
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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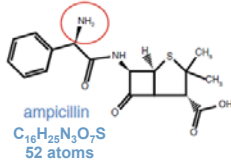
Biologicals are Complex

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

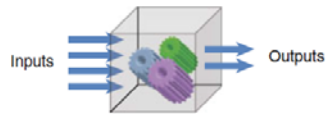
b Chemically synthesized drug

Defined process-structure-function

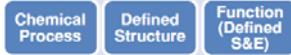
- Complete knowledge of chemistry and physics



- 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



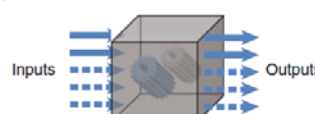
c Biologic

Correlated process-structure-function

- Partial knowledge of biology and chemistry



- Impossible to identify or measure all inputs and outputs



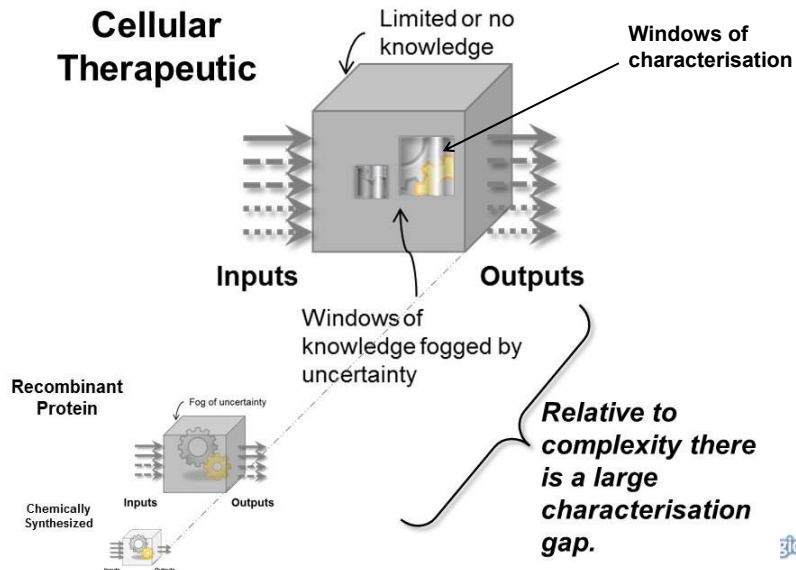
- Heterogeneous, partially defined active ingredient correlated to the safety and efficacy profile – contingent on process consistency



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Cell Therapy Products even more so

Cellular Therapeutic



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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

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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

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What is Comparability?

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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

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Hypothetical Case Study: Overview

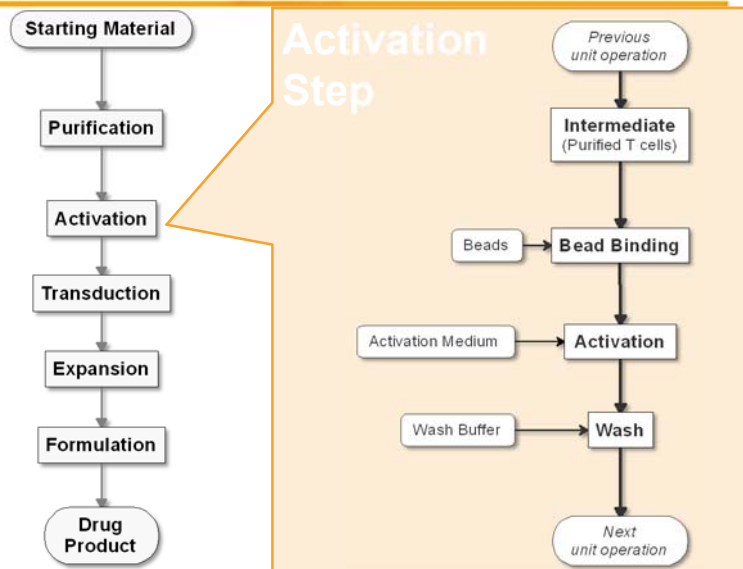
- To explain comparability;
 - Need to start with characterisation
 - cQA/QA of intermediates in process
 - Process control
 - Process parameters (cPP/PP)
 - In-process testing (critical and non-critical)
 - How characterisation leads to final process control strategy
 - Example process change
 - Objective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

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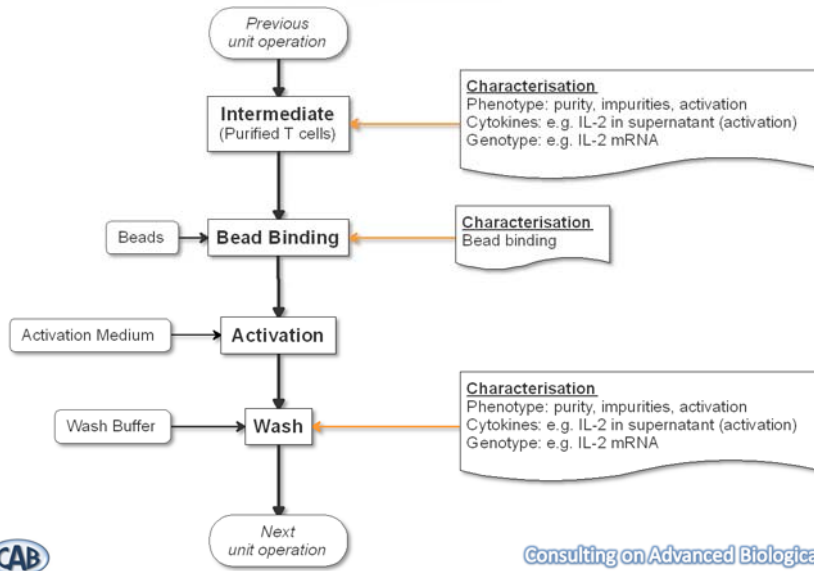
Hypothetical Case Study: CAR-T



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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-	Impurity, 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-	Impurity, 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

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Characterisation of intermediates: Learning Points

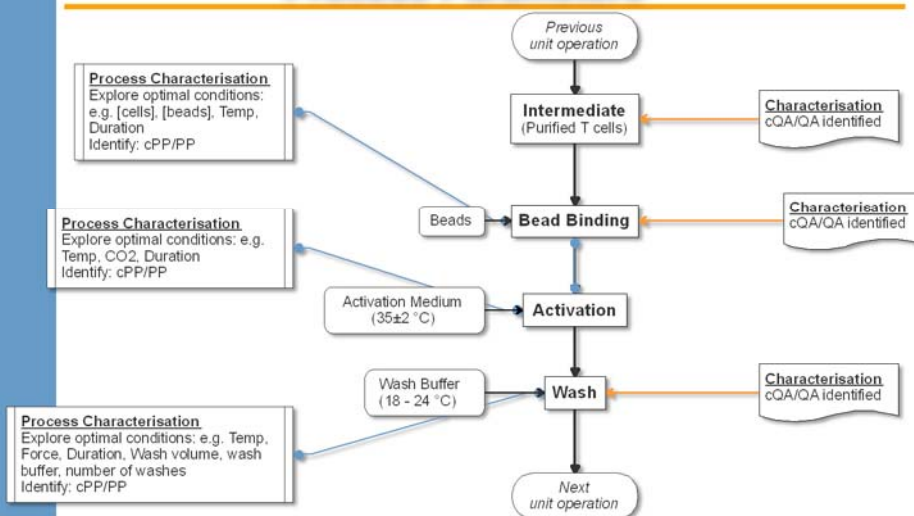
- Characterisation aims to identify the critical and other quality attributes (cQA/QA) of the intermediates
 - These are needed to;
 - Characterise the critical and other process parameters (cPP/PP)
 - Justify any in process controls (3.2.S.2.4)
- Characterisation should employ multiple methods for each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

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Characterisation of Unit Operations: Process Parameters



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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](#).

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Process Control: Considerations

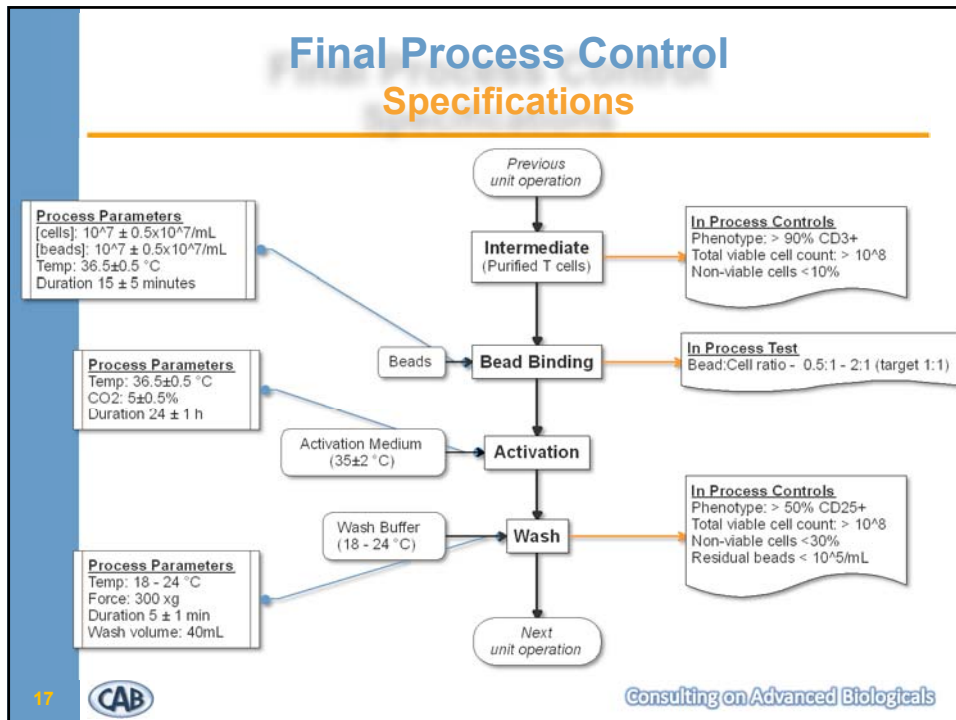
- Process Parameters **control** the unit operation
 - Need to define an operational range
- In process controls (critical) do not as such control anything
 - They largely confirm a unit operation was successful
 - Or confirm absence of contaminants, e.g. sterility.
- Additional in process testing (non-critical)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

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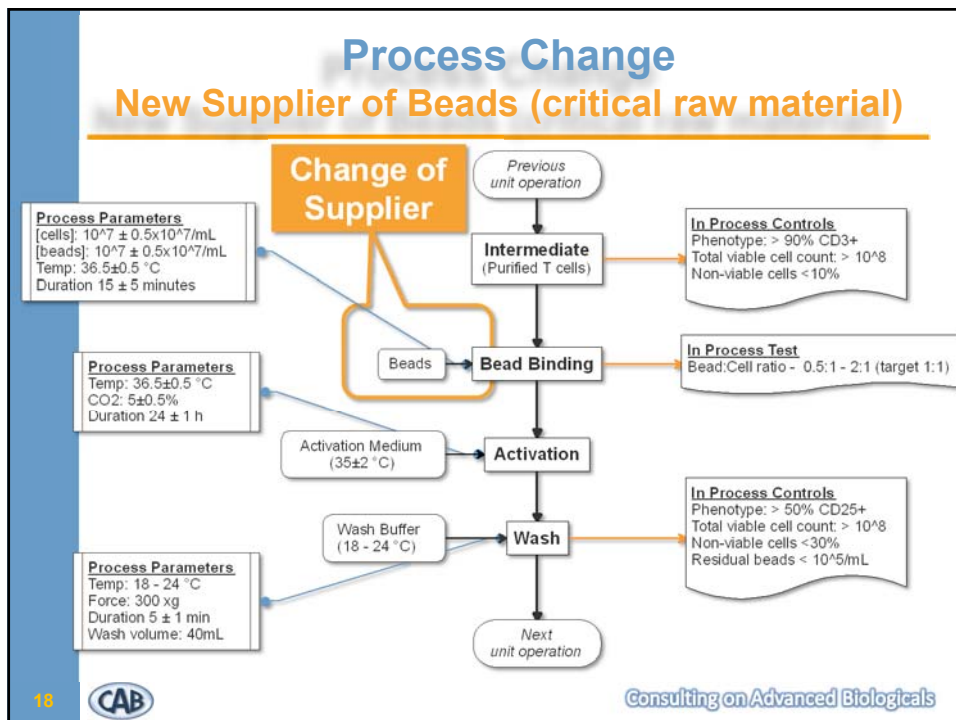


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Final Process Control Specifications



Process Change New Supplier of Beads (critical raw material)



Comparability Exercise: Considerations

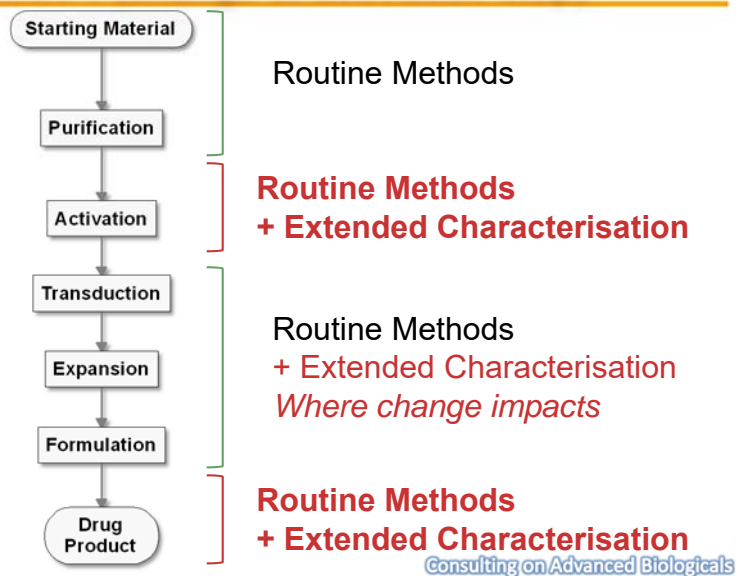
- The extent of characterisation depends on the change and its *potential* to alter the quality and therefore safety and/or efficacy of the product.
 - Extended characterisation based on process knowledge
- Pilot studies confirm change is possible and establish any necessary changes to the process parameters
 - 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)



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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)

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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

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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

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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.

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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.

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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.

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