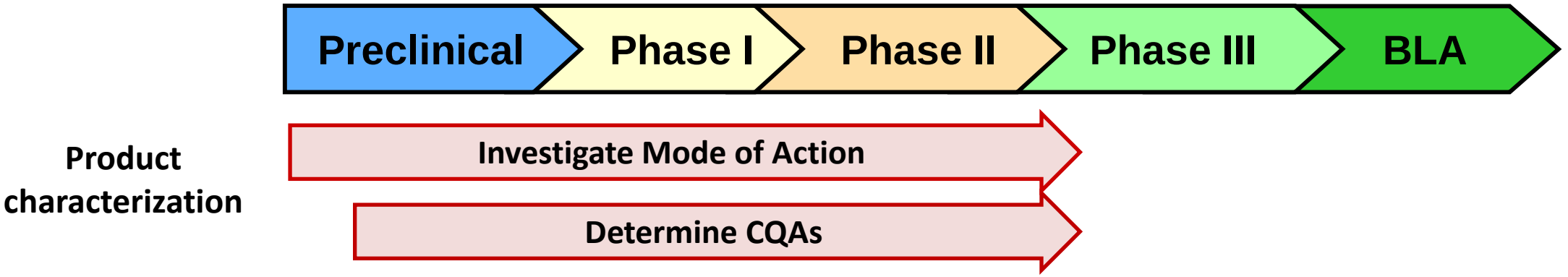
- Evaluate multiple measures of CQAs (especially potency)
  - Matrix of assays
  - Orthogonal methods
  - Stability indicating



Matrix Approach to CGT Product Testing

Biochemical	Enzyme activity Protein expression
Immunological	Immuno-typing (FACs) Cytokine expression (ELISA)
Cell-based	Cell proliferation/killing Cell differentiation Cell viability
Animal-based	*In vivo:* immune response *In vivo functionality:* Expression/persistence/homing/targeting
Biophysical	Cell integrity Cell adhesion/morphology Viral capsid integrity and purity Protein structure Post-translational modifications Formation of aggregates
Nucleic acid-based	qPCR Sequencing Transcriptional analysis RT-qPCR

Assay Development Timeline



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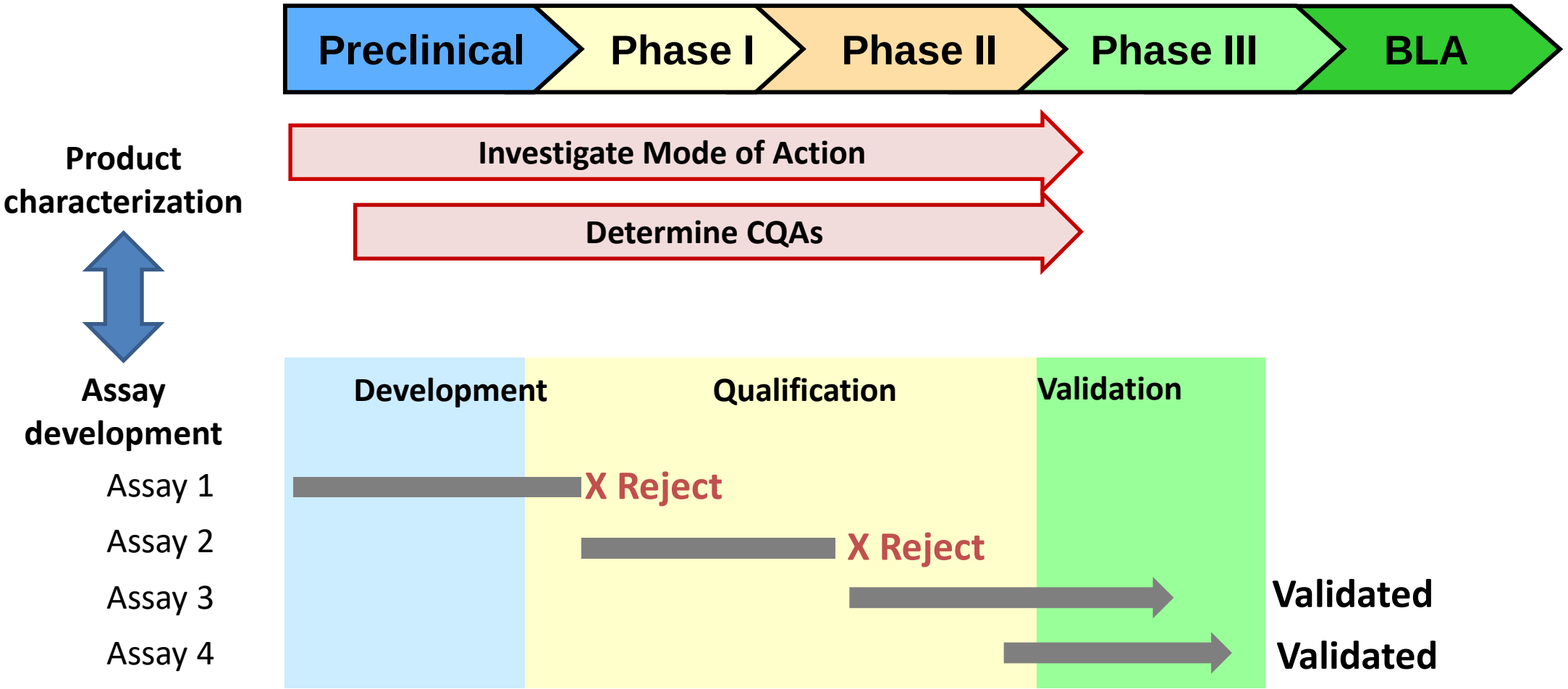

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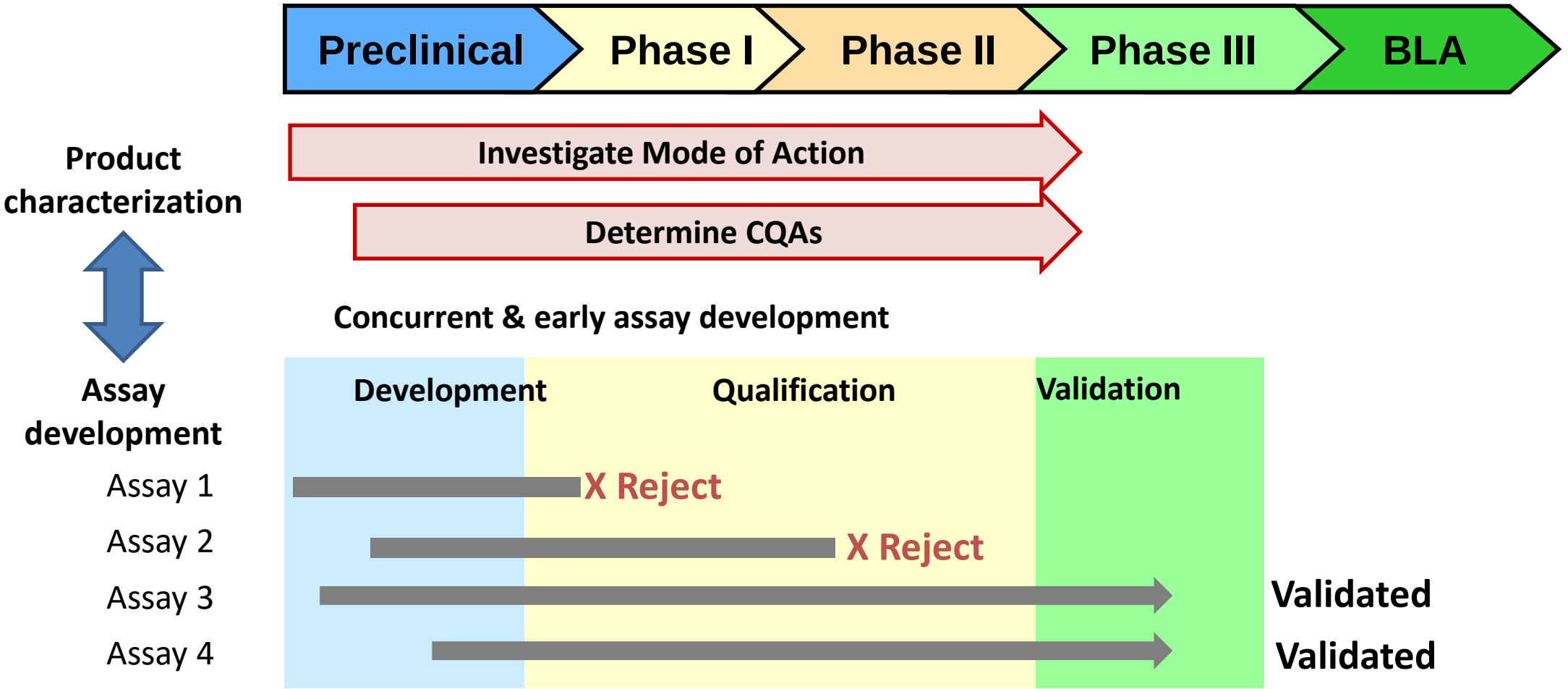


Common issues with CGT Product release specifications

- Specifications not capturing key product attributes (critical quality attributes)
- Criteria inconsistent with manufacturing experience
- Lack of supportive data or rationale
- Only measuring what you want and not what you don’t want
- Criteria set for a very wide range
  - Could add variability to clinical trial
  - May make it more difficult to qualify assays and processes
- Misinterpretation or over-interpretation of data

Impact of product variability

- There are advantages to targeting narrow versus wide tolerances for specifications
- Narrower tolerances make it easier to assess comparability

Goalpost

Narrow tolerances

Need to have a very good understanding of your process and product, with sufficient control points

Wide tolerances

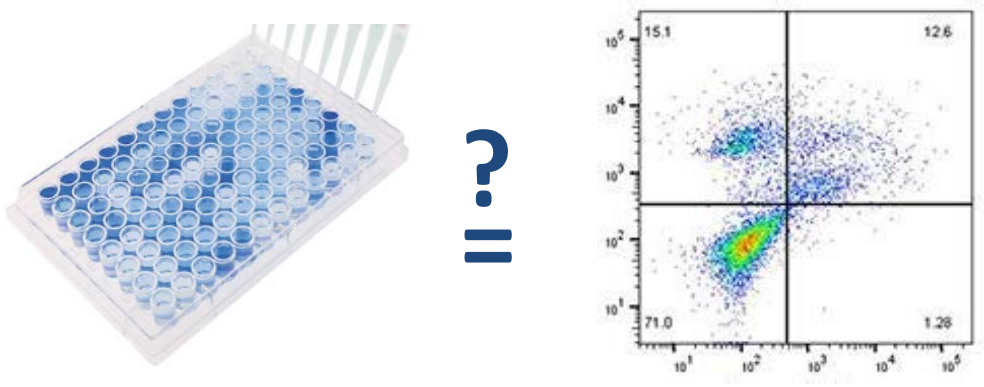
Difficult to rely on just lot release specifications to show consistency and comparability

Potency Assay Challenges

- Mode of action may not be fully known
- Time constraints for release testing
- Limited material available to test
- Limited availability of reference standards and controls
- Cell-based assays can be highly variable

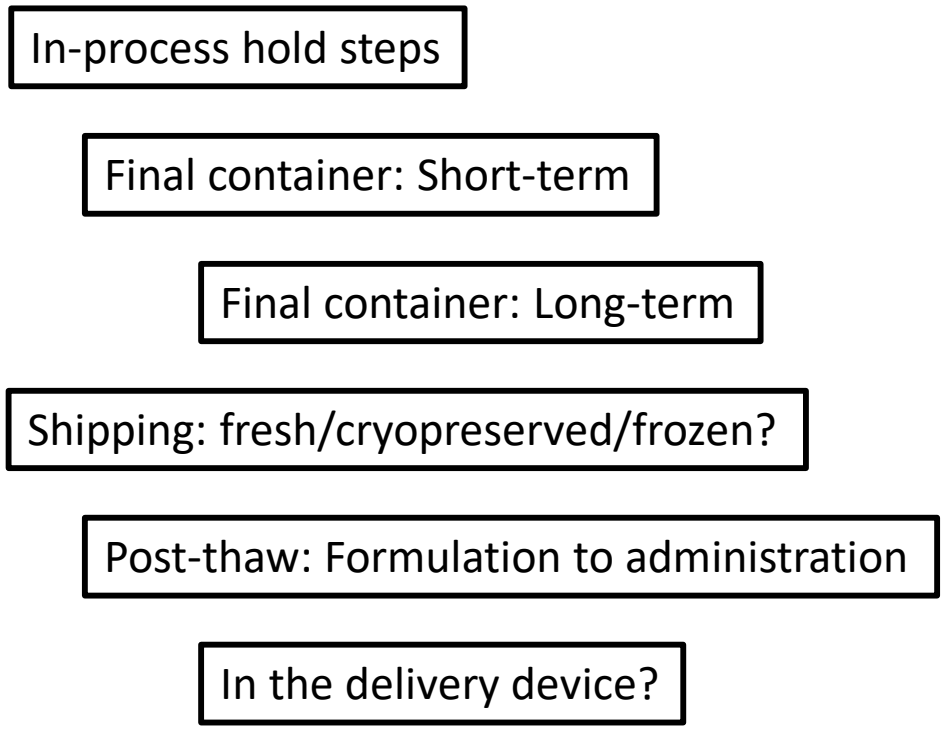
Changes to Analytical Testing

- Change in assay method
  - Assessment of how assays differ (output, sensitivity, reference material, etc.)
- Assay transfer or addition of testing sites
  - Demonstrate results are comparable between sites



- Side-by-side testing of the same material using both tests
- Establish comparability/correlation between the assay results
- May also impact stability studies

Stability Testing



- Carefully assess interference from components in the drug substance and drug product (residuals, excipients etc.)
- Include stability indicating assays
- Use new and sensitive technologies to characterize CGT Products stored under stress/accelerated conditions
- Device compatibility studies
  - Should include a measure of product strength/content and potency
  - Collect data using product doses, devices and conditions that will be used in the clinic

Summary

- The number of CGT Products being evaluated clinically has reached an all time high
- CGT Products are complex biologics requiring significant forethought regarding lifecycle management, particularly those in accelerated development
- Product and process characterization and assay development should be started early and continued throughout the product lifecycle
  - To develop a robust manufacturing process
  - To identify product CPPs and CQAs
  - To assist in the ability to establish product comparability
- Process and analytical testing changes are expected during the lifecycle of a CGT Product
  - Plan ahead, try to resolve potential CMC issues early in product development
  - When necessary, conduct thorough, well-designed comparability studies

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