Comparability for Advanced Therapy Medicinal Products

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Introduction

- Taster for the preconference workshop
- Hypothetical case study to illustrate the principles
- Common mistakes in comparability studies
- Conclusions

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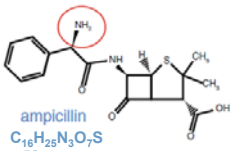
Biologicals are Complex

Grampp and Ramanan 2013 DOI 10.1007/s40259-013-0018-5

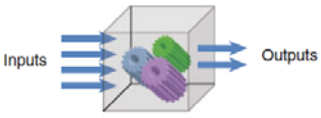
b Chemically synthesized drug
Defined process-structure-function

- Complete knowledge of chemistry and physics



ampicillin
$C_{16}H_{25}N_3O_7S$
52 atoms

- Knowledge and measurement of all relevant inputs and outputs

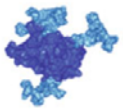


- One, defined active ingredient linked unambiguously via its identity to the safety and efficacy (S&E) profile

Chemical Process → Defined Structure → Function (Defined S&E)

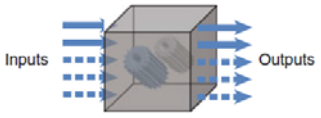
c Biologic
Correlated process-structure-function

- Partial knowledge of biology and chemistry



Erythropoietin
>4000 atoms

- Impossible to identify or measure all inputs and outputs



- Heterogeneous, partially defined active ingredient correlated to the safety and efficacy profile – contingent on process consistency

Biological Process → Complex Structure → Function

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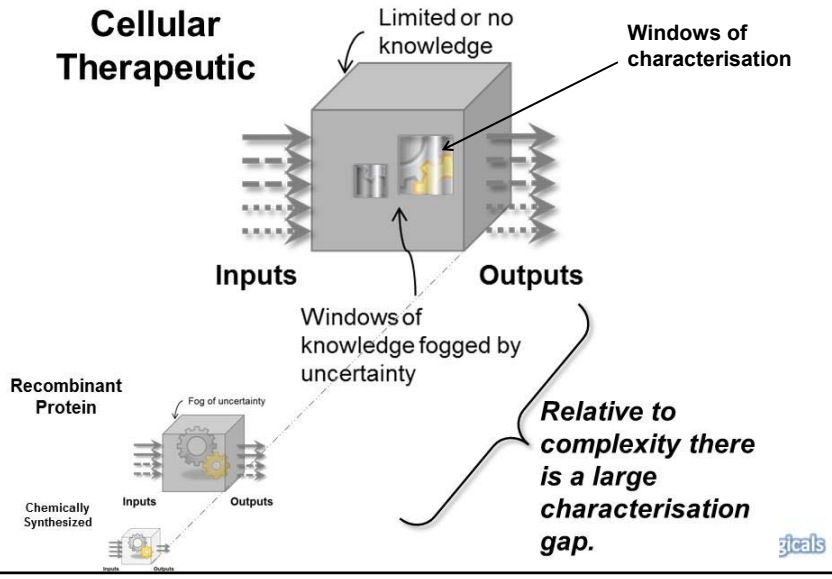
Cell Therapy Products even more so



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Comparability is more difficult for cell-based products

- The structure of a cell (cellular active substance) cannot be determined
  - Only small parts of the structure can be determined
  - In figure: *windows of characterisation*
- Furthermore, cells are heterogeneous populations
  - Have to compare patterns of gene/protein expression (similar to glycosylation patterns for therapeutic glycoproteins)
  - In figure: *fogged by uncertainty*

These bring considerable uncertainty when assessing comparability

The Need for Change

There are many reasons why changes are required:

- During development:
  - Transfer of research process to GMP
  - Materials changes
  - Process improvements
  - Change in presentation (e.g. fresh to frozen)
- Once on the market:
  - Materials changes
  - Process improvements
  - To comply with changing regulatory requirements
  - Scale up/out
  - Manufacturing site changes

What is Comparability?

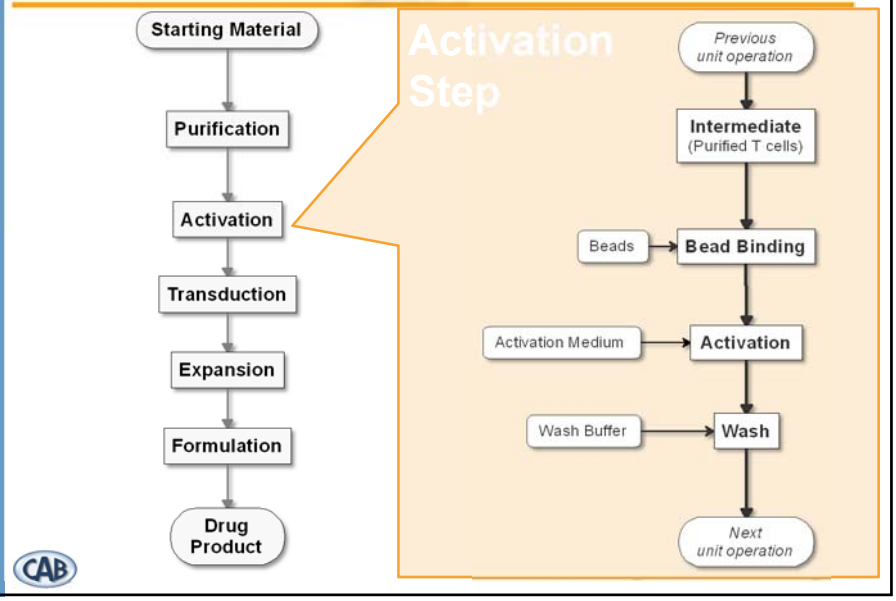
Hypothetical Case Study:
CAR-T

- This case study is completely fictitious
- The arguments for various testing are also fictitious
  - It's the general approach that is being discussed
- Please remember this and allow some artistic license.
- This case study assumes development is complete
  - Late development (note: major changes not recommended mid-clinical study); or
  - Post-approval

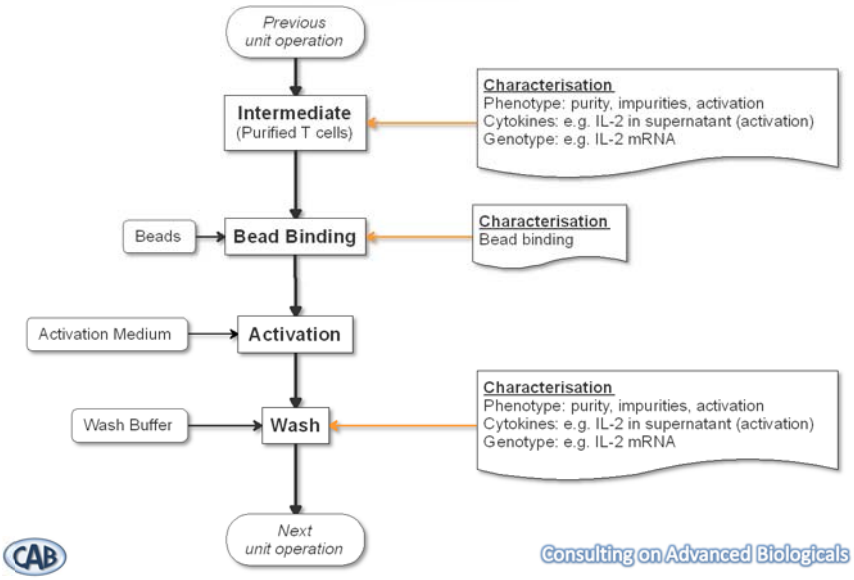
Hypothetical Case Study:
Overview

- To explain comparability;
  - Need to start with characterisation
    - cQA/QA of intermediates in process
    - Process control
      - Process parameters (cPP/PP)
      - In-process testing (critical and non-critical)
  - How characterisation leads to final process control strategy
  - Example process change
    - Objective of the comparability study
    - Take home messages

Hypothetical Case Study:
CAR-T



Characterisation of Unit Operations: Intermediates



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Characterisation of Unit Operations: Intermediates

Alternative Method (Measure receptor instead of ligand)

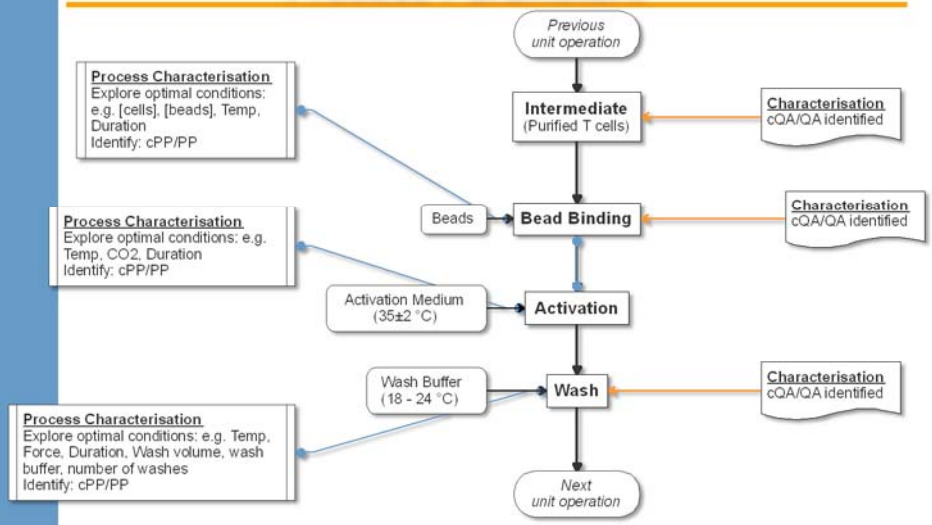
Orthogonal Methods (different measurement principle)

Analyte	Measurand	Purpose
Flow Cytometry		
FL1 - CD45	% CD45+CD3+	Purity, T cells
FL2 - CD3	% CD45+CD3+CD25+	Purity, Activated T cells
FL3 - CD25	% CD45-	Impurity, Non-leukocytes
	% CD45+CD3-	Impurity, Non-T cell
	% CD45+CD3+CD25-	Impuirty, Non-activated T cells
FL1 - CD45	% CD45+CD3+	Purity, T cells
FL2 - CD3	% CD45+CD3+IL-2+	Purity, Activated T cells
FL3 - IL-2*	% CD45+CD3+IL-2-	Impuirty, Non-activated T cells
*intracellular staining		
CDx etc.	*Various combinations*	*Other phenotypes of interest*
ELISA		
IL-2	[IL-2] /mL	Activation marker
Other Cytokine/s	*[cytokine] /mL*	*Activation or other marker*
qPCR		
IL-2 mRNA	Copies IL-2 mRNA /10^5 cells	Activation marker
Others	*Copies mRNA /10^5 cells*	*Other gene markers of activation*

Characterisation of intermediates:
Learning Points

- Characterisation aims to identify the critical and other quality attributes (cQA/QA) of the intermediates
  - These are needed to;
    - Characterise the critical and other process parameters (cPP/PP)
    - Justify any in process controls (3.2.S.2.4)
- Characterisation should employ multiple methods for each QA
  - Orthogonal methods
  - Alternative methods

Characterisation of Unit Operations:
Process Parameters

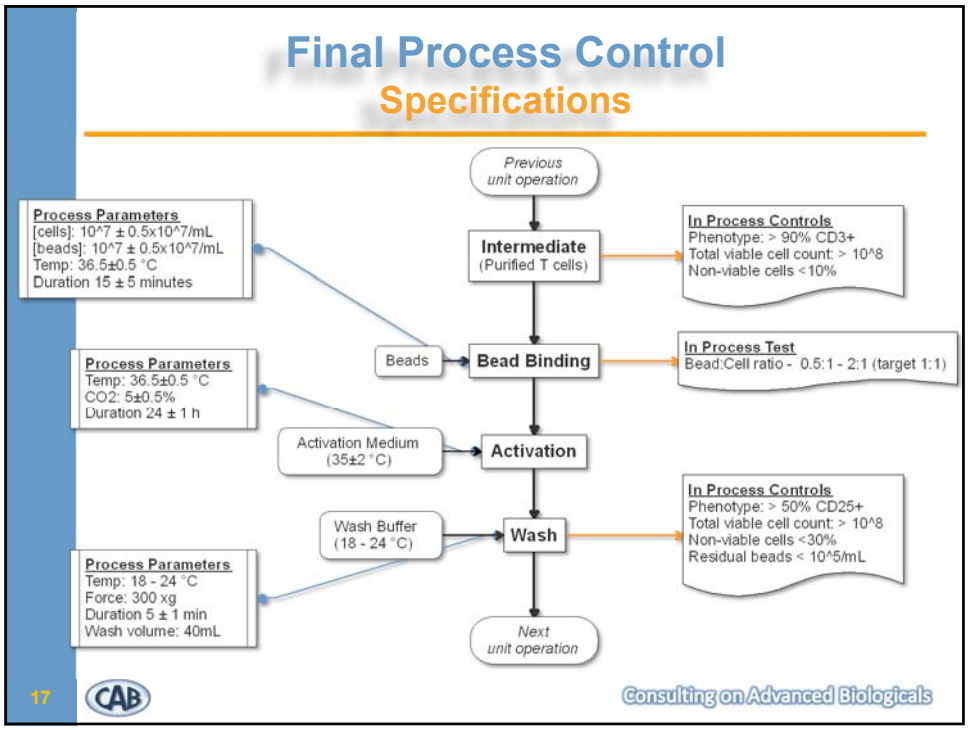


Characterisation of Process:
Learning Points

- Characterisation aims to confirm the critical and other process parameters (cPP/PP)
  - Understand the criticality of the PP
  - Define the normal operating ranges (NOR)
    - In 3.2.S.2.2 Description of manufacturing process and controls (text and process flow diagram)
  - May include action limits
- These data will be used (+other data) to:
  - Justify the operational ranges for these process parameters
    - In 3.2.S.2.4 Controls of critical steps and intermediates.

Process Control:
Considerations

- Process Parameters **control** the unit operation
  - Need to define an operational range
- In process controls (critical) do not as such control anything
  - They largely confirm a unit operation was successful
  - Or confirm absence of contaminants, e.g. sterility.
- Additional in process testing (non-critical) can be useful for process performance monitoring


Final Process Control
Specifications
Previous unit operation
Process Parameters
[cells]: 10^7 ± 0.5x10^7/mL
[beads]: 10^7 ± 0.5x10^7/mL
Temp: 36.5±0.5 °C
Duration 15 ± 5 minutes
Intermediate
(Purified T cells)
In Process Controls
Phenotype: > 90% CD3+
Total viable cell count: > 10^8
Non-viable cells <10%
Process Parameters
Temp: 36.5±0.5 °C
CO2: 5±0.5%
Duration 24 ± 1 h
Beads
Bead Binding
In Process Test
Bead:Cell ratio - 0.5:1 - 2:1 (target 1:1)
Activation Medium
(35±2 °C)
Activation
Wash Buffer
(18 - 24 °C)
Wash
In Process Controls
Phenotype: > 50% CD25+
Total viable cell count: > 10^8
Non-viable cells <30%
Residual beads < 10^5/mL
Process Parameters
Temp: 18 - 24 °C
Force: 300 xg
Duration 5 ± 1 min
Wash volume: 40mL
Next unit operation
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CAB
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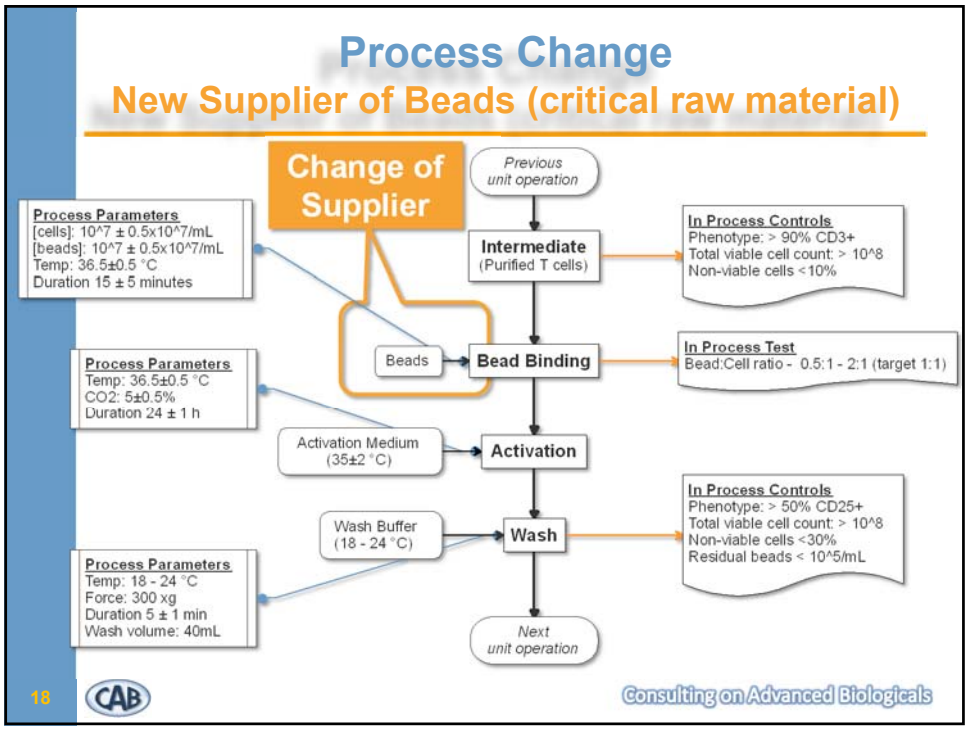
Process Change
New Supplier of Beads (critical raw material)
Change of Supplier
Previous unit operation
Process Parameters
[cells]: 10^7 ± 0.5x10^7/mL
[beads]: 10^7 ± 0.5x10^7/mL
Temp: 36.5±0.5 °C
Duration 15 ± 5 minutes
Intermediate
(Purified T cells)
In Process Controls
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In Process Controls
Phenotype: > 50% CD25+
Total viable cell count: > 10^8
Non-viable cells <30%
Residual beads < 10^5/mL
Process Parameters
Temp: 18 - 24 °C
Force: 300 xg
Duration 5 ± 1 min
Wash volume: 40mL
Next unit operation
18
CAB
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Comparability Exercise:
Considerations

- The extent of characterisation depends on the change and its *potential* to alter the quality and therefore safety and/or efficacy of the product.
  - Extended characterisation based on process knowledge
- Pilot studies confirm change is possible and establish any necessary changes to the process parameters
  - e.g. bead:cell ratio, duration of activation etc.
- The comparability study should then **aim to actively look for differences**
  - Extended characterisation (orthogonal and alternative methods)
  - Methods sensitive to change (consider stability methods)

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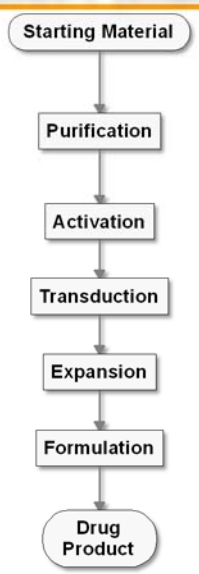
Hypothetical Case Study:
CAR-T (change at activation step)



Routine Methods

Routine Methods
+ Extended Characterisation

Routine Methods
+ Extended Characterisation
Where change impacts

Routine Methods
+ Extended Characterisation

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Comparability Exercise:
Considerations

- The protocol should predefine the acceptance criteria for comparability
  - Considering each attribute tested
- Comparability normally **includes stability**
- You are trying to demonstrate the change doesn't alter the product, so try and eliminate all controllable sources of variability
  - Same starting material (donor)
  - Same raw materials (for critical raw materials the same batch might be important)
  - Test samples together if necessary (e.g. bioassays such as potency)

Specifications:
Learning Points

- **Specifications are a sub-set of what is required to fully characterise**
  - the starting/raw materials, intermediates, drug substance (where declared), drug product and process.
- They are demonstrated through process qualification/validation to be sufficient to confirm the quality of the product from;
  - A specific manufacturing process
  - A specific facility and equipment
  - Using specific starting/raw materials
- Any change to this requires re-characterisation
  - Use of both routine and extended characterisation
  - = Comparability exercise

Common Mistakes with Comparability
Comparability is NOT these

COMPARABILITY IS NOT:

- Meeting existing specifications
  - Because these are a subset of those needed to fully characterise
  - The routine analytical method may not be sensitive to small changes
  - Not all QA that could alter will be routinely tested
- Comparison to historic batches
  - These undergo routine release testing only
    - Essentially the same as meeting specifications
  - Unless these were fully characterised

Concluding Comparability
Considerations #1

- Comparability is determined from the '**totality of the data**'
- Do not conclude attribute by attribute that each are comparable
  - Just present data and any statistical analysis
  - At most, "no significant difference" or "highly similar"
  - Conclude at end based on all available data and other considerations.

Concluding Comparability
Considerations #2

- Differences may be considered comparable if they can be concluded to have **no significant impact on safety and efficacy**
- Improved safety, e.g. reduced impurities, while different can usually be considered comparable.
- Increased or decreased potency cannot normally be considered comparable.
  - Depends on reliability of the potency assay/s
    - Routine release assay may be a surrogate assay
    - Extended characterisation should include additional potency methods.
  - May need nonclinical and/or clinical data to confirm.

Conclusions

- Plan well
- Comparability cannot be demonstrated in most cases by release specifications alone
- Extended characterisation – orthogonal/additional methods and additional samples (dependent on nature of change)
- Remember that stability is part of comparability
- Non-clinical and even clinical may be needed for major changes
  - e.g. where quality identifies a change but cannot rule out an impact on safety and/or efficacy.