Manufacturing control and comparability considerations for cell therapy products

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Learning objectives

- Understand some of the unique challenges associated with cell therapy product development
- Discuss control strategies that are important
- Discuss considerations for monitoring product quality and evaluating comparability after a change

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

Spectrum of products

“Individualized” — **“Off the shelf”**

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

Confusion surrounding reagent grades

Research grade reagents- packaging says “not for clinical use, for research purposes only” - so it can’t be used, right?

Possibly it could if:

- Risks are assessed
- Is properly qualified
- Justification is provided (e.g., no higher quality available)

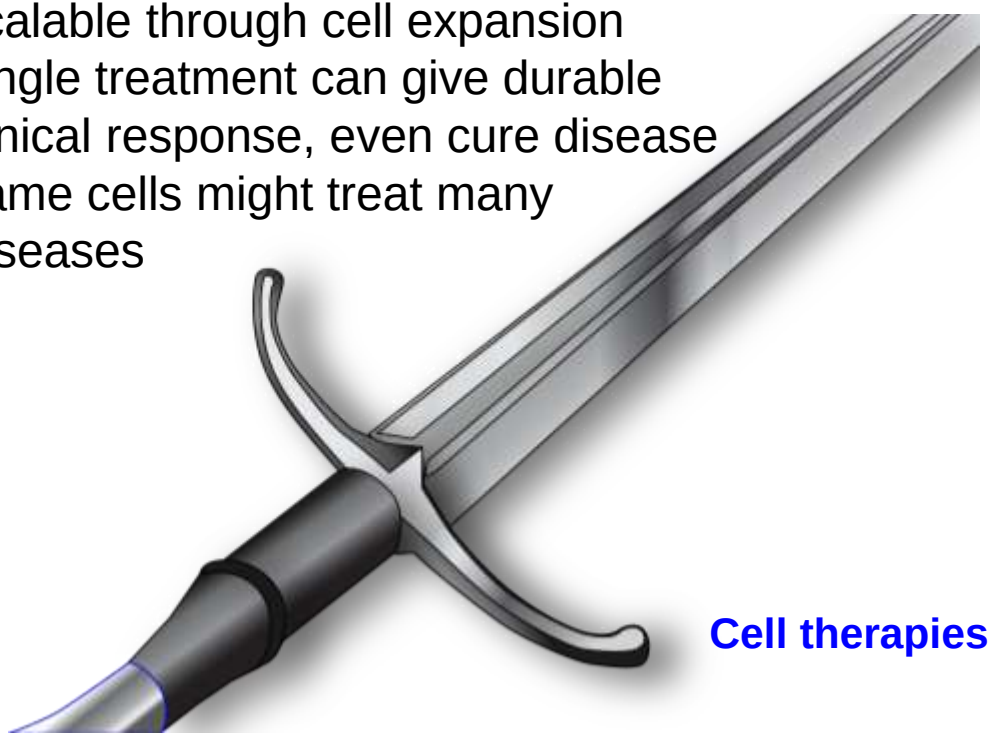
“GMP grade”

- GMP is not a grade nor a universal standard
- It is a series of controls used to help ensure manufacturing consistency and product quality and safety
- The fact that a reagent was made in a GMP facility does not necessarily guarantee adequate safety or quality
- The term is used broadly, and you should find out what controls and testing are involved from each supplier

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

Tissue engineered products: concerns related to cellular component

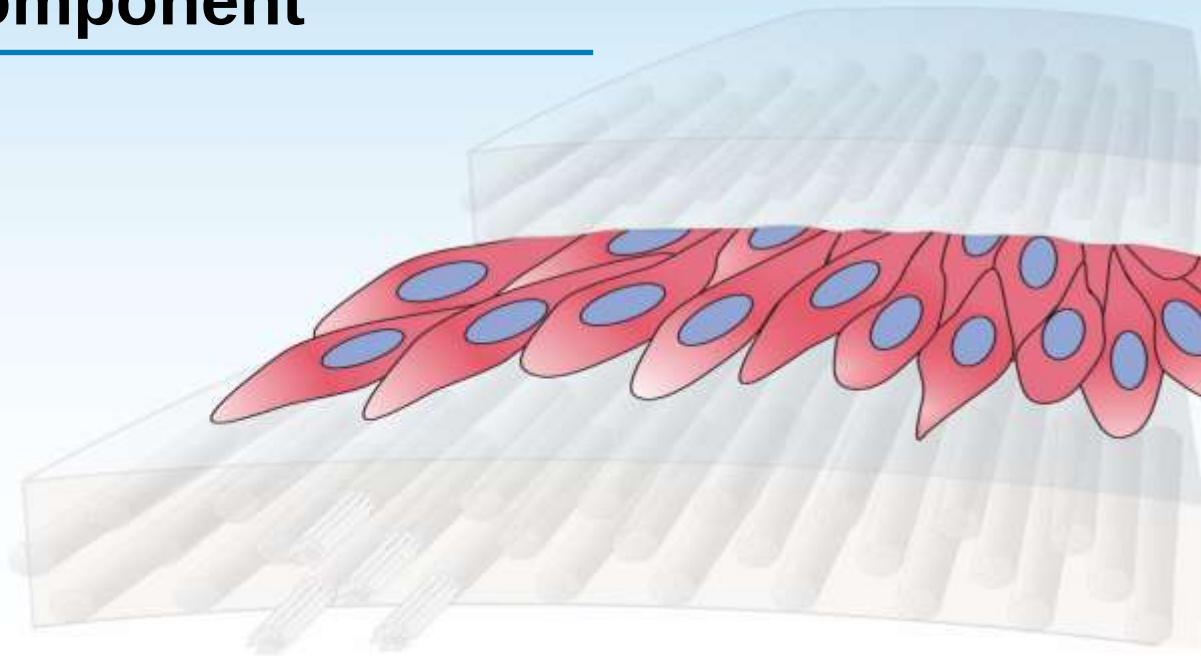
Quality of reagents used to prepare cells?

Cell bank safety testing?

Use of feeder layer?

Quality of manufacturing facility?

Level of product characterization?



Aseptic processing?

Cell viability?

Product stability?

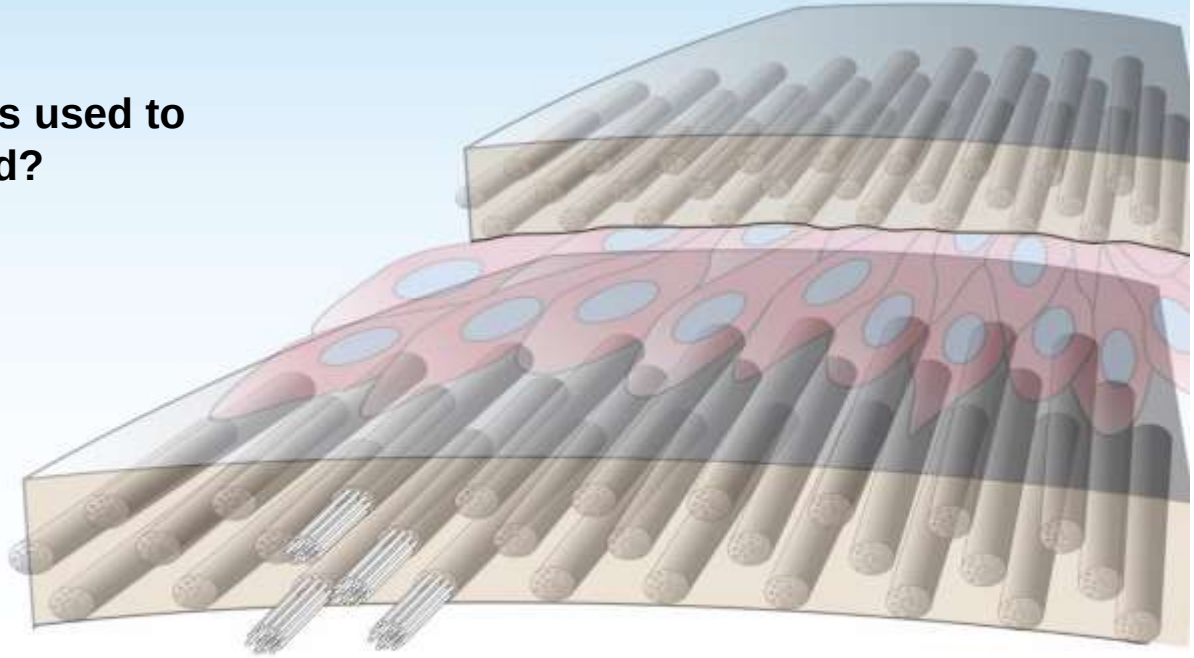
Regulatory concerns related to scaffolds

Quality of materials used to synthesize scaffold?

Residual reagents?

Biocompatibility with cells and tissues?

Equipment and facility used?



How will scaffold be sterilized?

Physical strength and integrity?

Stability in vitro and in vivo?

Concerns for combined cell and scaffold products

Impact of cells on properties of scaffold?

Impact of scaffold on cell phenotypes?

Remodeling in vivo?

How will the construct be tested?

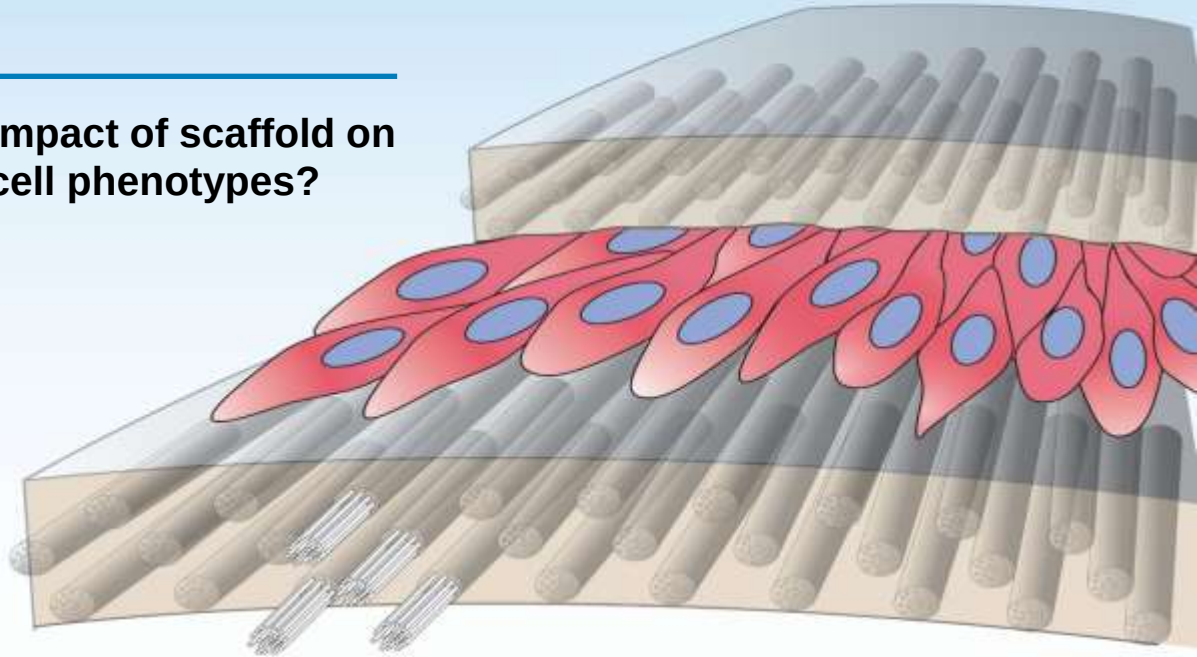
Uniformity?

Reproducibility?

How will it be shipped?

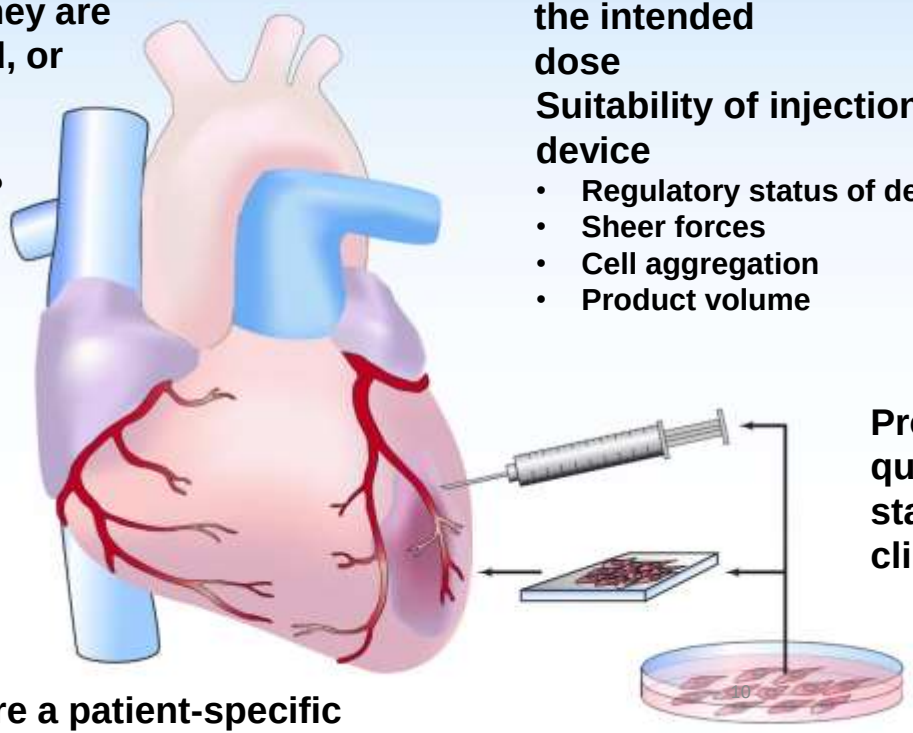
Handling at clinical site?

Stability?



Product administration concerns

Do cells stay where they are intended, or migrate where needed?



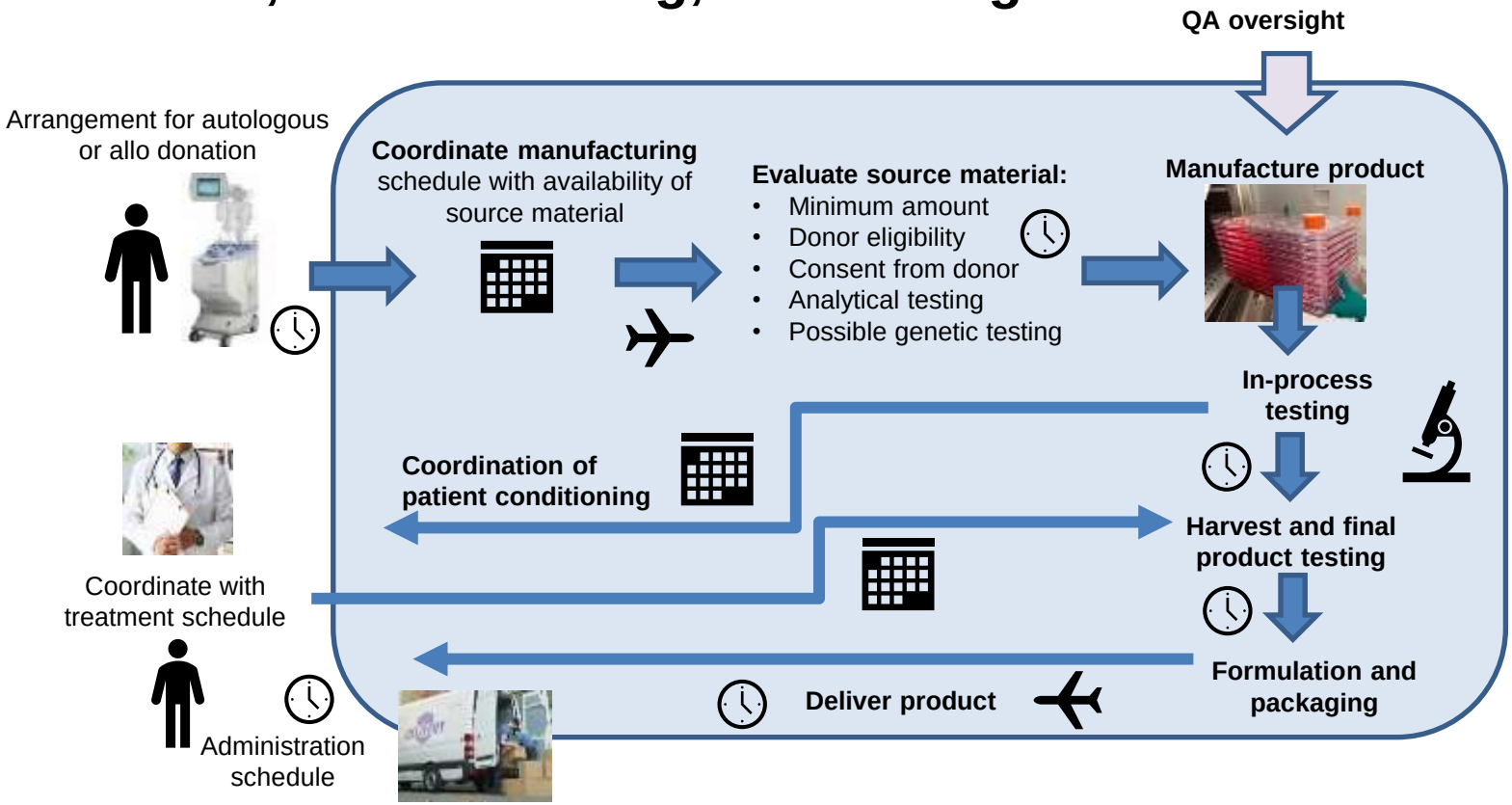
Ability to deliver the intended dose
Suitability of injection device

- **Regulatory status of device**
- **Sheer forces**
- **Cell aggregation**
- **Product volume**

Product quality and stability at clinical site

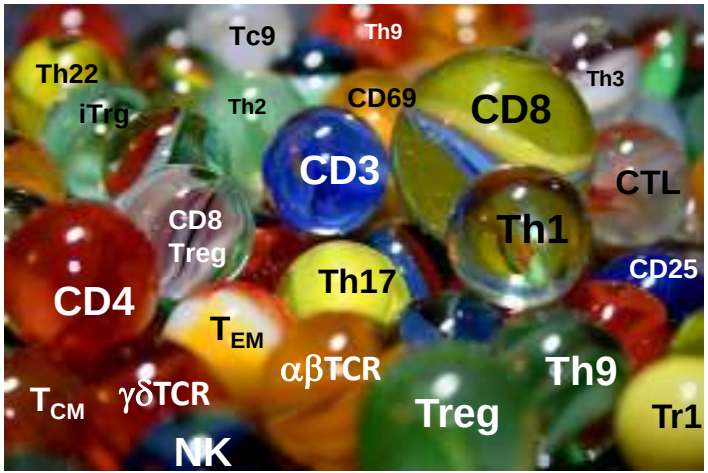
How will you ensure a patient-specific product goes to the right patient?

Coordination of patient's clinical care, donor, manufacturing, and testing



Establishing specifications

ICH Q6B and Q11: “Specifications are critical quality standards (CQAs) that are proposed and justified by the manufacturer and approved by regulatory authorities…. Specifications are chosen to confirm the quality of the DS and DP rather than to establish full characterization, and should focus on those characteristics found to be useful in ensuring the safety and efficacy of the DS and DP.”



Too much?

Determining the right level of testing is not easy

- **Measure what you need to control**
- **Focus on both what you want and don’t want in your product**

Too little?

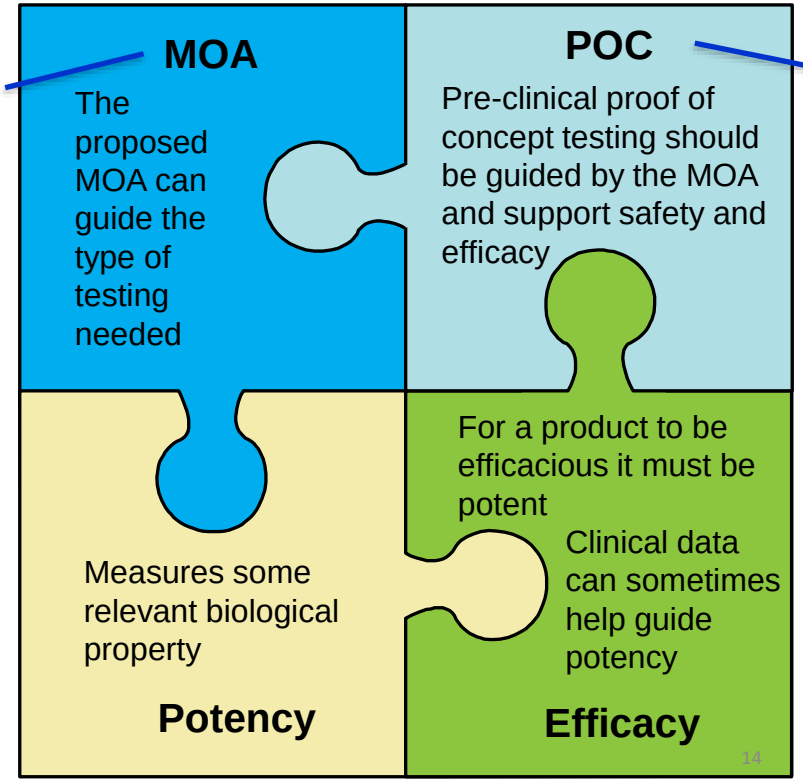
Common issues with choosing product release specifications

- Specifications not capturing key product attributes (critical quality attributes)
- Criteria inconsistent with manufacturing and/or clinical 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

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!

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

Challenge question #1

Which of the following *is not* true about cell therapy manufacturing controls?

A. Meaningful, sensitive potency assays are particularly challenging to develop
B. As long as a manufacturer uses “GMP grade” reagents, all regulatory concerns are addressed
C. Manufacturing and testing logistics can be very challenging
D. Cells are very sensitive to manufacturing conditions which offers advantages for product development, but also presents challenges to properly control manufacturing

Variability of patient-specific products

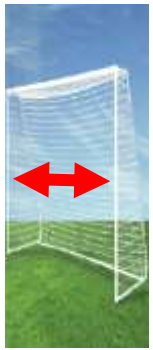
Patient-specific products might use source material from each individual patient, and every patient is different, therefore every lot will be unique - so variability is both expected and acceptable, right?

- **Variability inherent in the source material -** help control through appropriate acceptance criteria and reduce through process design
- **Variability contributed by the manufacturing process**:
  - Control through appropriate critical quality attribute and critical process parameters
  - Don’t just study the “average” product lot - evaluate whole product range

Impact of wide acceptance criteria

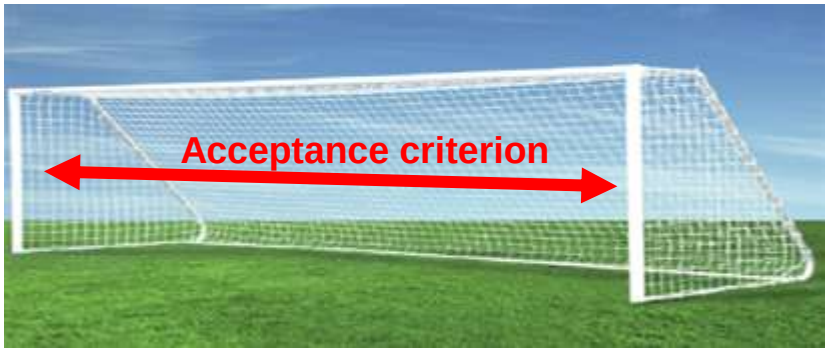
- There are advantages to targeting narrow versus wide tolerances for product release specifications
- Narrower tolerances make it easier to assess comparability

Narrow tolerances



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

Wide tolerances



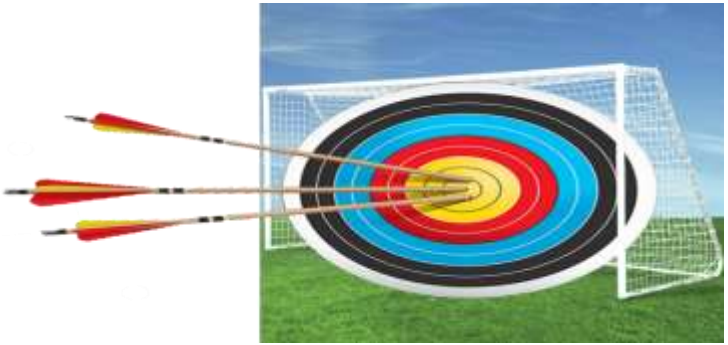
Difficult to rely on just lot release specifications to show consistency and comparability

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

Evaluating deviations and potential impact- a multistep analysis

Did the DS/DP meet minimum release criteria?

How did this lot compare with all historical lots?

How did this lot compare with historical lots with similar starting/intermediate properties?

Have there been other incidents and has there been a trend or drift in one direction or another?

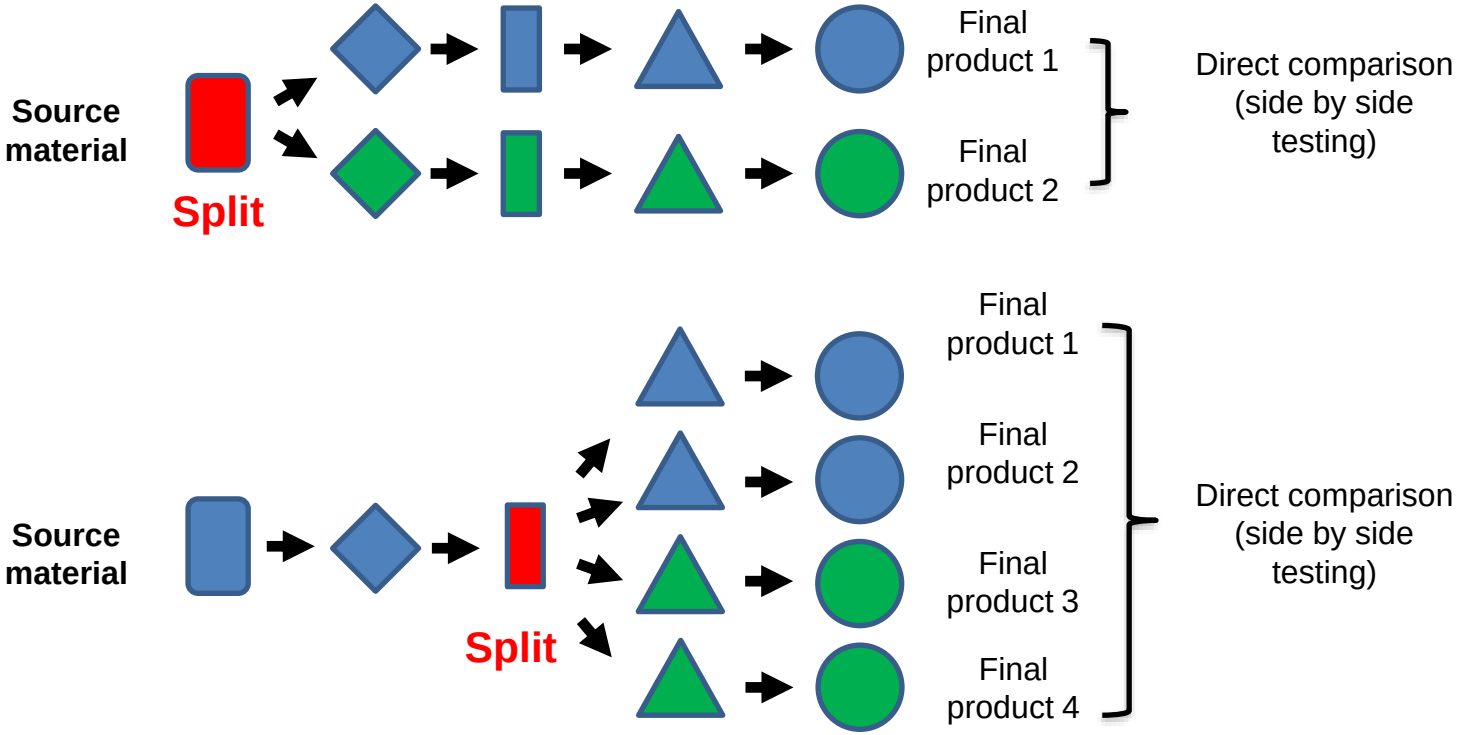
Especially important when you are making multiple lots at once, because a shift in quality could occur quickly

Your ability to demonstrate comparability will be limited by:

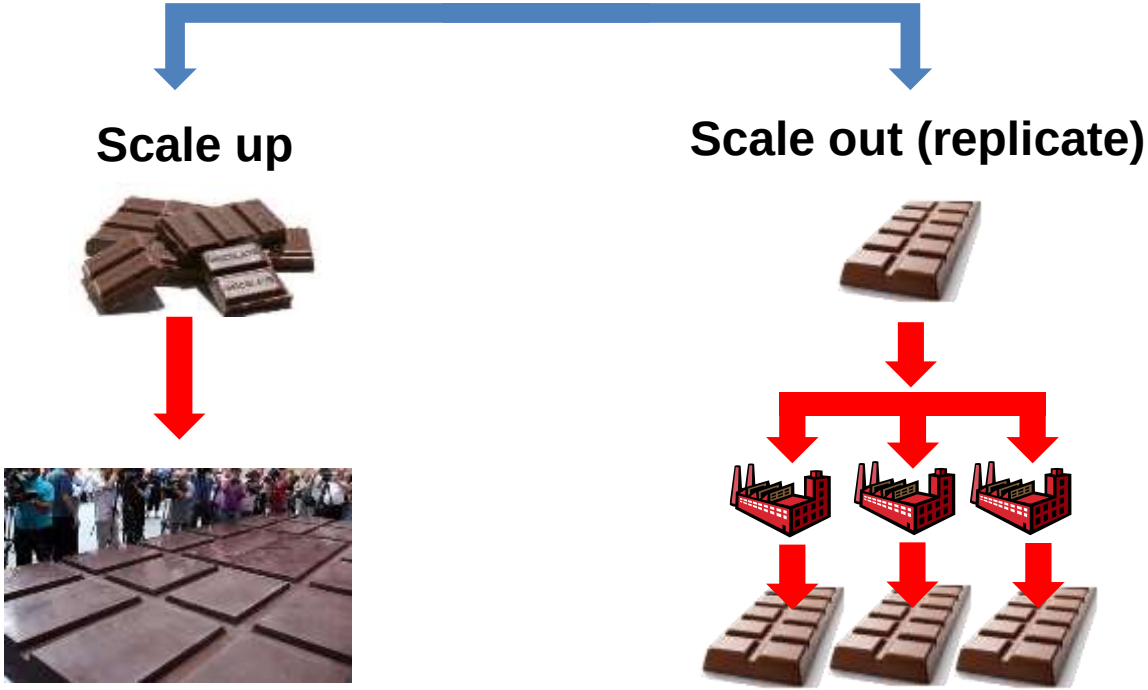
- Consistency of manufacturing process before the change
- Variability of your analytical methods
- Level of product characterization
- Knowledge of comparability margin:
  - Level of correlation of product attributes with clinical outcome
  - When clinical correlation is poor you'll have to justify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

Split manufacturing for comparability assessment

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



Different strategies to increase manufacturing scale



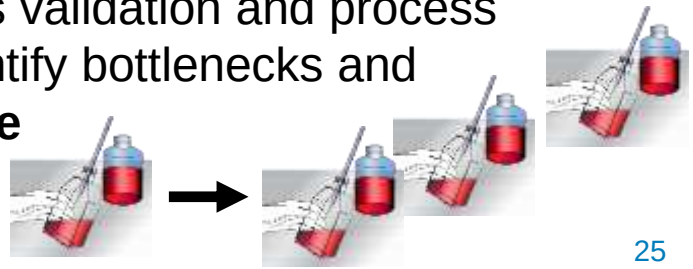
Scale-up considerations

- 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**



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.
- 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

Challenge question #2

Which of the following *best describes* comparability studies for cell therapy products:

A. Cell therapies are well characterized biologics and therefore easy to demonstrate comparability
B. Comparability study design is the same regardless of cell therapy product type
C. Comparability can be challenging when there is no correlation between product attributes and clinical outcome
D. Product variability for cell therapies is typically similar to recombinant proteins and other types of biologics

Summary

- Cell therapies have tremendous potential, but also present significant challenges to manufacturing and testing – these challenges vary by product type
- Quality and safety of materials used in manufacturing is very important
- 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
- Patient-specific products often involve careful coordination between the clinical site and manufacturing/testing/shipping: logistics can be challenging
- When scaling up/out you need to ensure quality is maintained
- Product development needs to keep pace with clinical development

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