Comparability: Managing Process Changes

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Introduction

- Why comparability is difficult
  - What we are trying to achieve
  - Why cells make this less certain
- Common mistakes in comparability studies
  - Why they need to be so thorough
- Conclusions

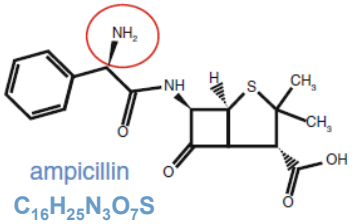
Biologicals are Complex

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

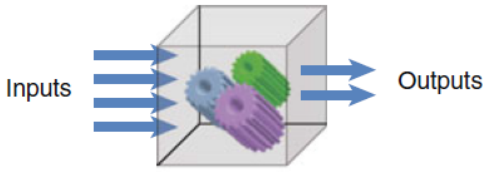


ampicillin

$C_{16}H_{25}N_3O_7S$

52 atoms

- Knowledge and measurement of all relevant inputs and outputs



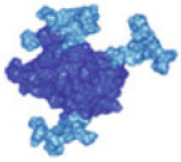
- One, defined active ingredient linked unambiguously via its identity to the safety and efficacy (S&E) profile

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

c Biologic

Correlated process-structure-function

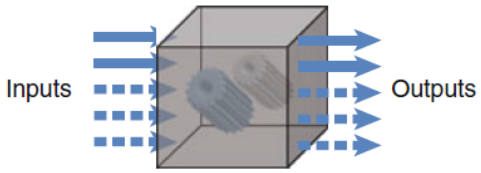
- Partial knowledge of biology and chemistry



Erythropoietin

>4000 atoms

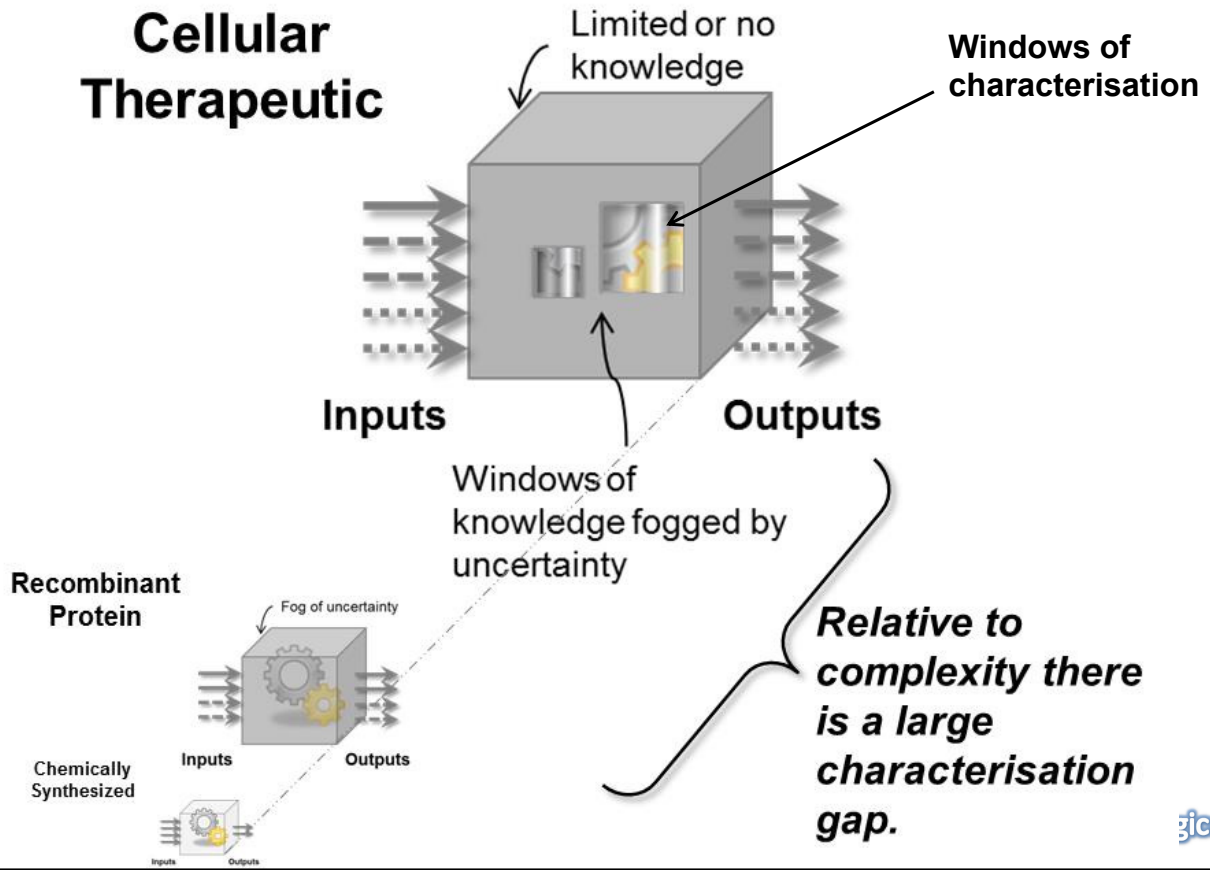
- Impossible to identify or measure all inputs and outputs



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

Biological Process → Complex Structure → Function

Cell Therapy Products even more so



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

Identifying critical quality attributes (CQA) is uncertain

- Full knowledge of the structure and function of a cell will not be known
- Mechanism/s of action (MoA) will be uncertain
  - MoA is also dependent on the disease to be treated
  - Disease mechanism/s will not be fully understood
- Identified/claimed CQA are therefore (at best) educated/informed guesses.
  - They may not be CQA
  - You may never be certain

These bring considerable uncertainty when assessing comparability

Likely most important methods for comparability

Given the structure cannot be fully determined:

- Methods that measure cell functions
  - Related to (assumed) MoA
  - One or more of which will be considered 'potency' assays
  - Can be in vitro
  - Can be in vivo (many limitations, but can be reassuring)
- Don't forget stability (reconfirmation) is an important part of comparability

The Need for Change

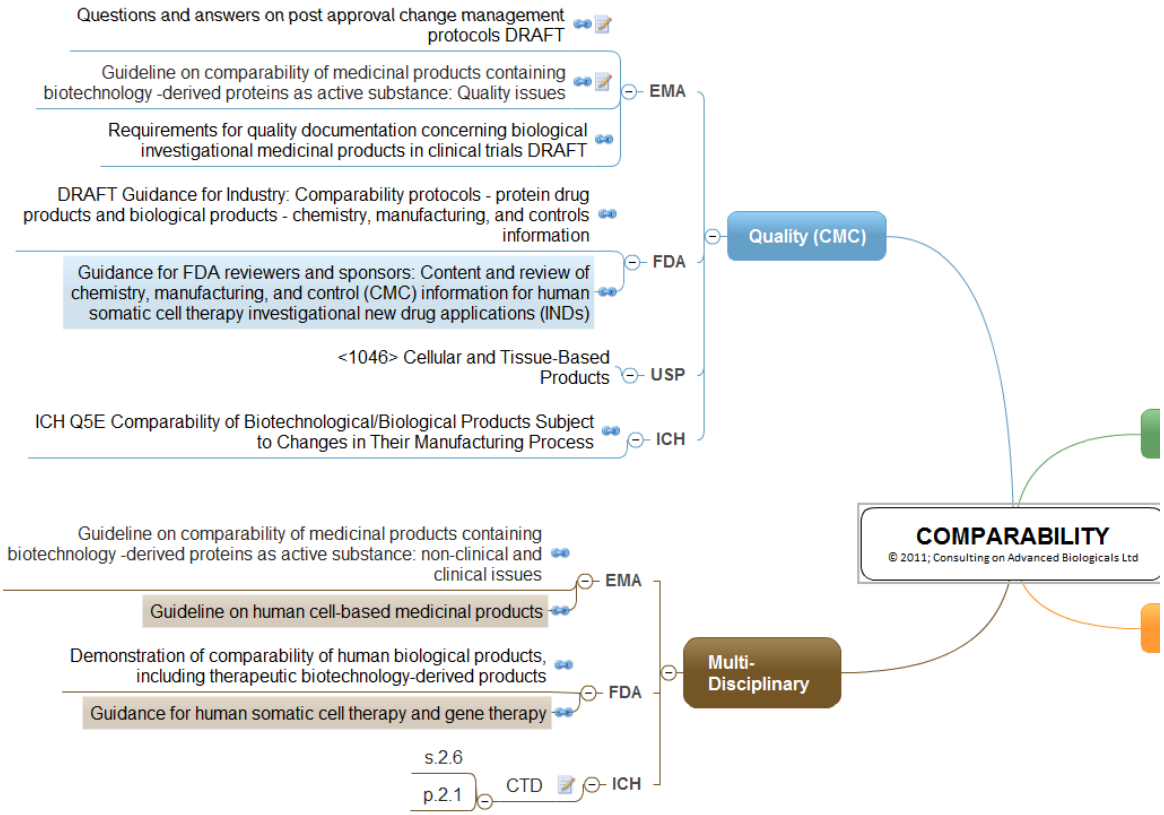
There are many reasons why changes are required:

- 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

The need to plan
Or: *More easily said than done*

- Major changes will bring major risks because of the uncertainties identified.
- Early planning
  - Target Product Profile (TPP)
- Think ahead to commercial process
- Plan to avoid major changes as far as possible
  - But they almost certainly will happen at some point.

Comparability Guidelines



http://advbiols.com/documents/Comparabilityguidance1110.swf

Common Mistakes with Comparability

Meeting Current Specifications is NOT Sufficient!

- Characterisation of the product and process identifies test methods that are useful as IPC/release specifications.
  - Some of these will hopefully be CQA
- Manufacturing experience (and other factors) are used to set specifications for a stable qualified process.
- Changing that process means the validity of these specifications needs to be reconfirmed.
  - Include ‘extended characterisation’.
    - Additional methods
    - Additional samples

Extended Characterisation

- All analytical methods have limitations, utilise orthogonal methods (different measurement principle) to confirm validity of routine method result:
  - ELISA measures total protein (mass/vol), it does not confirm the protein is biologically active
  - Use a bioassay for protein activity (units /vol or mass)
- Other characteristics (not routinely tested):
  - Routine method: Trypan blue
  - Orthogonal: nuclear stain such as DAPI or PI, metabolic dye (e.g. trizolium salts)
  - Expanded method: apoptosis/cell cycle (PI/DAPI) or Annexin V (apoptosis).

Comparability Protocol: Comparability of Product (only)

- Manufacturing objective = product consistency
  - but product cannot be fully defined
- Evaluation of the product only may not identify changes that impact quality, safety, efficacy.
  - uncertainty in identifying CQA
- Differences in the changed step (and beyond) may alert you to likely changes in product
  - i.e. equivalence of pre/post-changed manufacturing step/s
    - do they achieve the same outcome?

Comparability Protocol: Comparability of manufacturing step

- Need to consider the impact of the change on the step
  - Step may need re-optimisation
  - Step may improve e.g. yield/purity
    - impact on next step (e.g. yield change)
    - Knock-on impact throughout process
  - May need to spike-in impurity to check capacity of a new purification step;
    - e.g. ability of wash step to remove impurity (especially where safety concern) when switching from manual to automated washing.

Minimise all controllable sources of variability

- Unchanged materials – not just same supplier but where complex materials (e.g. serum, growth factors) the same batch (Lot) of material.
- Where possible run the old and new head-to-head; e.g.
  - Donor 1, split biopsy and run half through each process; or vials from same WCB
  - Test samples together (reduces analytical variation)
    - Method qualification and reference materials
  - Compared paired results; predefined (where possible) acceptance criteria
- Comparison to historic batches: even where extended testing including is suboptimal (reasons above) but may be useful secondary analysis.

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 a vital part of comparability
- Non-clinical and even clinical may be needed for major changes.