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
Biologics are Complex


**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

**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**
- Limited or no knowledge
- Windows of characterisation

Windows of knowledge fogged by uncertainty

Relative to complexity there is a large characterisation gap.
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.
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.