Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products

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Talk Outline

- Challenges for establishing CGT product comparability
- Comparability assessment expectations for manufacturing process changes
- Comparability allows leveraging clinical data from pre- and post-change products
- Comparability consideration for different strategies to increase manufacturing scale

Cell & gene therapies (CGT) 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

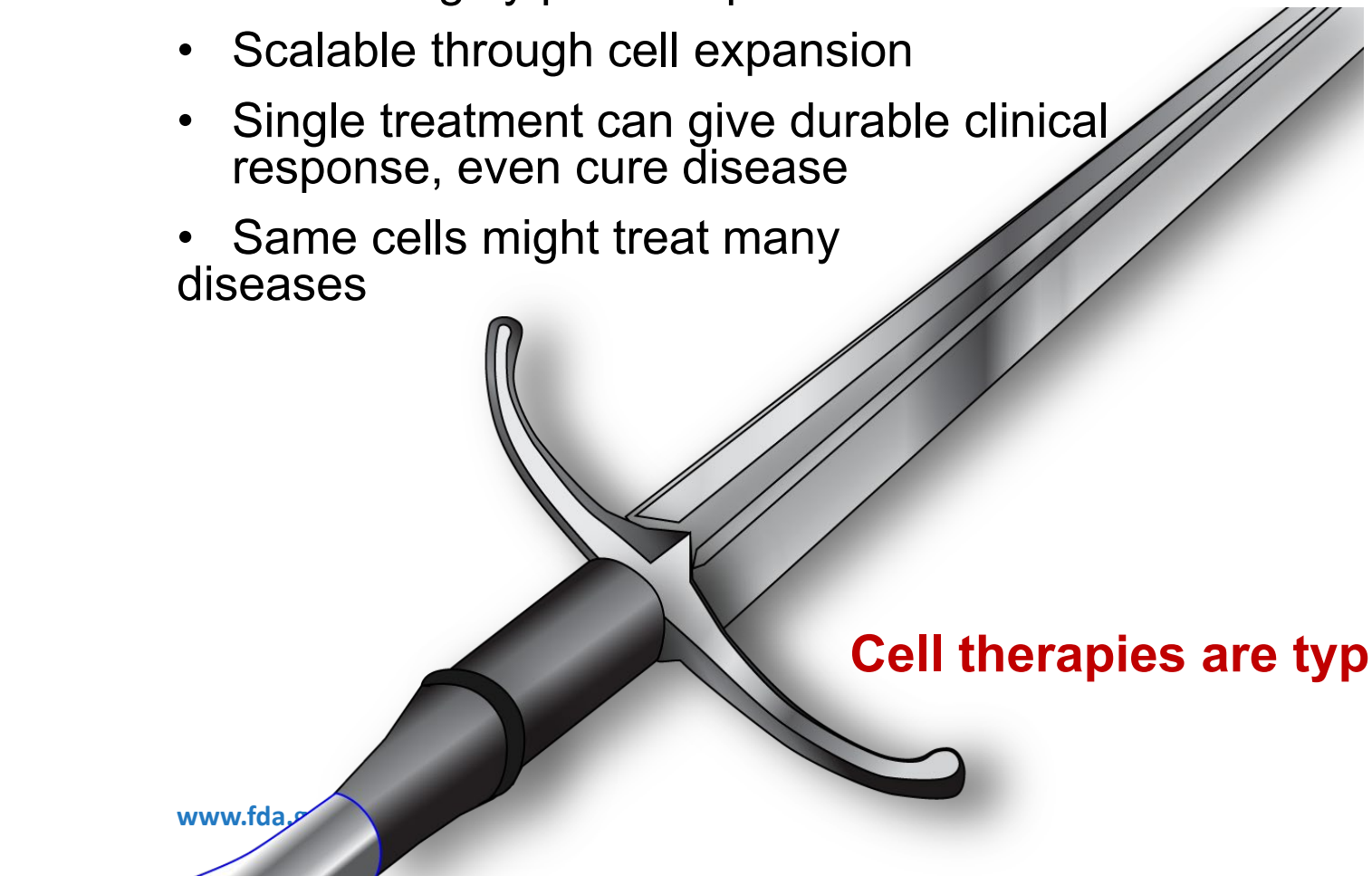
- Product tracking and logistics
- High product variability
- Limited material or time for testing
- Short shelf life
- Scale-out

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

The double-edge nature of CGT

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

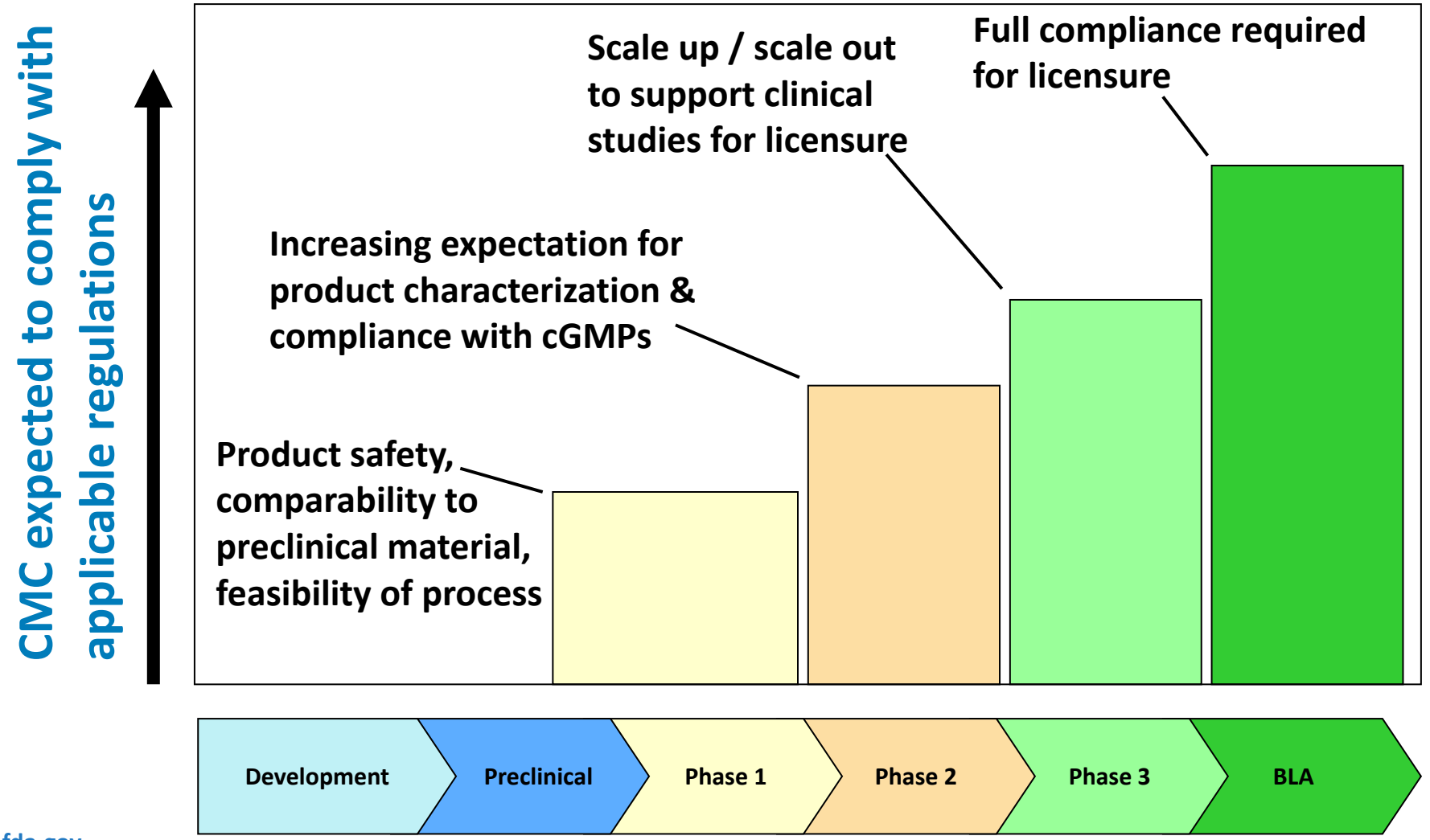


Challenges:

- 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

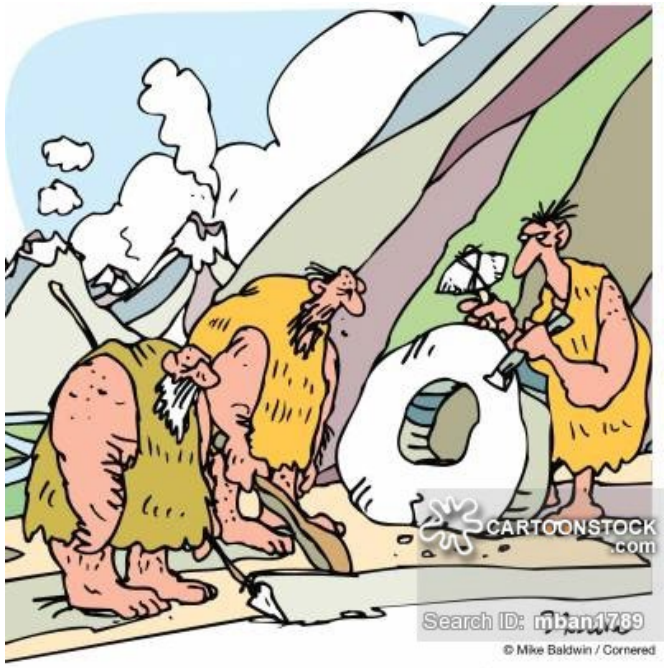
Cell therapies are typically not well-characterized

CGT product development should progress in parallel with clinical development



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

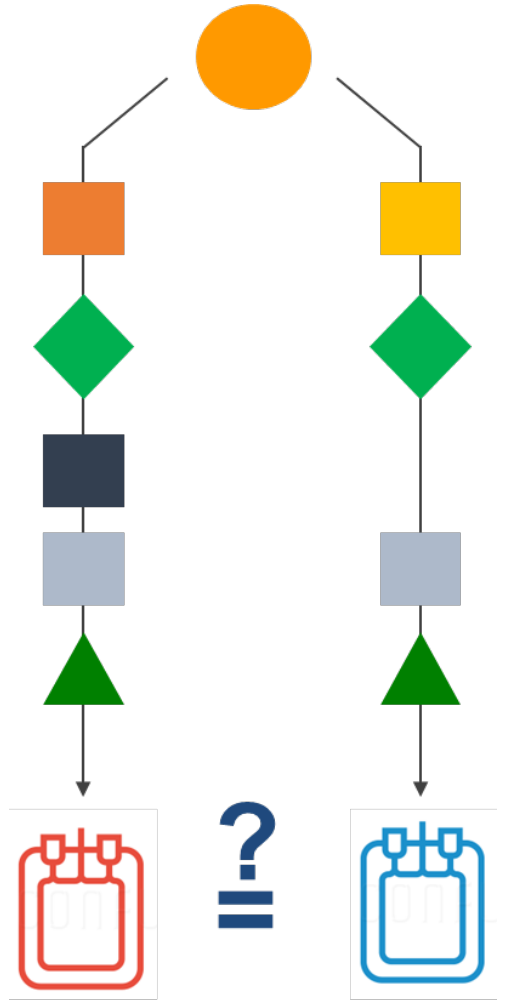


"What's with kids nowadays? Walking upright's not good enough for you?"

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

Manufacturing process changes

- Change in reagent, process step, etc.
- Comparability assessment requirements are affected by
  - Early vs. late stage of development
  - Minor vs. major change
  - Patient risk
- Change may be to improve an attribute or manufacturing process
  - Reduce culture time
  - Improve purity



Product comparability

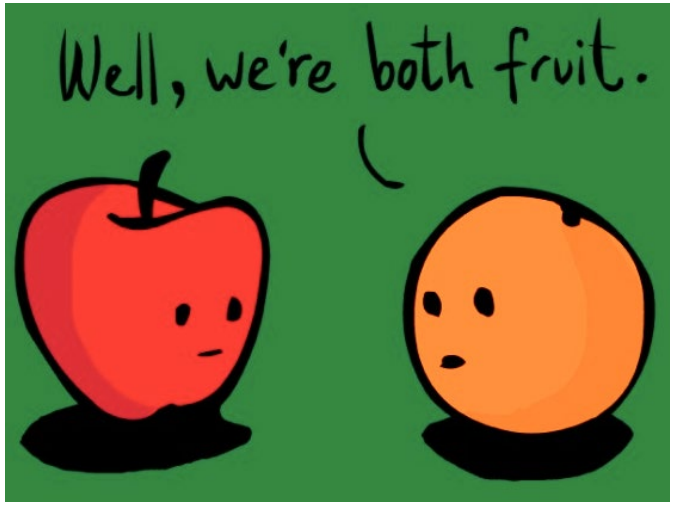
Determinations of product comparability **can be based solely on quality considerations if the manufacturer can provide assurance of comparability through analytical studies.** Additional evidence from nonclinical or clinical studies is considered appropriate when quality data are insufficient to establish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

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

What are comparable products?

…does not necessarily mean that the quality attributes of the **prechange and postchange product** are identical, but that they **are highly similar and that the existing knowledge is sufficiently predictive to ensure** that any differences in quality attributes have **no adverse impact upon safety or efficacy of the drug product**.

Refer to ICH Q5E and FDA Guidance for Industry Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process



Challenges for establishing CGT product comparability

- Limited manufacturing experience:
  - Not many lots produced
  - Not enough retention or test samples available
  - Source material may be difficult to obtain for non-clinical and product development purpose
- Limited in-process testing: process variables and critical process parameters not well understood, and limited in-process testing to monitor
- Limited product characterization: critical quality attributes 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

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)

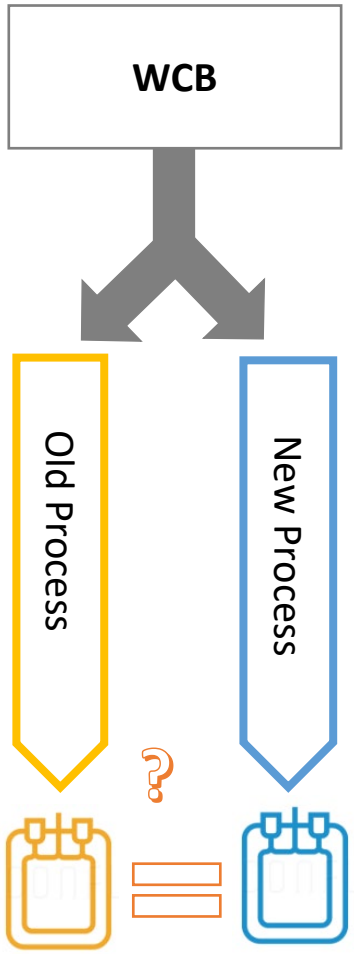
Analytical comparability study considerations

- 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 safety and efficacy for a marketing application (BLA)

Comparability allows leveraging clinical data from pre- and post-change products

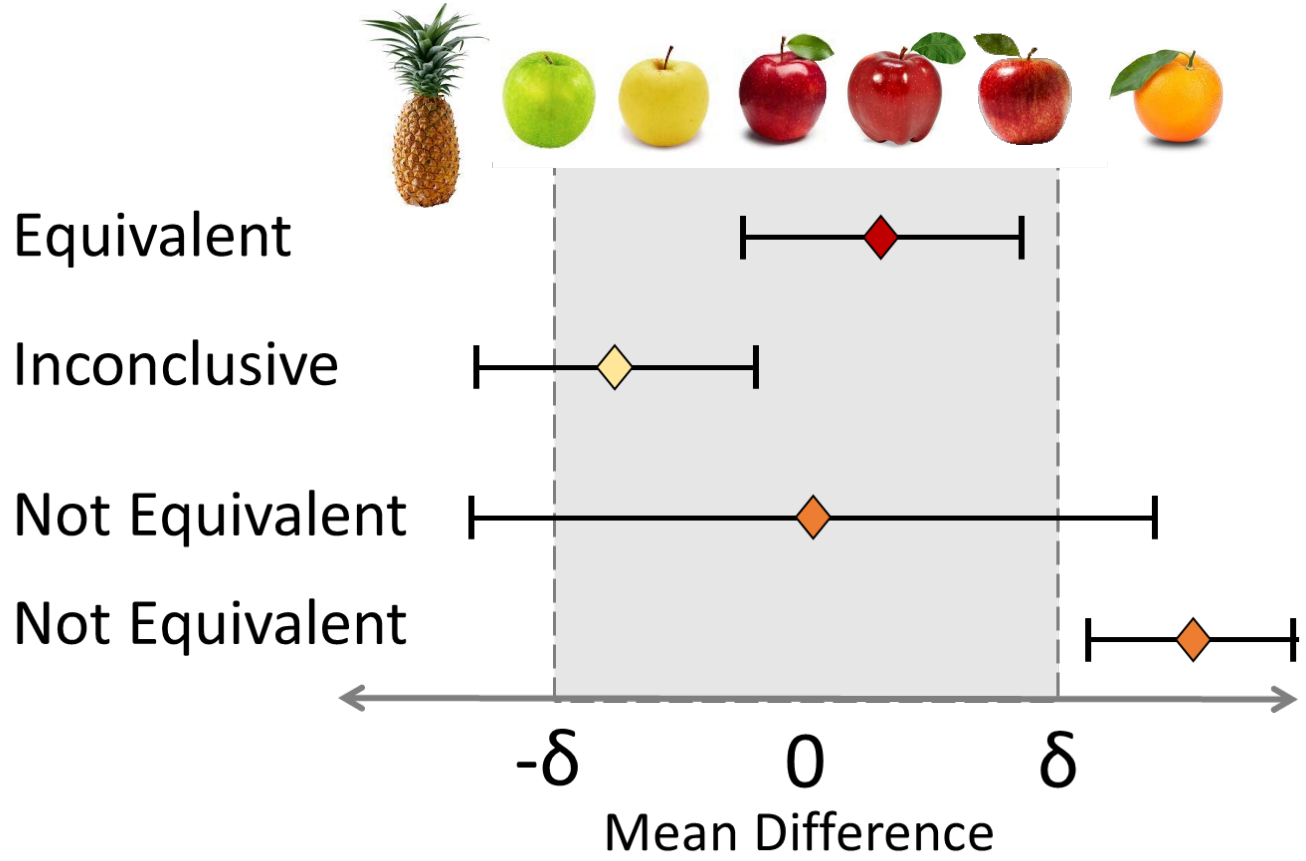
Analytical comparability study considerations

- Side by side analysis with sufficient lots to do robust statistical analysis.
- 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.
- Discuss with FDA prior to implementation



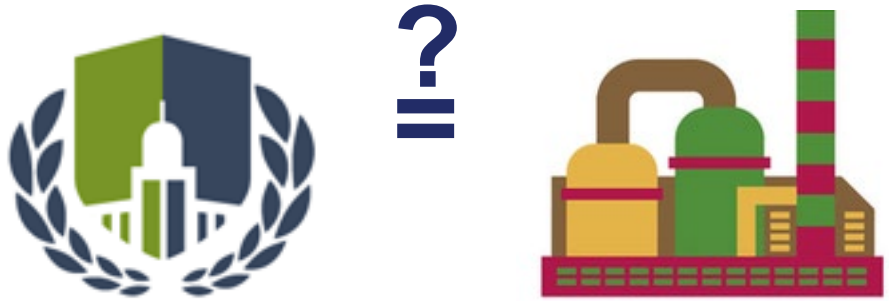
Analytical comparability analysis

- Predefine acceptance criteria for each attribute being evaluated
- Use appropriate robust statistical methods (e.g., equivalence testing)



Facility Changes

Comparability allows leveraging clinical data from pre- and post-change products



- Include proposed commercial manufacturing site prior to Phase 3/registrational study
- Often associated with manufacturing process changes
- Depending on your product, comparison to historical experience may be insufficient

Multiple Manufacturing Facilities

Comparability supports clinical data analysis throughout study

- Comparability between manufacturing facilities is a concern independent of stage of development
- Recommend comparison to a single “reference” site
- Recommend same SOPs, reagents, training programs, qualification requirements, and equipment are used across manufacturing facilities
- Defined acceptance criteria for product quality attributes will support production of comparable products across manufacturing sites

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.
- 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
- To approve a BLA, all assays and methods have to be validated and the facility has to be ready for commercial production

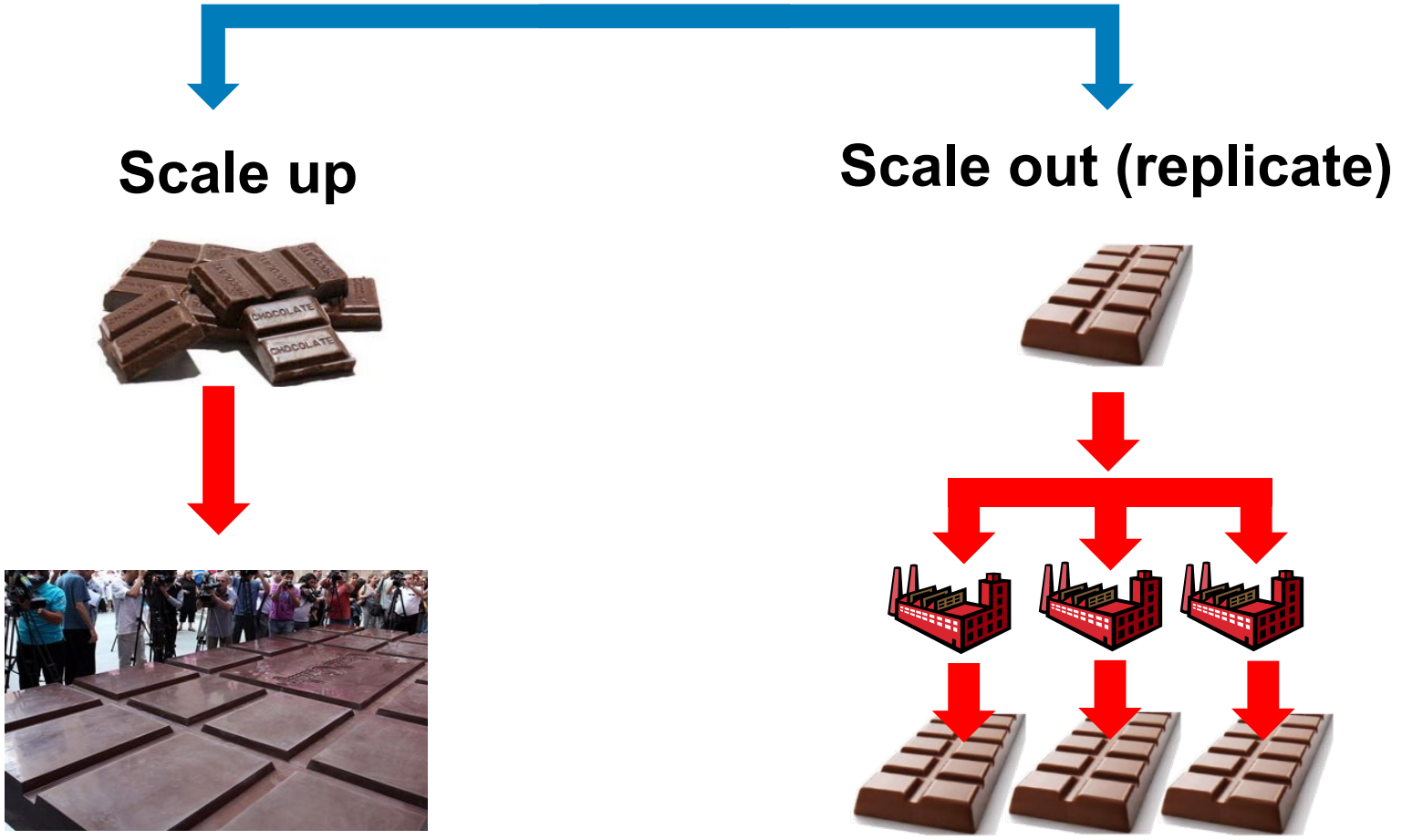
Don’t put off important work

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.

Different strategies to increase manufacturing scale

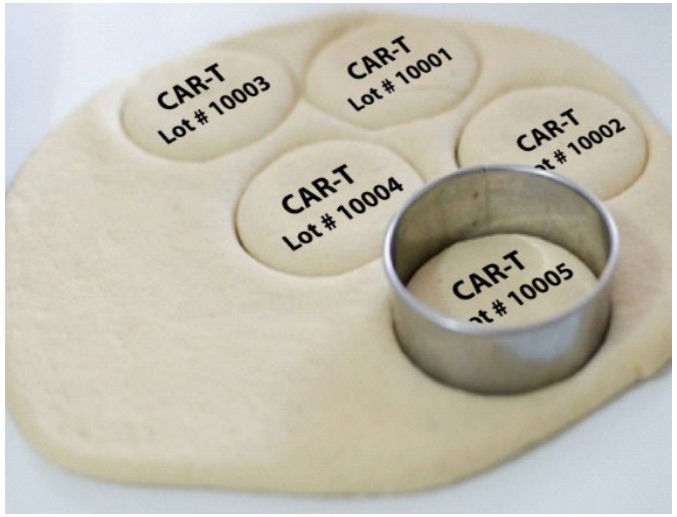


Scale-up considerations

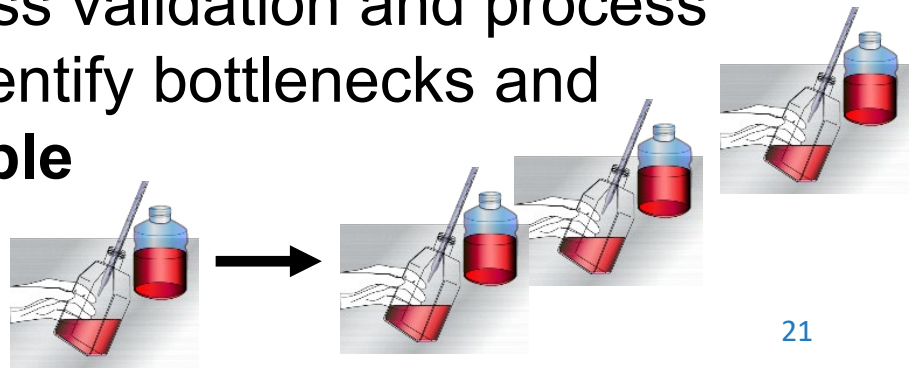
- Increase in yield:
  - Increased by culturing for longer- in some cases length in time in culture and the number of passages can profoundly impact product properties
  - Incubation with growth factors/cytokines/reagents to stimulate proliferation – can affect differentiation or activation state
- Cells 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**

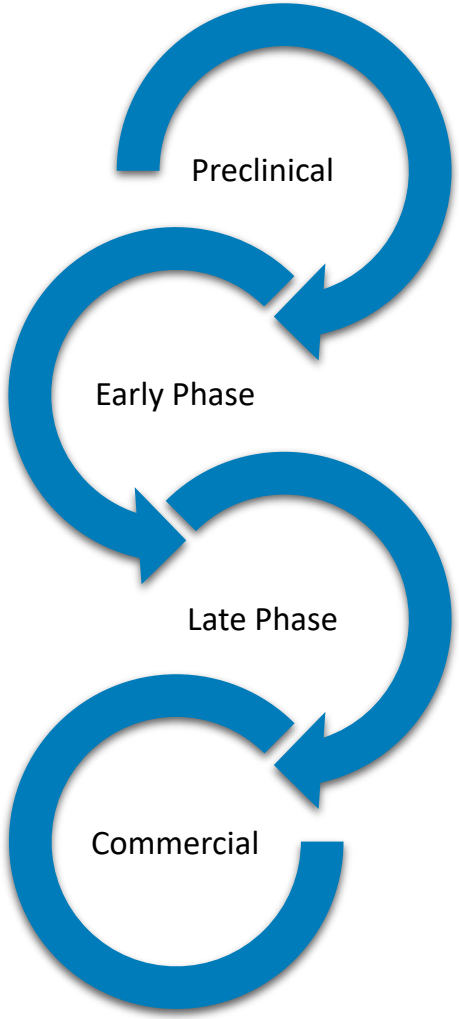


- Recommend that, in addition to aseptic process validation and process validation, a capacity study is performed to identify bottlenecks and **ensure that adequate resources are available**



Summary

- Many cell therapies are highly variable by nature and that can pose challenges for ensuring every patient gets a quality product, and for assessing manufacturing consistency and comparability
- Product and process characterization and assay development should be started early and continued throughout the product lifecycle
- Make manufacture changes prior to initiating clinical studies intended to support efficacy for a marketing application (BLA)
- Comparability study recommendations are based on:
  - Risk of change
  - Stage of development
  - Impact on product CQAs
  - Impact on interpreting clinical study data
- Comparability allows leveraging clinical data from pre- and post-change products
- Talk to regulators about challenging issues or novel approaches



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