Early Stage Manufacturing Considerations for Cell Therapy Products

CASSS
Cell & Gene Therapy Products
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Topics

- Common manufacturing concerns
  - Concerns that apply to most products
  - Specific challenges
- The importance of MOA, CQA, CPP, KPP, and TPP
- Product variability
- Overlooked issues in product development

Cell therapy and cell-based GT products are regulated as…

- Human Cell & Tissue Products (HCT/Ps)
  - 21 CFR 1271
- Biologics
  - 21 CFR 600's
- Drugs
  - 21 CFR Part 312 -Investigational New Drug (IND)
  - 21 CFR Parts 210/211 Current Good Manufacturing Practices
- Device regulations can apply in some cases, such as when a structural scaffold is used in combination with cells, or when an injection device is used
  - 21 CFR 800s

Cell & gene therapies encompass a wide spectrum of products, each with their 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

For Phase 1 the emphasis is on safety

- Preclinical animal studies should have been conducted using product manufactured like it will be used in the clinic
- Safety of source material, reagents, and processing
- Safety testing (sterility, endotoxin, mycoplasma, identity and purity, etc.)
- *In vitro* proof of concept data should support prospect of benefit (especially for pediatric products)
- Demonstrate the ability to manufacture the product
- Establish specifications to ensure minimum quality
- Should have preliminary shipping and stability data

Donor testing and screening for infectious agents

- Required for human cells, tissues, or cellular or tissue-based “351” products when source material is collected from allogeneic human donors (21 CFR 1271)
- CBER guidance documents provide additional detail on:
  - What infectious agents must be tested
  - When donors must be tested
  - How they are tested and the types of test kits
  - Where the testing must take place
- In addition to donor blood testing, donor screening (medical questionnaire) must be performed
- Donor eligibility screening and testing requirements often differ by country. For example, other countries may not be using:
  - FDA licensed test kits
  - CLIA certified lab
  - Performing all the nucleic acid and antibody-based testing required
- If using source material from non-US donors, we recommend you consult with FDA very early in product development for advice

Ancillary materials

Research grade reagents- packaging says "not for clinical use, for research purposes only"

- so it can't be used, right?

It can if properly qualified

Human-derived materials

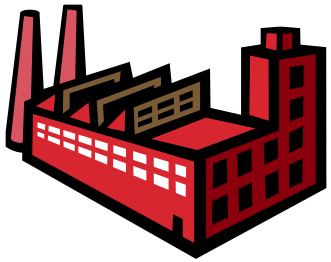
- Human serum albumin - need to use licensed products
- Autologous or pooled human serum- donor eligibility questions

Animal-derived materials

- Adventitious agents
- BSE/TSE issues for bovine products require attention to the country of origin and age of the herd
- "Serum-free" media does not always solve the problem

CGMP considerations

- For phase 1 there is more flexibility in how CGMPs compliance is achieved
- The suitability of a facility depends on the nature of the product – not all “state of the art facilities” are ideal for every product
- GMP may *“improve”* the product, but mostly it allows you to *control* product quality and safety, and to help ensure manufacturing consistency
- GMP cannot prevent manufacturing errors from happening, but can help ensure that controls are in place to catch them and take appropriate corrective actions



Terminology

- Mechanism Of Action (**MOA**) is your hypothesis about how you believe the product will work in the patient based on properties of the product
- Critical Quality Attribute (**CQA**) are a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to assure the desired product quality. (ICH Q8R2)
- Critical Process Parameter (**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 (ICH Q8R2)
- Key Process Parameter (**KPP)** are parameters of the manufacturing process that may not be directly linked to critical product quality attributes, but need to be tightly controlled to assure process consistency as it relates to product quality
- A Target Product Profile (**TPP)** is a format for a summary of a drug development program described in terms of labeling concepts

For early product development, work backwards

1

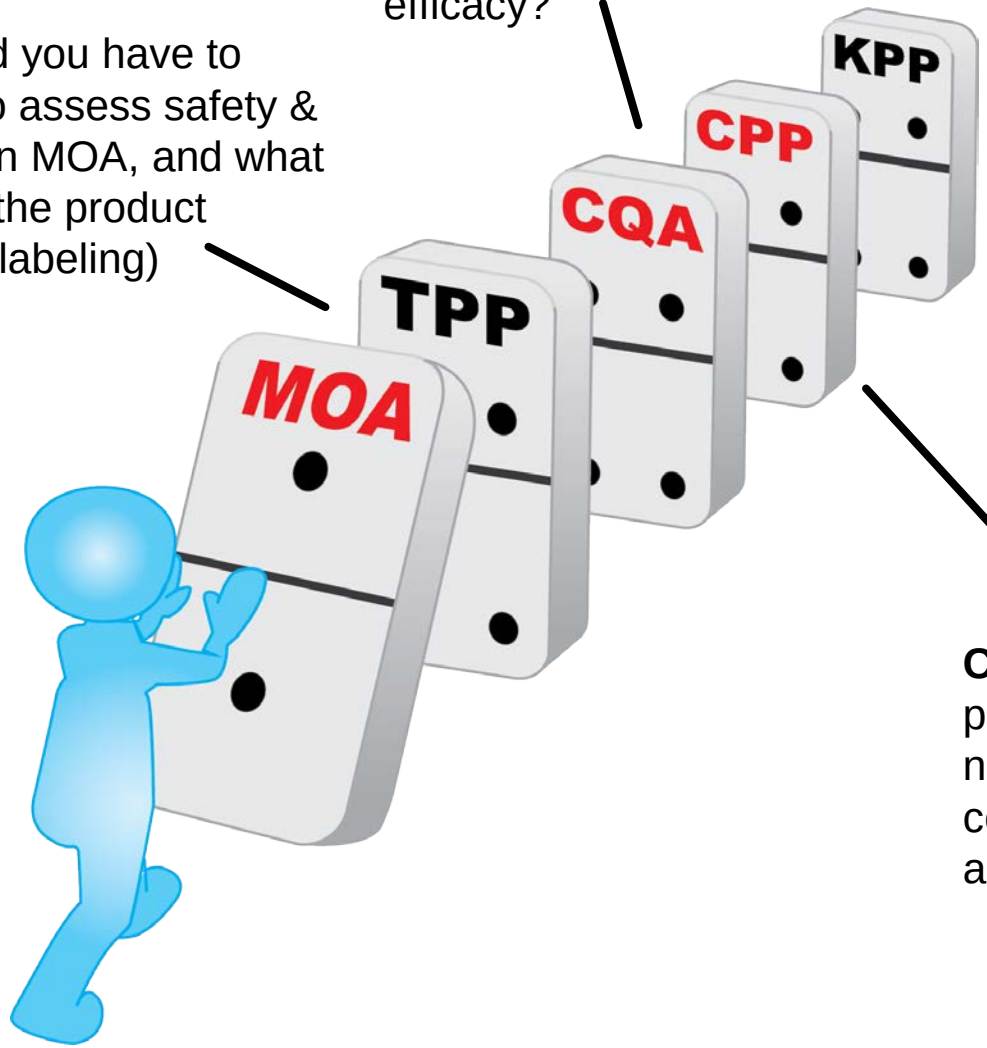
MOA – How is the product supposed to work in the patient?

2

TPP- what would you have to study clinically to assess safety & efficacy based on MOA, and what properties does the product need? (product labeling)

3

CQA – What critical properties do you need to control to achieve the desired safety and potential efficacy?



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CPP – What processes need to be controlled to achieve CQA?

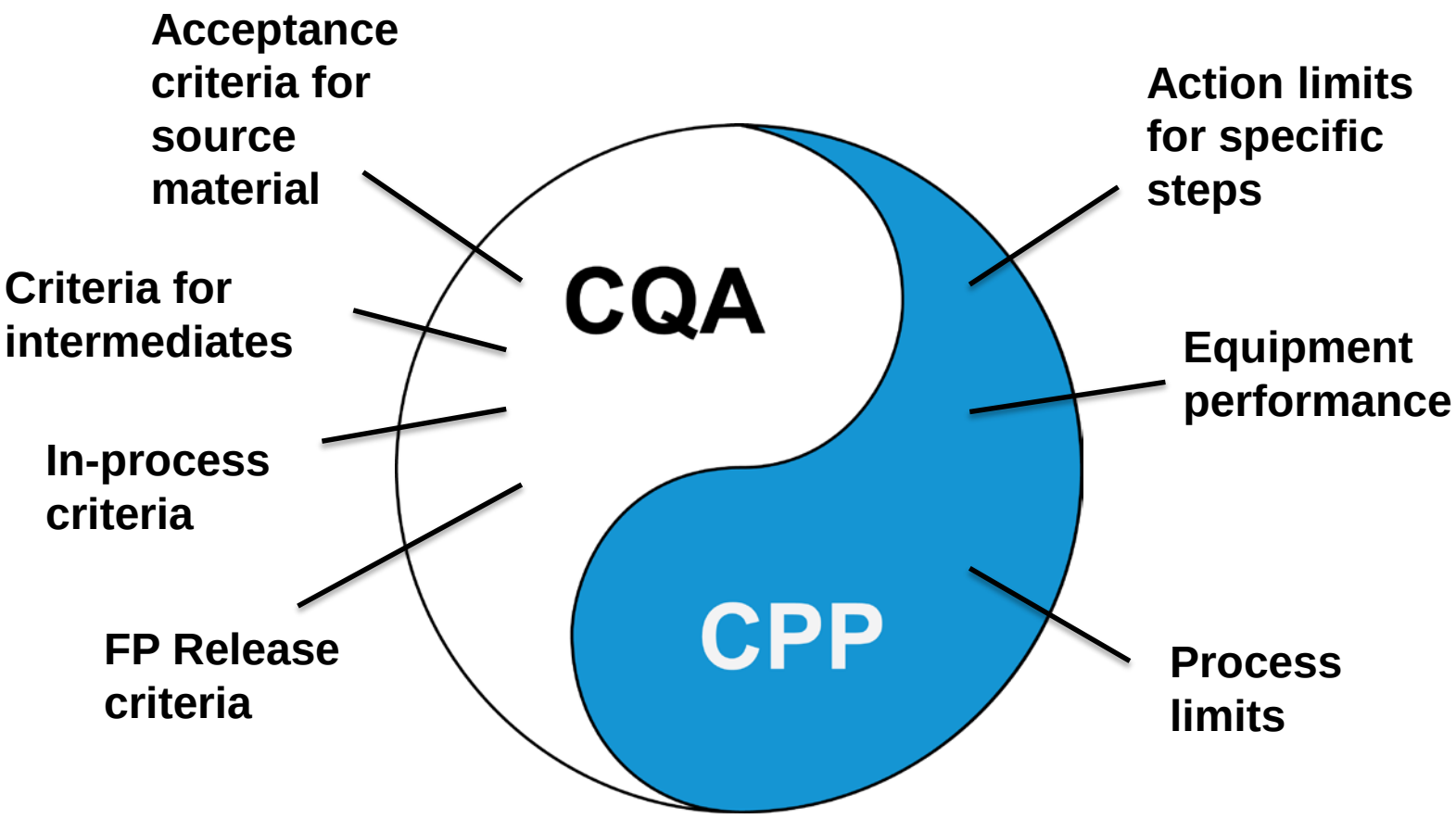
5

KPP– what controls do you need to achieve a consistent process?

Example: Stem cell-based product for the treatment of burns

MOA	The cellular product helps restore normal skin structure and function by facilitating tissue replacement and repair.
TPP	Clinical studies are intended to show improved skin structure through directly contributing keratinocytes and endothelial cells, and demonstrate safety by the lack of tumor formation
CQA	Stem cells have the ability to differentiate into keratinocytes and endothelial cells, and contain < X% undifferentiated cells
CPP	To generate sufficient numbers of keratinocytes and endothelial cells, need to culture in specific growth factor cocktail and feed every 3 days
KPP	Growth factor concentration range of 10-15 ng/ml results in product lots with similar levels of target cell populations

CQA and CPP are used together to help ensure quality and manufacturing consistency

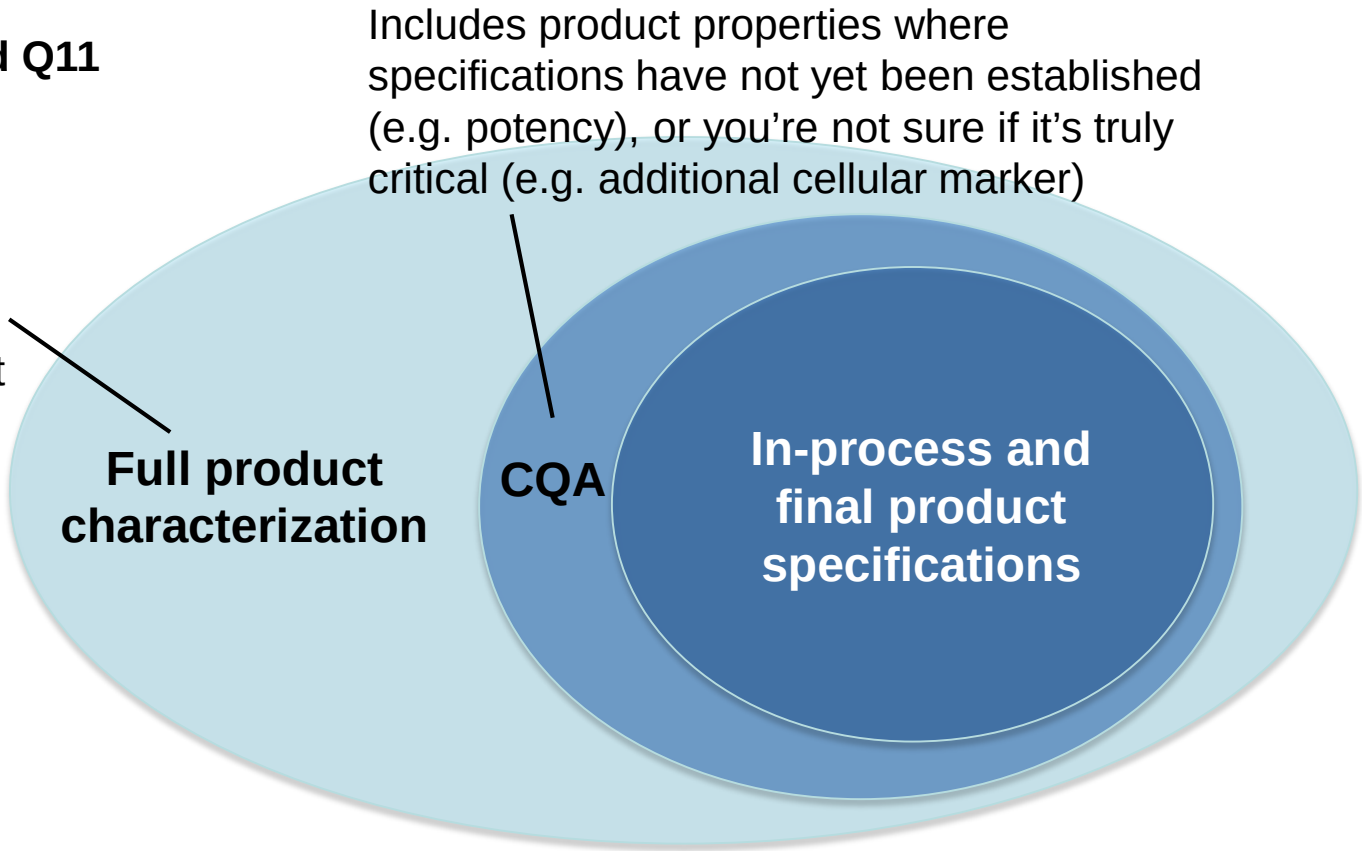


Process Parameters have boundaries within which a given process yields an expected result that is defined in terms of CQAs

Establishing specifications

"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."

- ICH Q6B and Q11



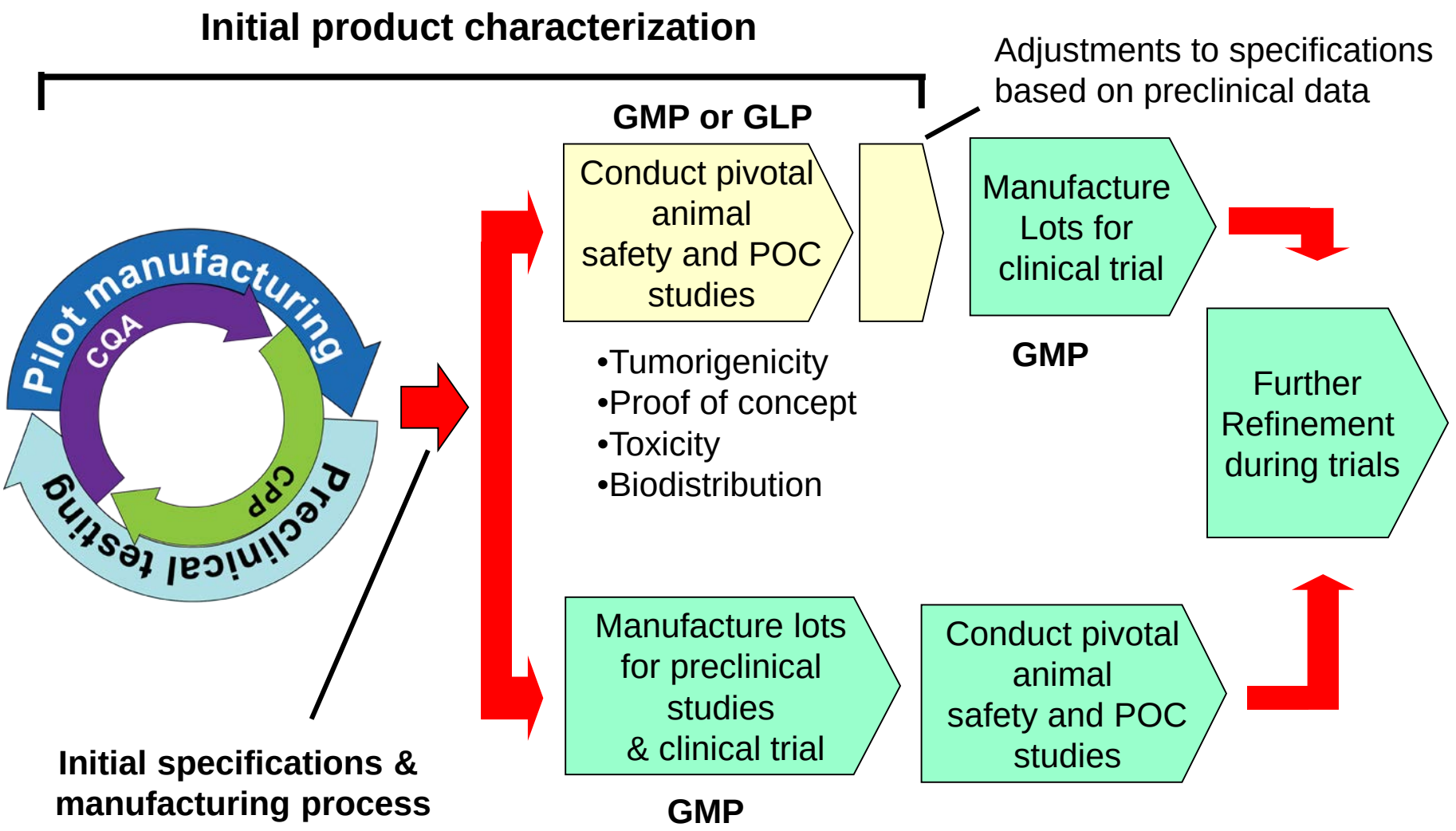
Lot release specifications are at the center of many manufacturing elements

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

Common issues with choosing 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

Typical early product development approach for CQA and CPP



CQA and CPP are not meant to be static- they should be continually evaluated and revised as needed

- 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 CPP and CQA

Carved in stone

Continually upgrading

- Changes to CQA could include either revising existing criteria, or adding or removing a specification (as supported by product characterization data)
- But since these have tremendous impact, revise cautiously!

Variability of patient-specific products

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

Yes and No

Every snowflake is unique, but are generated randomly based on the atmospheric conditions at the time. Your process should be defined, and your final product should be more predictable because your process should strive for consistency.

- Variability inherent in the source material- help control with appropriate acceptance criteria
- Variability contributed by the manufacturing process:
  - Control through appropriate CQA,CPP, KPPs
  - Don’t just study the “average” product lot- evaluate whole product range

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

Specifications as a goalpost

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

You should aim like this…

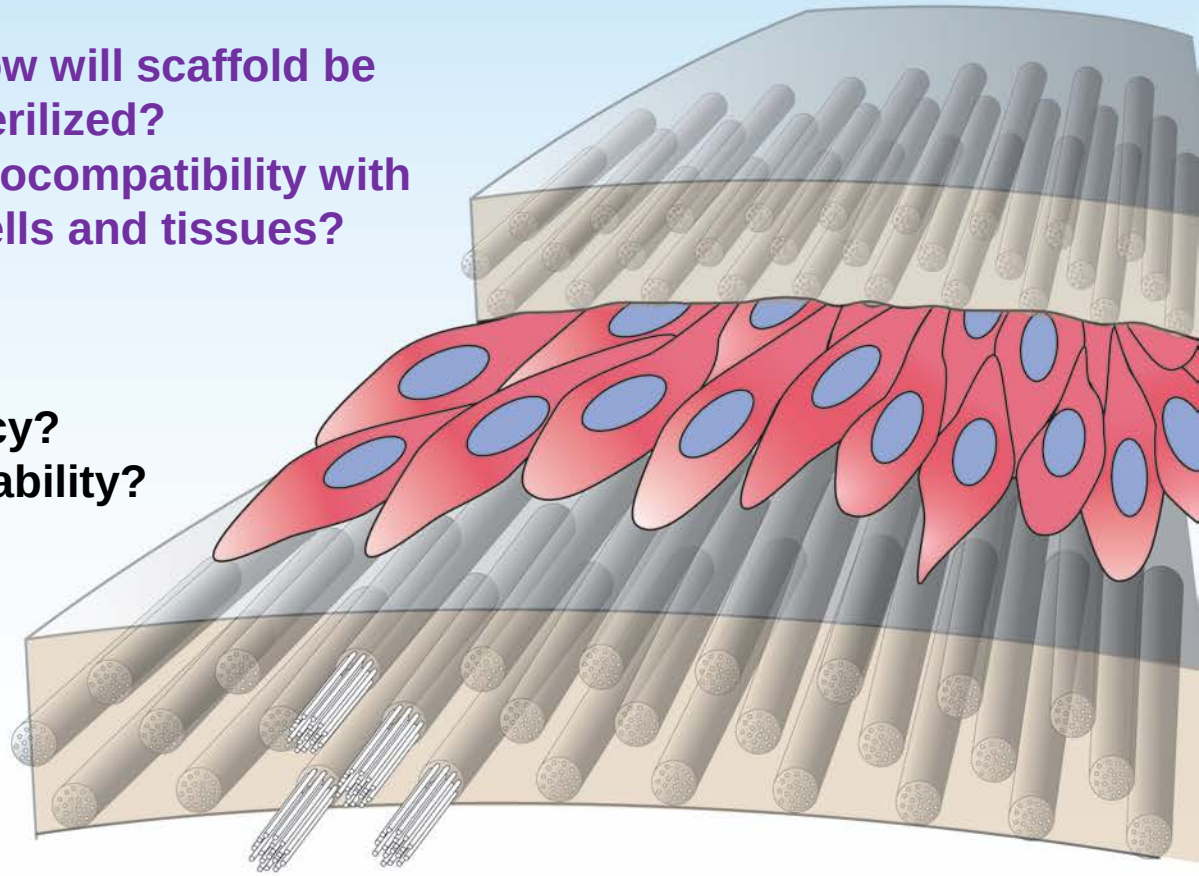
Not this…

What you end up with for a final product lot should reflect what you started with

Concerns for combined cell and scaffold products

Scaffold concerns:

- Physical strength and integrity?
- Impact of scaffold on cell phenotypes?
- How will scaffold be sterilized?
- Biocompatibility with cells and tissues?



Cell concerns:

- Level of product characterization?
- Impact of cells on properties of scaffold?
- Cell bank safety testing?
- Potency?
- Cell viability?

Combination concerns:

- Quality of materials?
- Residual reagents?
- Quality of manufacturing facility?
- Aseptic processing?
- How will the construct be tested?
- Uniformity?
- Reproducibility?
- How will it be shipped?
- Product stability?
- Handling at clinical site?

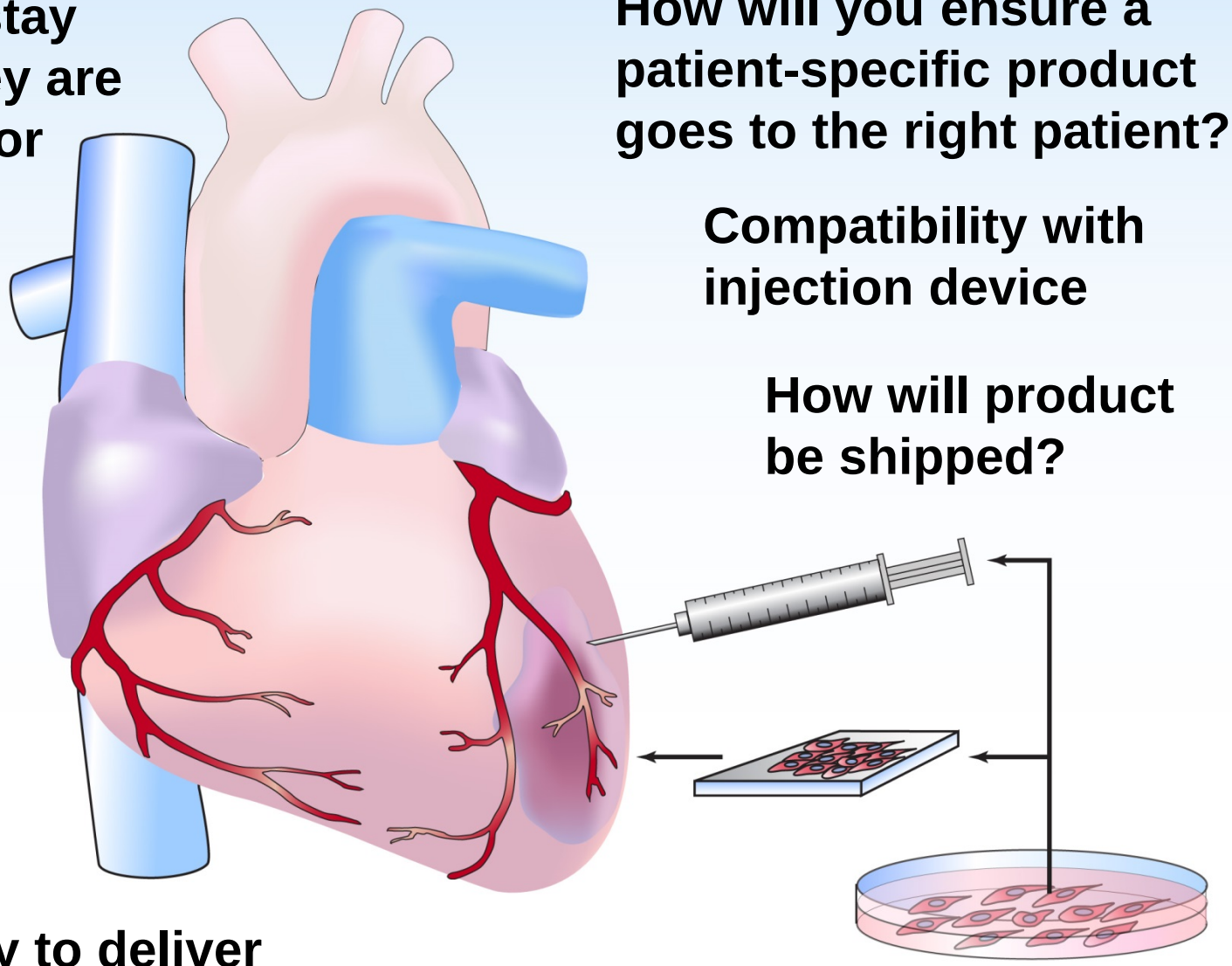
Product administration concerns

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

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

Compatibility with injection device

How will product be shipped?



Ability to deliver the intended dose

Product stability in the operating room

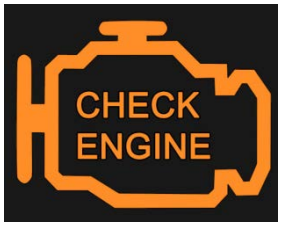
A little planning up front can help avoid problems later

Many review issues are easier to address earlier than later in the product lifecycle

Think ahead about:

- Suitability of methods or assays
- Increasing expectations with clinical phase
- What might be acceptable for an IND but not a BLA
- Temporary fix vs. long term manufacturing solution

Running clinical studies without adequate product characterization…



…is kind of like driving your car without a functioning check engine light- everything may be fine, but how do you know?

You don't want to end up stalled on the side of the road

And you don't want to find out at the end of your clinical trial that your product wasn't as high of quality and as consistent as you thought it was

Seeking advice from the FDA- how to maximize the productivity of meetings

- Make sure your meeting package has the relevant information needed- the advice given is based on the information you provide
- Ask *specific* questions
- Presentations: overview presentations are usually not needed, and the FDA will not comment on new data not previously provided
- There are limits on the number of formal meetings you are allowed, so use each meeting wisely
- The FDA is not a consulting firm and must be neutral, we therefore cannot:
  - Advise you which specific reagent, medical device, manufacturing equipment, or method you should use
  - Design your protocols or studies for you – we can only tell you what is and is not acceptable

Take home messages

- Some risks are common to all cell and gene therapies (e.g., ancillary materials, facilities, aseptic processing, etc.), whereas other are more unique to certain types of products (autologous lots versus large cell banks)
- Think carefully about what you are expecting clinically of your product and work backwards
- Risk assessment is easier to evaluate and risk management easier to achieve if your product is well characterized and your manufacturing process is well understood
- It is generally easier and less risky to make changes early in product development than later
- CQA, CPP, and specifications should be continually evaluated and revised as needed
- Think beyond manufacturing to logistics, how products will be shipped, stored, and handled at clinical sites

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