Regulation of Cell and Gene Therapies
SITC Cancer Immunotherapy Winter School
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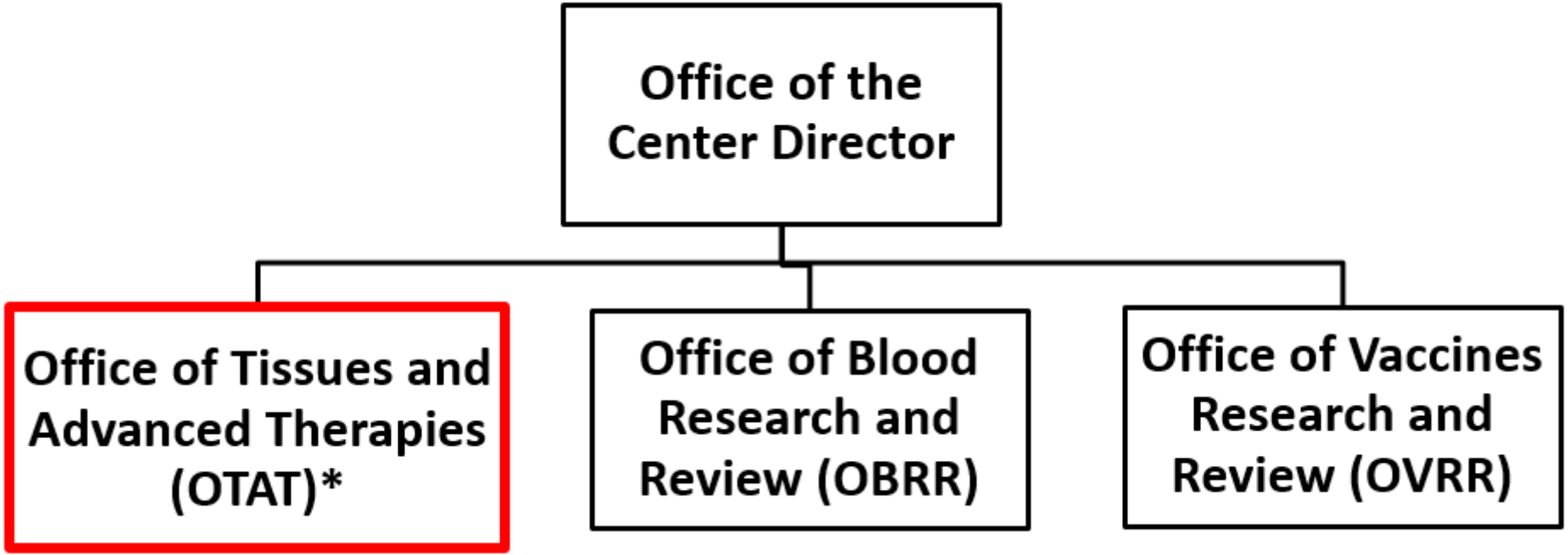
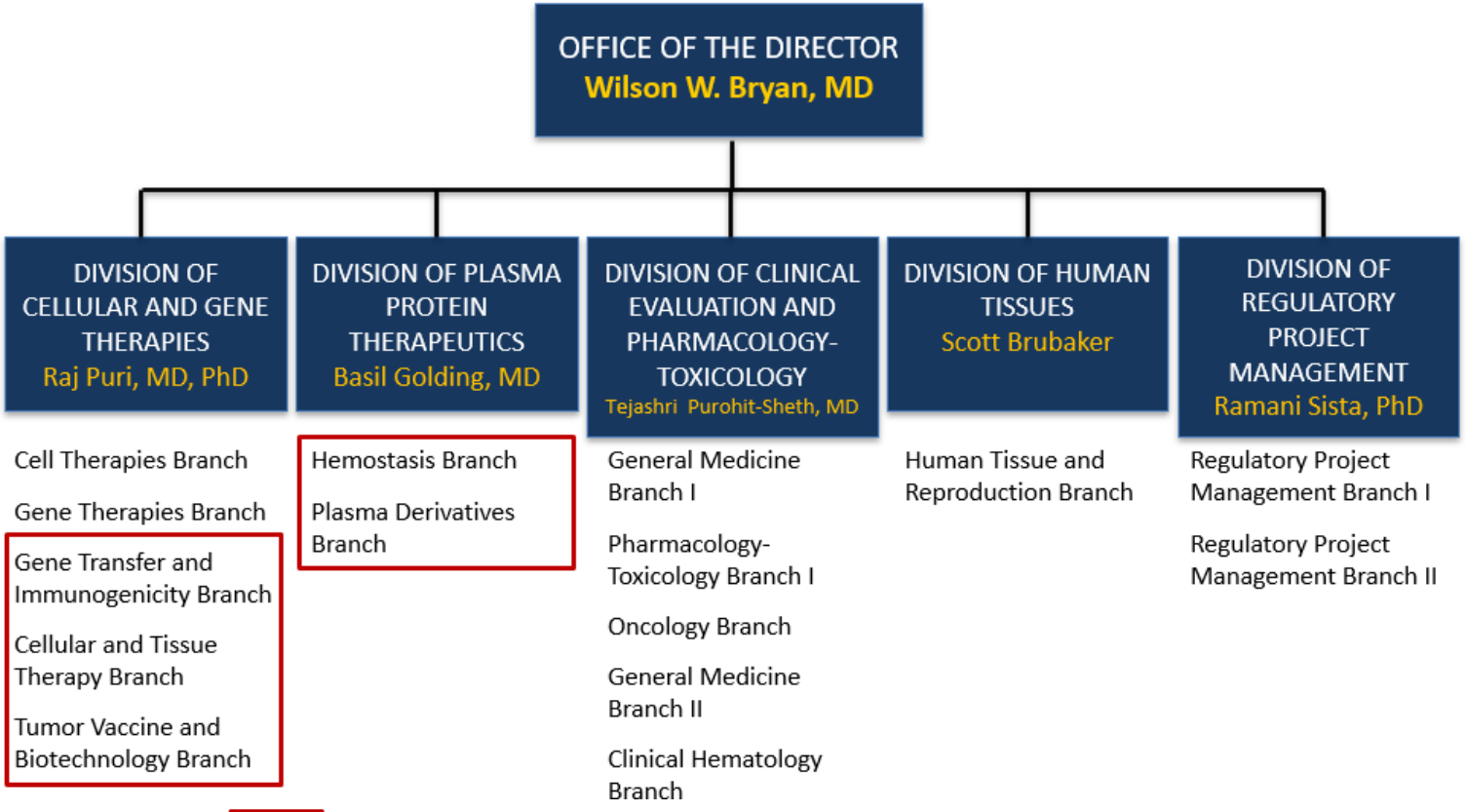
U.S. Food & Drug Administration

Center for Biologics Evaluation and Research (CBER) - Product Review Offices



*Formerly the Office of Cellular, Tissue, and Gene Therapies (OCTGT)

Office of Tissues and Advanced Therapies (OTAT)



Units that include lab research

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
- Anti-tumor and anti-viral T cells
- Innate Immune Cells
- Chondrocytes
- Hepatocytes
- Xenotransplantation products

Diversity of Cell & Gene Therapy (CGT) products

- Therapeutic vaccines and other antigen-specific active immunotherapies
  - Cancer vaccines and immunotherapies, such as dendritic cells, lymphocyte-based therapies, cancer cell-based therapies, peptides, proteins
  - Non-infectious disease therapeutic vaccines, such as peptides, proteins, small molecules

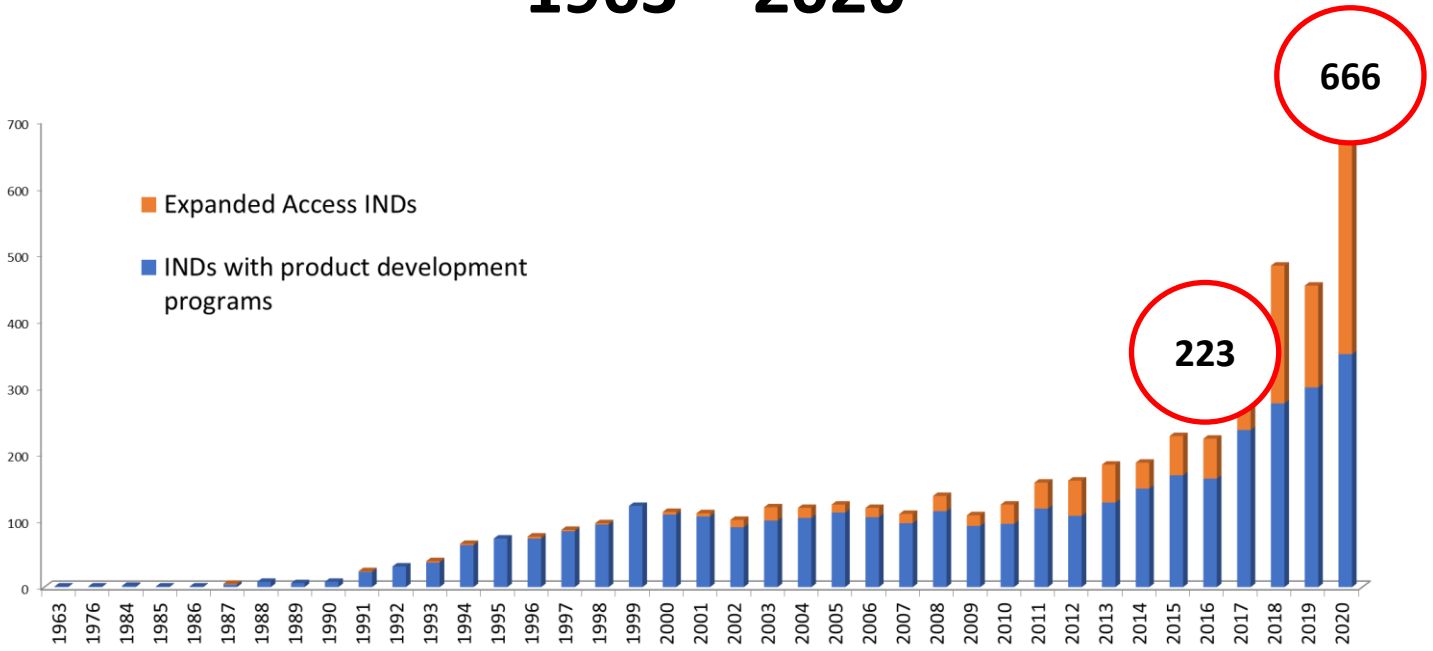
OTAT: BLA approvals in 2021

- **BREYANZI lisocabtagene maraleucel**
  - Treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B
- **ABECMA idecabtagene vicleucel**
  - Treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody
- **RYPLAZIM plasminogen human-tvmh**
  - Treatment of patients with plasminogen deficiency type 1 (hypoplasminogenemia)

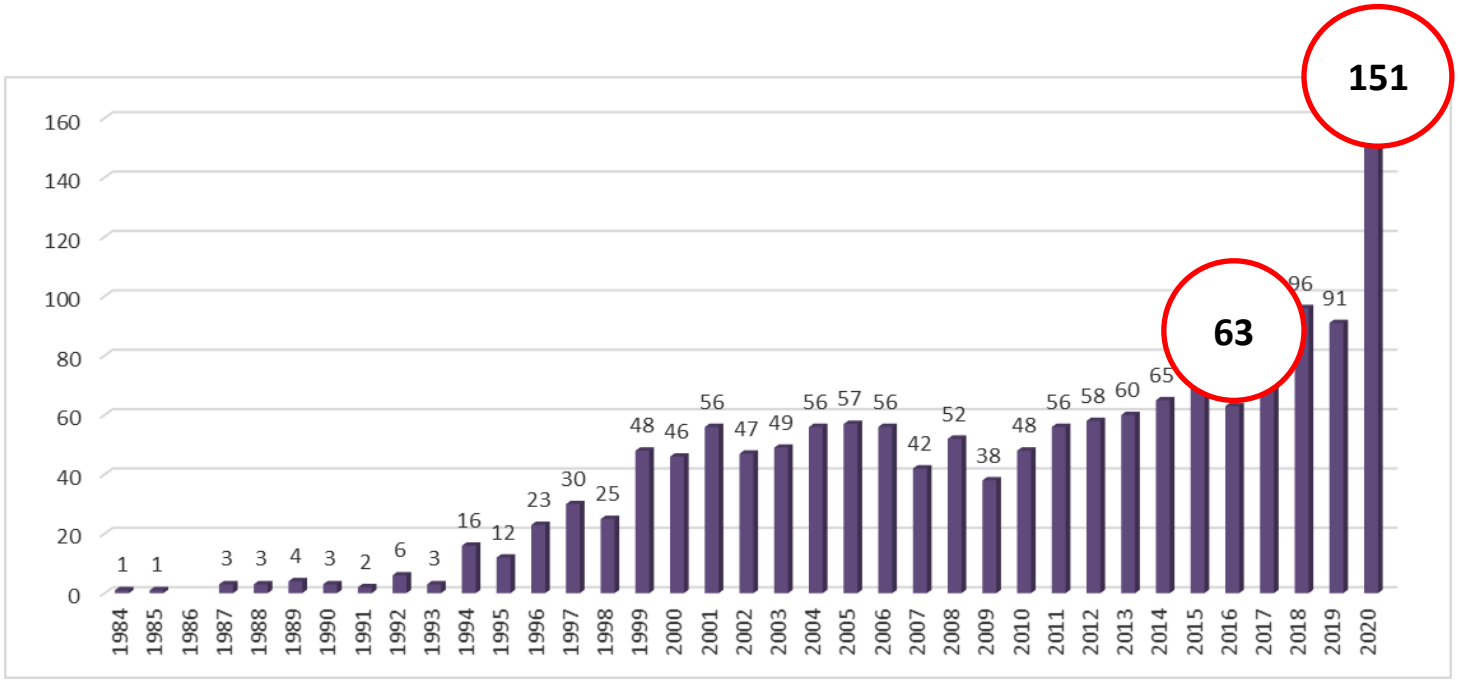
OTAT: BLA approvals in 2021 (cont.)

- **STRATAGRAFT allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen-dsat**
  - Treatment of adults with thermal burns containing intact dermal elements for which surgical intervention is clinically indicated (deep partial-thickness burns)
- **RETHYMIC allogeneic processed thymus tissue–agdc:**
  - Treatment of immune reconstitution in pediatric patients with congenital athymia

All OTAT INDS
(i.e., Research and Expanded Access (EA))
1963 – 2020



Research INDs: Cell Therapy



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

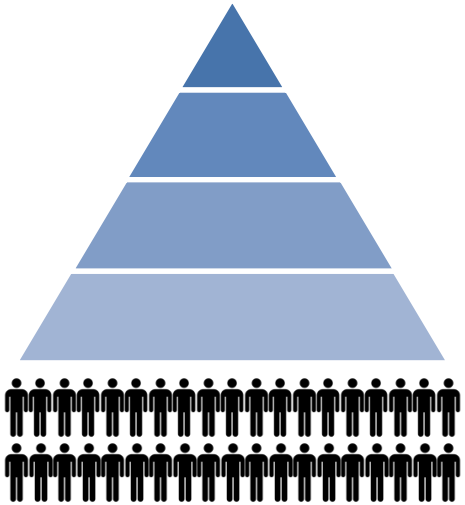
- Product tracking and logistics
- High product variability
- Limited material or time for testing
- Short shelf life
- Scale-out

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

CGT product manufacturing paradigms

Conventional Drug/Biologic

1 product lot



Many patients

Raw materials

CGMPs

Advanced manufacturing

In process and lot release testing

Scale up/scale out

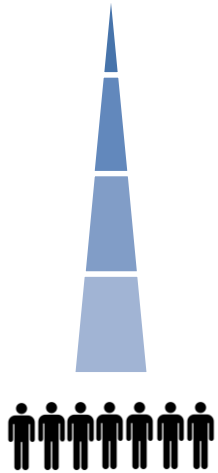
Comparability

Distribution

Impact of manufacturing failure

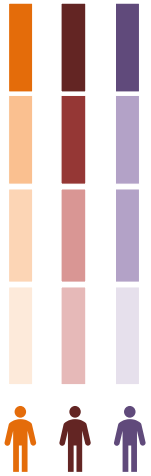
Cell & Gene Therapy Products

1 product lot



Few patients

1 product lot



Single patient

The double-edge nature of cell therapies

Advantages:

- Multiple potential mechanisms of action
- Can be highly patient-specific
- Scalable through cell expansion
- Single treatment can give durable clinical response, even cure disease
- Same cells might treat many diseases

Challenges:

- Difficult to establish critical quality attributes
- Very sensitive to growth conditions
- Lack of some high-grade ancillary materials
- Limited stability of materials, intermediates, and products
- Limitations on testing
- Often high lot-to-lot variability
- Logistics
- Lack of reference standards

Cell therapies are typically not well-characterized

Regulatory review at FDA is highly product dependent

- Scale – one “lot” for some products could treat thousands of patients, whereas patient-specific products treat just one
- Manufacturing procedures, technologies, and methods can differ widely
- Comprehensive testing is challenging for products with little test material or very short shelf lives
- Risk of product depends greatly on source material and how the product is made
- High inherent variability of some product types makes demonstrating manufacturing comparability and consistency challenging

There is no “one size fits all” approach to cell therapies

Cell therapies represent a huge spectrum of products

Each product type has its own challenges

Examples:

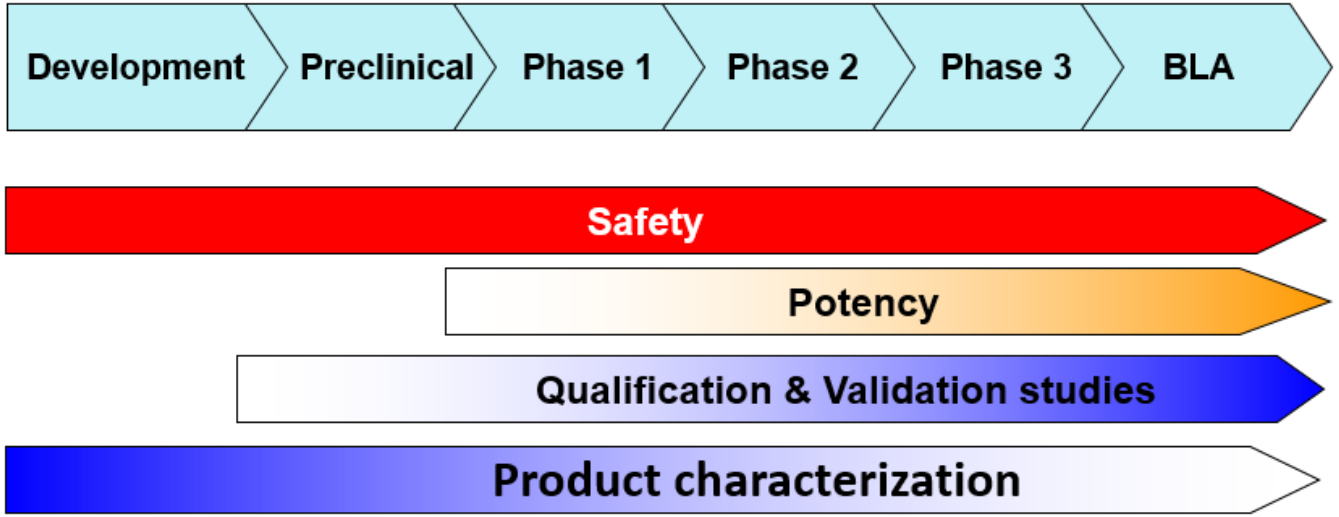
- Multipotent cells
- Complex mixtures of cells
- Tissue engineered products

Need to consider:

- What it is
- How it is made
- What it is supposed to do

Product development lifecycle

The stage of product development guides the review concerns, with safety being the primary concern at all stages

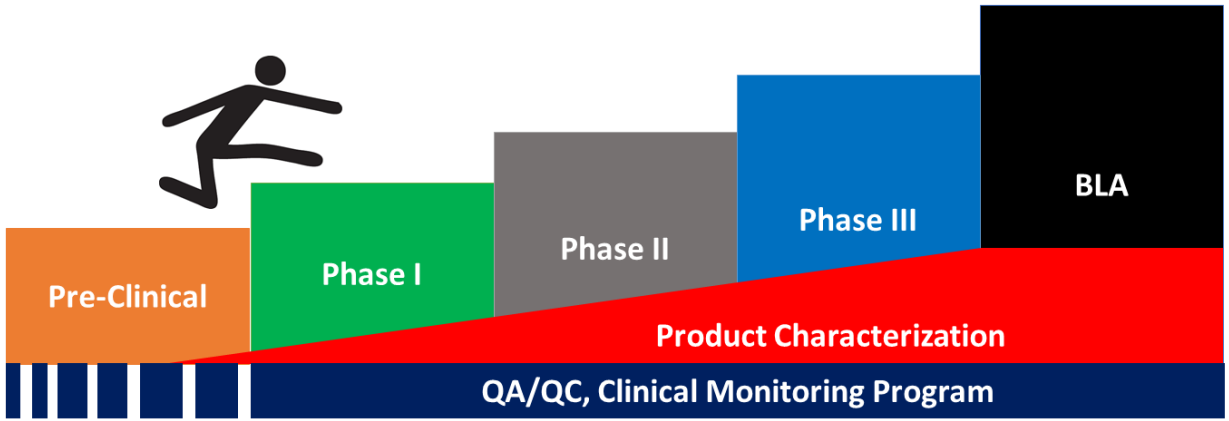


- We encourage sponsors to qualify or validate their assays and processes, and develop a potency assay early
- Safety and quality must be designed into the product

Product development lifecycle

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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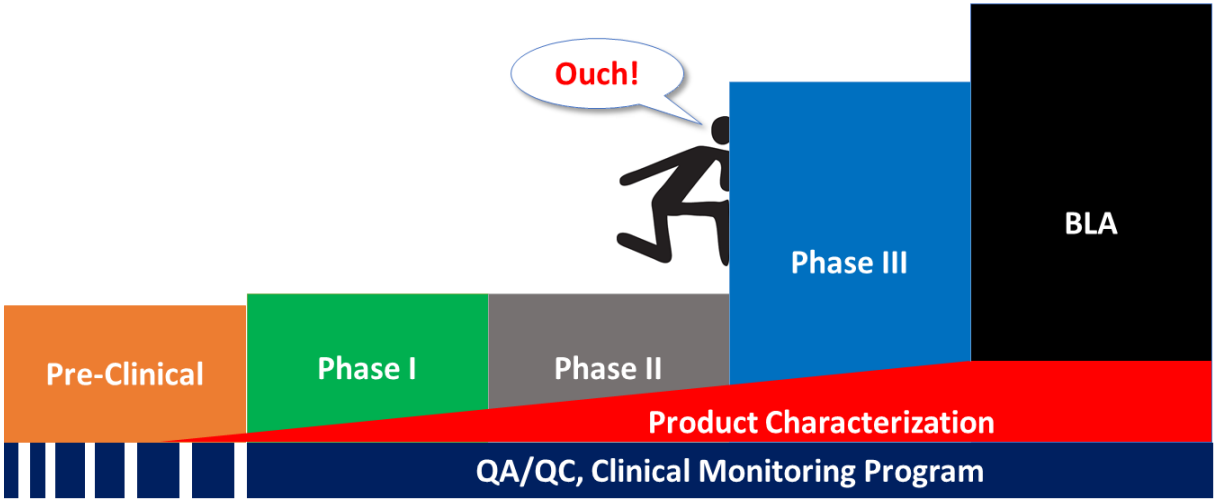


Don’t put off important work

Should I not just wait and see how good the Phase 3 clinical data looks and then tackle complex CMC items?

Waiting until late in the product lifecycle to tackle critical product issues can put you in a difficult position if Phase 3 clinical data intended to support licensure looks favorable, but there is much CMC work to be done.

Though accumulated manufacturing experience can be helpful, it is best to take a stepwise approach during the product lifecycle.

It is important to keep CMC aligned with clinical development

- It is not advisable to begin studies intended to support licensure if you still are undecided about what your manufacturing process will be or what you intend to measure.
- To approve a BLA, all assays and methods have to be validated and the facility has to be ready for commercial production.
- Do not underestimate the time and resources needed to bring manufacturing up to the level of Phase 3 and commercial production.
- Establishment of quality attributes, measurement of potency, and demonstration of product stability can be particularly challenging.

Accelerated development

- Promising clinical results and accelerated clinical studies…

  … give less time for product development
- Assay development can lag behind clinical studies
- **Requirements for licensure are unchanged**
- Especially problematic for stability studies
  - Initiate stability studies earlier

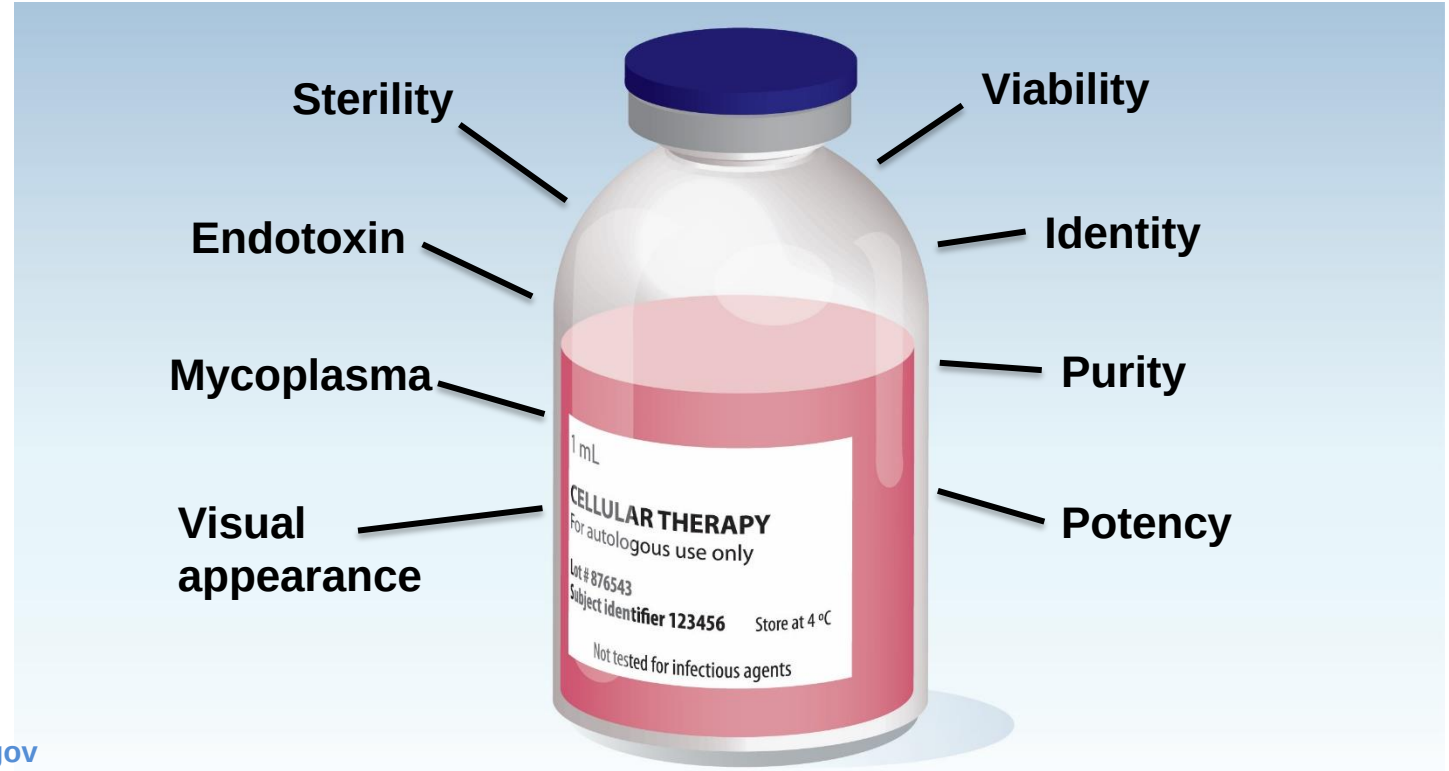
    …but need potency assay for stability
  - Potential issues if manufacturing or testing methods change
- **Plan early for BLA and commercialization**

Lot release specifications are at the center of many manufacturing elements

It is important to choose them carefully and apply them where needed

Lot release specifications exist to set expectations for product safety and quality

Lots that don't meet these cut-offs should not be distributed and used



Who decides on lot release specifications and assays used to define a product?

Some lot release specifications are stipulated by regulations:

- Donor eligibility
- Sterility, endotoxin

Some are based on recommendations in guidance documents:

- Viability of at least 70% for cell therapies, mycoplasma

Most lot release specifications are established by the sponsor and justified based on manufacturing experience and clinical need:

- Identity and purity
- Potency
- Dose/volume/concentration

Common issues with choosing product release specifications

- Specifications not capturing key product 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
- Misinterpretation or over-interpretation of data

Specifications are not meant to be static- they should be continually evaluated/revised as needed

Carved in stone

Continually upgraded

- Additional product characterization data may indicate a better way of ensuring quality
- Clinical outcome data may provide clues as to what product properties are the most important
- Additional manufacturing experience may guide critical quality attributes and specifications

Understanding your product and process

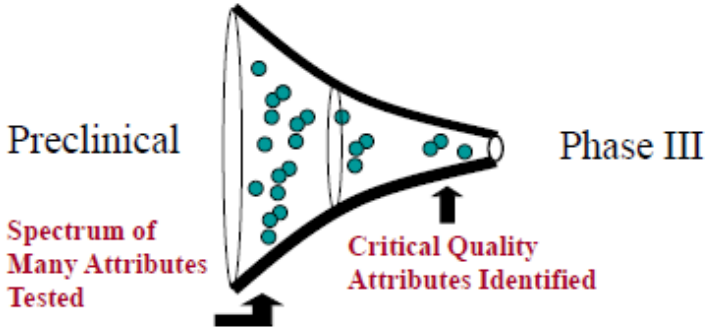
Terminology:

- Mechanism Of Action (MOA) is how you believe the product will work in recipients based on properties of the product
- Quality Target Product Profile (QTPP) is a summary of characteristics needed to ensure the quality, safety and efficacy of the product that considers the product's MOA, drug product quality criteria (e.g., sterility, potency, purity, stability), the specific clinical indication, and the logistics of product storage/shipping/administration
- Critical Quality Attributes (CQAs) are physical, chemical, biological, or microbiological properties or characteristics that should be within an appropriate limit, range, or distribution to ensure the desired product quality
- Critical Process Parameters (CPP) are process parameters whose variability has an impact on a CQA and therefore should be monitored or controlled to assure the process produces the desired product quality

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)*

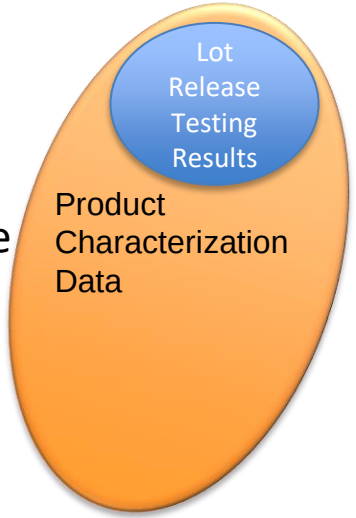
- Explore many CQAs during early development
  - Report results early in development
  - Choose relevant tests for later phase studies
- Evaluate multiple measures of CQAs (especially potency)
  - Matrix of assays
  - Orthogonal methods
  - Stability indicating



Understanding your product and process

Establishing CQAs and CPPs for cell-based products has unique challenges:

- Cells are much more complex than most other broad categories of drugs, and only so many attributes can be controlled practically
- Cellular products may have multiple or unknown mechanisms of action
- Bioassays measuring cellular activities often have more variability than non-biological analytical assays, yet bioassays are necessary to measure functional attributes.



CQAs and CPPs should be continually evaluated and revised if needed:

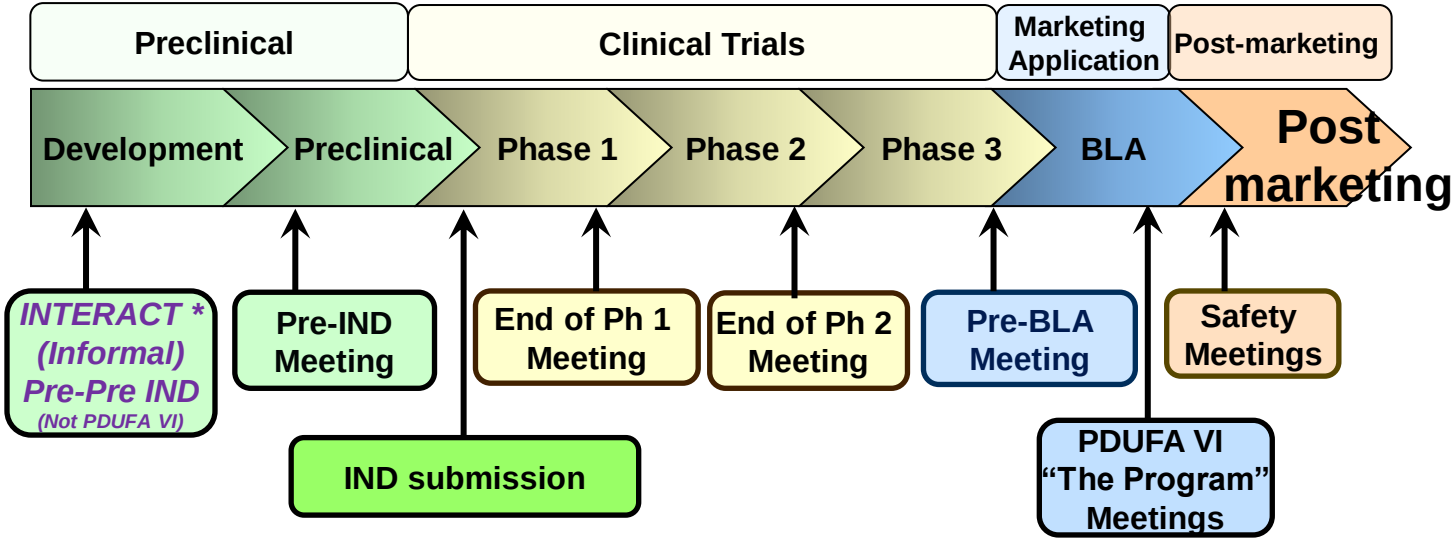
- Product characterization data collected during early-stage studies may identify attributes that better capture product quality
- Clinical outcome data may provide clues as to what product attributes are most important

Product characterization throughout development

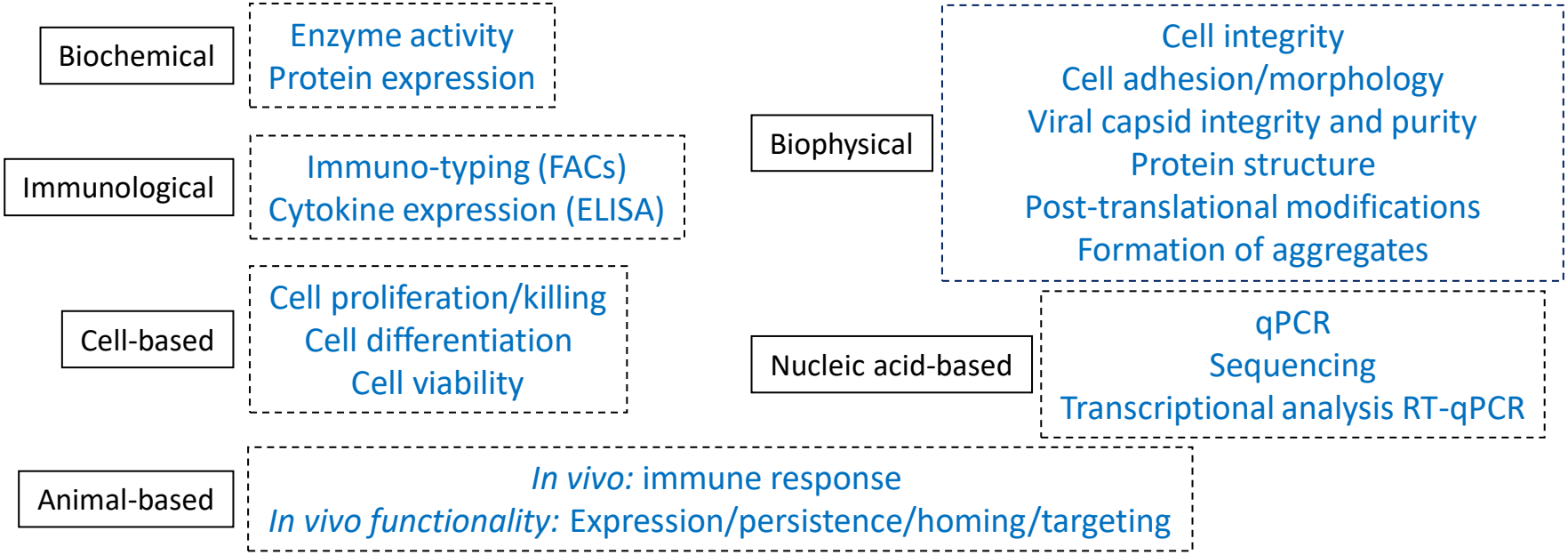
The importance of understanding product attributes:

- 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

Opportunities for interaction during product development



Matrix approach to CGT product testing



Potency: Regulatory definitions

- 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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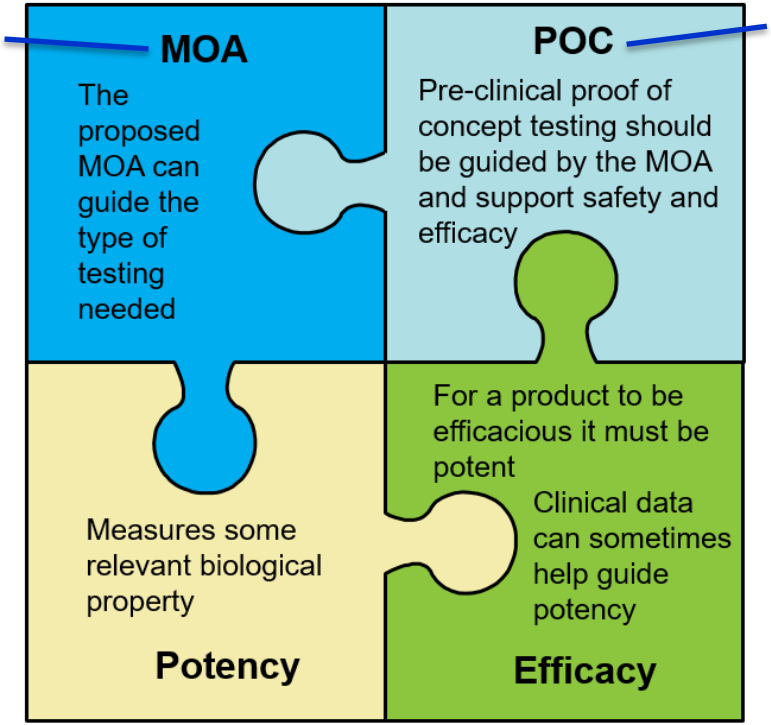
What makes a good potency assay?

- Reflects mode of action (MOA)
- Reproducible
- Accurate
- Robust
- Practical
- Stability indicating
- Supports comparability studies
- **Potency assays are product specific**
- **A single assay may be insufficient – explore orthogonal methods and matrix approaches**

Relationship between mechanism of action and potency

Mechanism of Action

Proof of concept



Although it is not a regulatory requirement to fully define the mechanism of action, **having an understanding of how the product is likely to work** can be very helpful

- A potency assay should reflect the MOA
- More than one measure of potency (potency matrix) may be needed
- Developing a good potency assay is not easy – start early!

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

Potency assay development

- What attributes reflect product performance?
- What potency assays are most appropriate
  - Cytokine production?
  - Tumor cell killing?
  - Phenotype?
- Limit-based release criteria may be appropriate
  - Early stage: broad criterion may be appropriate
  - Later stage: lower limit for efficacy and upper limit for safety

Potency assay development

- Preclinical and early clinical development
  - Methods guided by preclinical data and proposed MOA
  - Ensure activity/strength of product for dosing
- Throughout clinical development
  - Continue to characterize product and develop assays
  - Explore multiple measures of potency
- By Phase 3 (pivotal studies)
  - Well defined and qualified potency assay
  - Part of lot release: May refine specification(s) if needed
- Prior to BLA submission
  - Validated potency assay

Timeline affected by clinical development

Potency assay development

For INDs, **sufficient information is required at each phase of an investigation to ensure proper identity, quality, purity, strength, and/or potency**. The amount of information on analytical procedures and methods suitability will vary with the phase of the investigation.

- Guidance for Industry: Analytical Procedures and Methods Validation for Drugs and Biologics (2015)

Early Phase Studies:

- Explore a variety of product characteristics to refine potency assay
- Develop reference material
- Qualify assays used for product release and stability testing (suitable for the intended purpose)

Late Phase Studies:

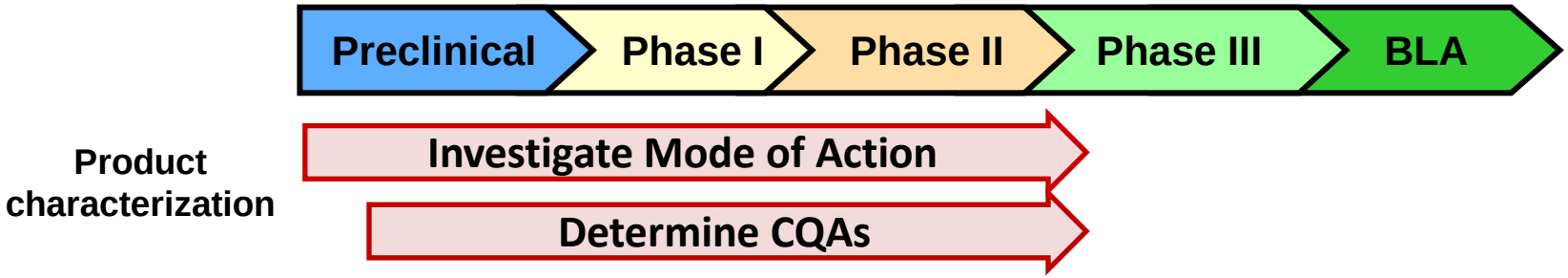
- Validate potency assay(s)
- Evaluate release criteria
- Qualify reference materials & controls
- Generate stability data

Selection of commercial potency assay

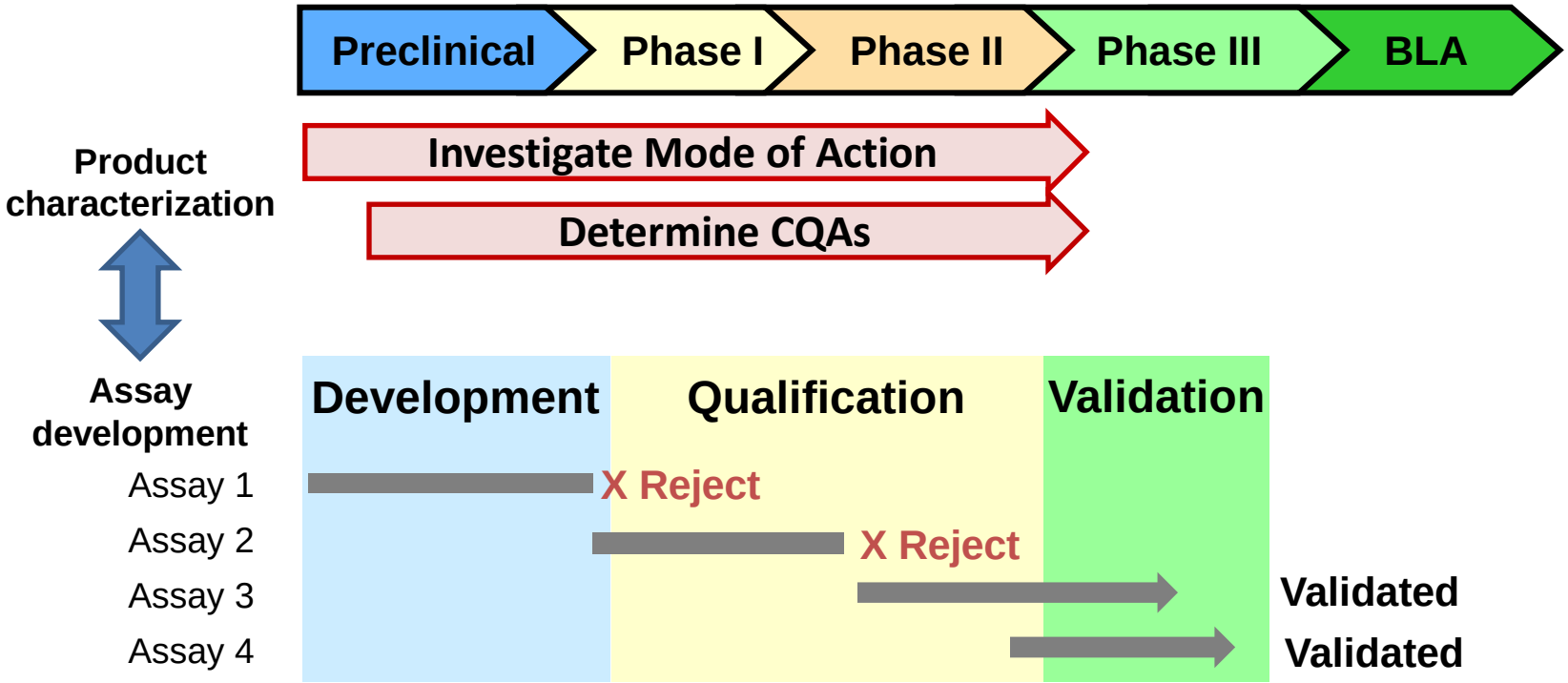
Potency assay or assay matrix design and acceptance criteria should establish appropriate limits for potency to assure that product lots are well-defined, biologically active, and consistently manufactured

- Validated and quantitative
- Aligns with product release timeline
  - clinical data may be used to establish a correlation(s) between biological activity and a more practical potency measurement(s)
- Lot release acceptance criterion will be based on lots used in clinical studies providing evidence of safety and effectiveness
- Stability-indicating

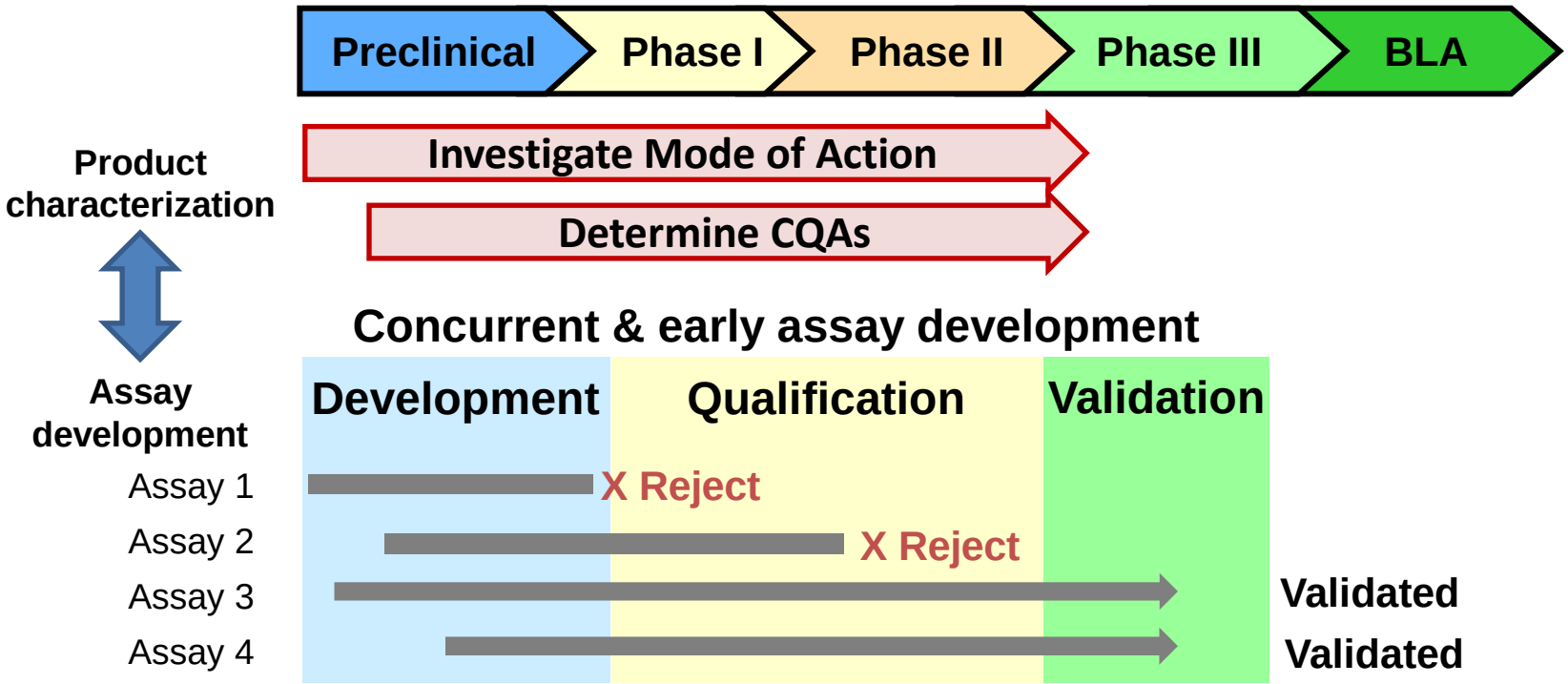
Assay development timeline



Assay development timeline



Assay development timeline



Assay validation

- **During assay development**
  - Evaluate assay performance and suitability
- **Analyze and validate all relevant assay parameters**
  - Accuracy
  - Detection limits
  - Precision (repeatability, intermediate precision)
  - Specificity
  - Linearity and range
  - Robustness
  - System suitability
- **Not all assays are created equal**
  - Some will be harder to validate than others

See also: ICH Q2(R1) Validation of analytical procedures

Impact of wide acceptance criteria

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

Narrow tolerances

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

Wide tolerances

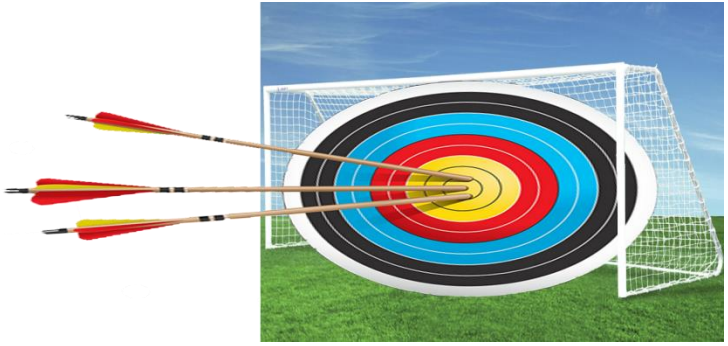
Difficult to rely on just lot release specifications to show consistency and comparability

Specifications as a goal

When a product has substantial inherent variability, you need to consider what you are targeting

For manufacturing you should aim like this…

Not this…



What you end up with for a final product lot should be a reflection of what you started with

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

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.**

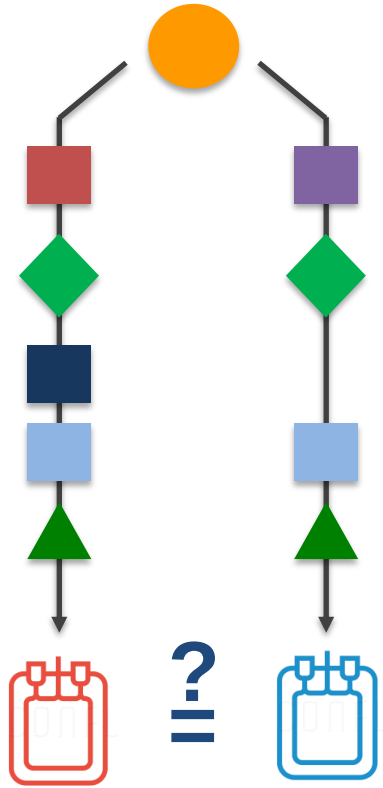
- Determinations of product comparability **can be based solely on quality considerations if the manufacturer can provide assurance of comparability through analytical studies.** Additional evidence from nonclinical or clinical studies is considered appropriate when quality data are insufficient to establish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

Your ability to demonstrate comparability will be limited by:

- Consistency of manufacturing process before the change
- Variability of your analytical methods
- Level of product characterization
- Knowledge of comparability margin:
  - Level of correlation of product attributes with clinical outcome
  - When clinical correlation is poor, you'll have to justify your comparability acceptance criteria by other means (e.g., scientifically)

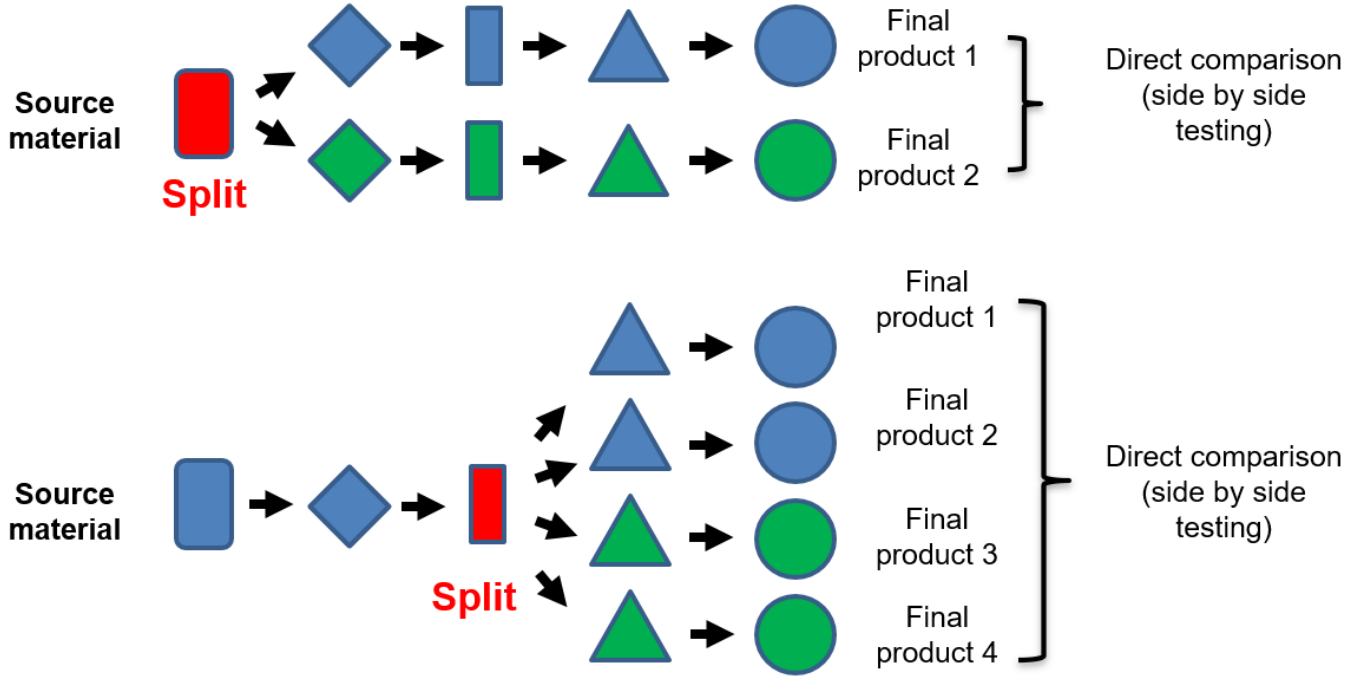
Analytical comparability study considerations

- 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.

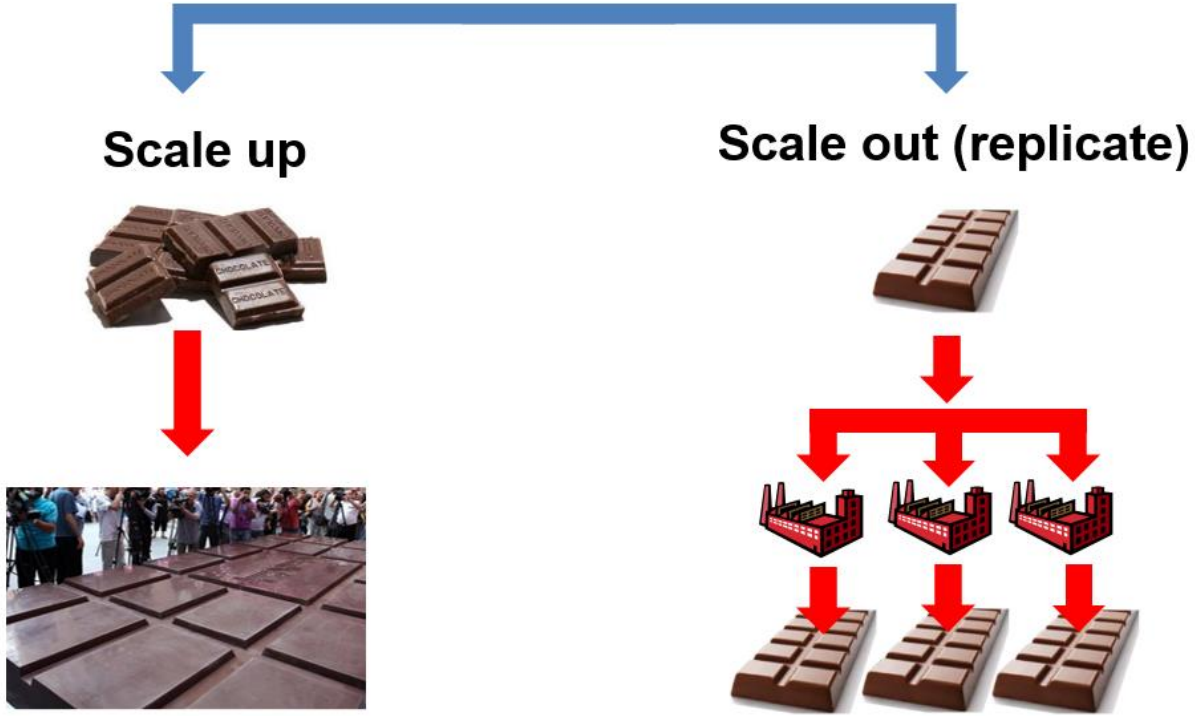


Split manufacturing for comparability assessment

Dividing source material to circumvent lot-to-lot variability:



Different strategies to increase manufacturing scale

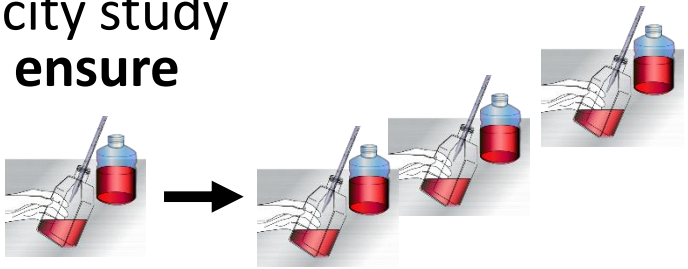


Scale-up considerations

- Increase in yield:
  - Increased by culturing for longer- in some cases length in time in culture and the number of passages can profoundly impact product properties
  - Incubation with growth factors/cytokines/reagents to stimulate proliferation – can affect differentiation or activation state
- Cells can also be sensitive to cell density and ratio of cell types
- Adherent cultures and suspension cultures may need different strategies
- Not all processes scale well:
  - Working with huge numbers of flasks can be problematic
  - Time sensitive steps (such as enzymatic treatment)

Scale-out manufacturing considerations

- While it may be easiest to process all lots identically, each lot has unique properties and may react differently to the same conditions – **could contribute to product variability.**
- There can be increased risk when processing **multiple lots simultaneously – material qualification and process monitoring are critical.**
- Recommend that, in addition to aseptic process validation and process validation, a capacity study is performed to identify bottlenecks and **ensure that adequate resources are available**



Summary

CGT products are complex biologics requiring significant forethought regarding lifecycle management

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

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

OTAT Learn
Webinar Series

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

22 webinars on various product development topics, such as:

- Introduction and Scope of OCTGT
- IND Basics in OCTGT
- Sponsor Meetings with OCTGT
- “361” Human Cells, Tissues, & Cellular and Tissue-Based Products
- The Chemistry, Manufacturing and Controls (CMC) Section of a Gene Therapy IND
- Advanced Topics: Successful Development of Quality Cell and Gene Therapy Products
- Cellular Therapy Products
- Preclinical Considerations for Products Regulated in OCTGT
- Regulatory Obligations for Investigator-Sponsored Research

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- **OTAT Learn Webinar Series:**
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- **CBER website:** www.fda.gov/BiologicsBloodVaccines/default.htm

  Phone: 1-800-835-4709 or 240-402-8010

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