Quality Considerations for Technology Transfer

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Introduction

- Why comparability will be needed
  - What we are trying to achieve
  - Why cells make this less certain
- Quality considerations
  - Process
  - Analytical Methods
  - Reference materials (measurement and product)
- Conclusions

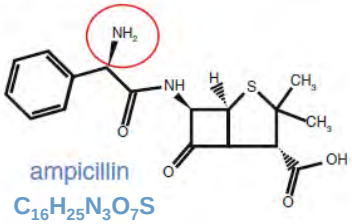
Biologicals are Complex

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

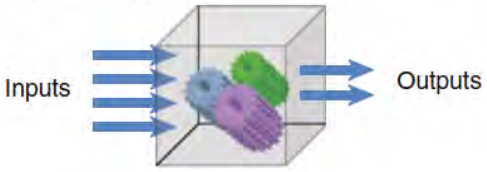


ampicillin

$C_{16}H_{25}N_3O_7S$

52 atoms

- Knowledge and measurement of all relevant inputs and outputs



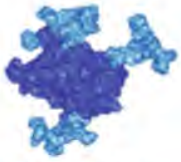
- One, defined active ingredient linked unambiguously via its identity to the safety and efficacy (S&E) profile

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

c Biologic

Correlated process-structure-function

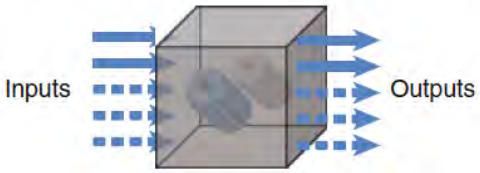
- Partial knowledge of biology and chemistry



Erythropoietin

>4000 atoms

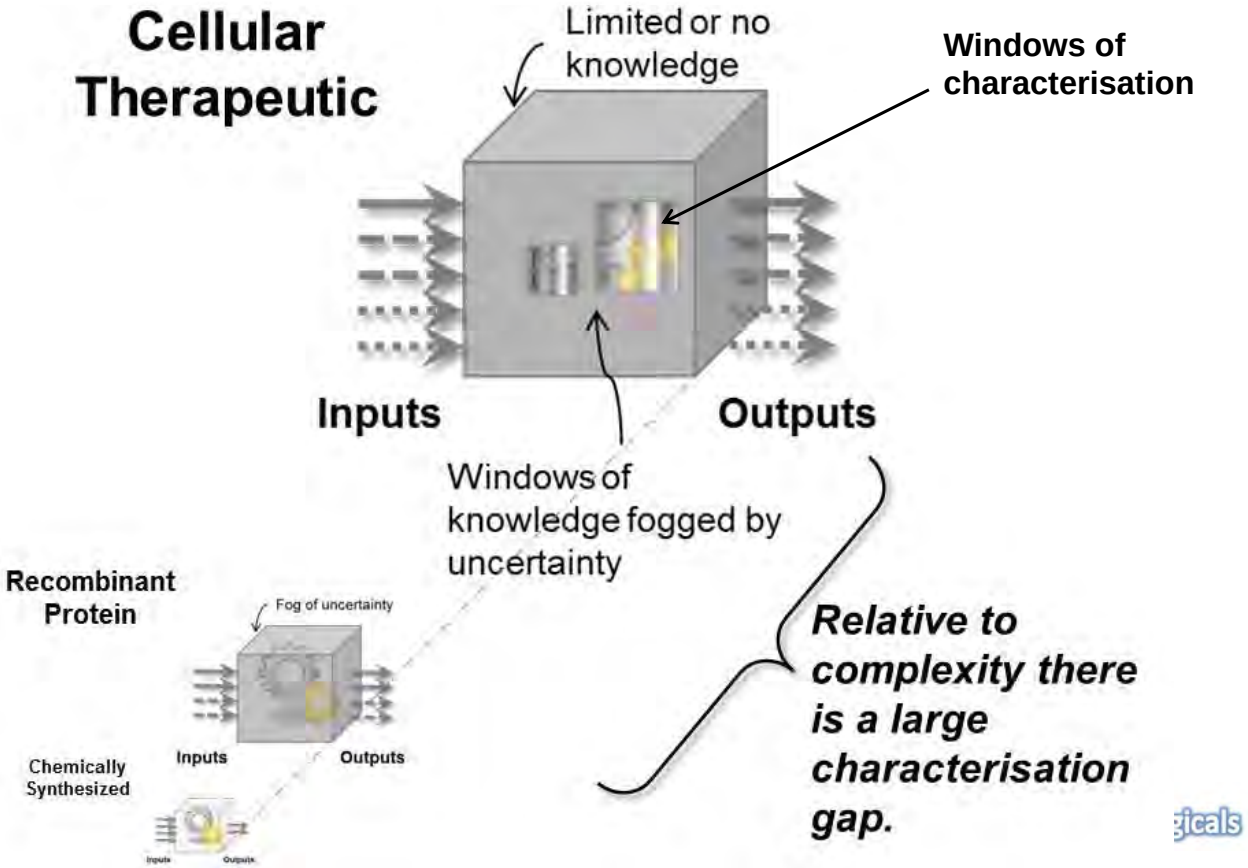
- Impossible to identify or measure all inputs and outputs



- 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:

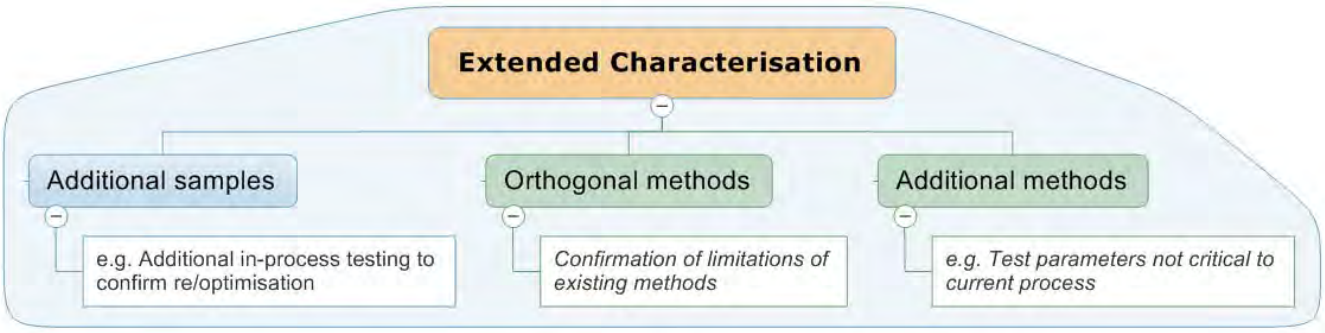
- Methods that measure cell functions
  - Related to (assumed) MoA
  - One or more of which will be considered 'potency' assays
  - Can be in vitro
  - Can be in vivo (many limitations, but can be reassuring)

- However these methods are often not particularly sensitive to change and for comparability we need methods that are sensitive to change.

Why Meeting Current Specifications is NOT Sufficient!

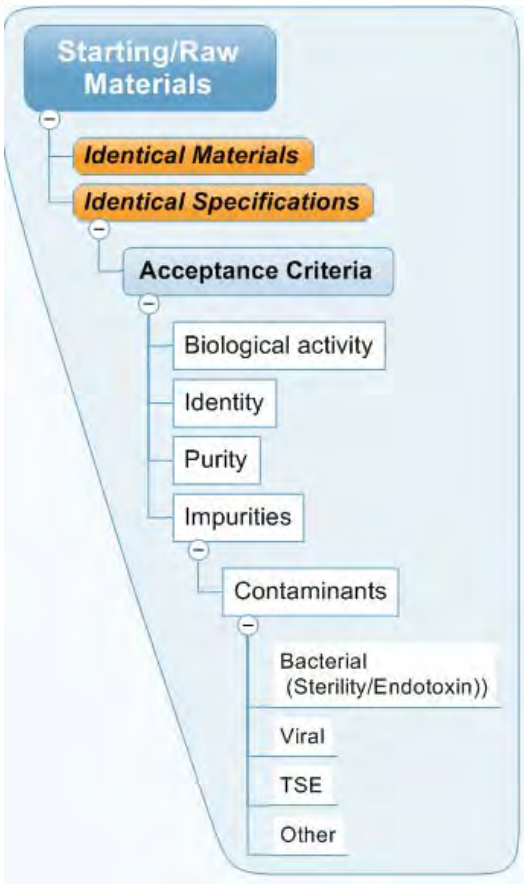
- Characterisation of the product and process identifies test methods that are useful as IPC/release specifications.
  - Some of these will hopefully be CQA
- Manufacturing experience (and other factors) are used to set specifications for a stable qualified process.
- Changing that process means the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

Extended Characterisation



Starting and Raw Materials

http://advbiols.com/documents/Techtransfercomparabilityv1.swf



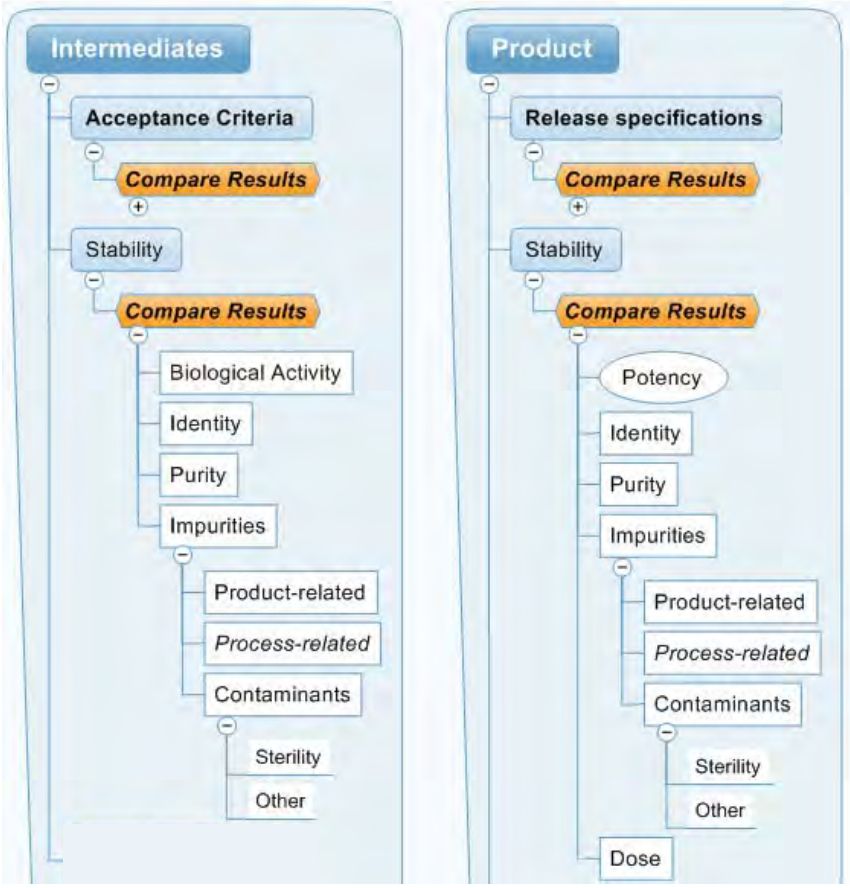
General

- Same materials (same batch)
- Same specifications

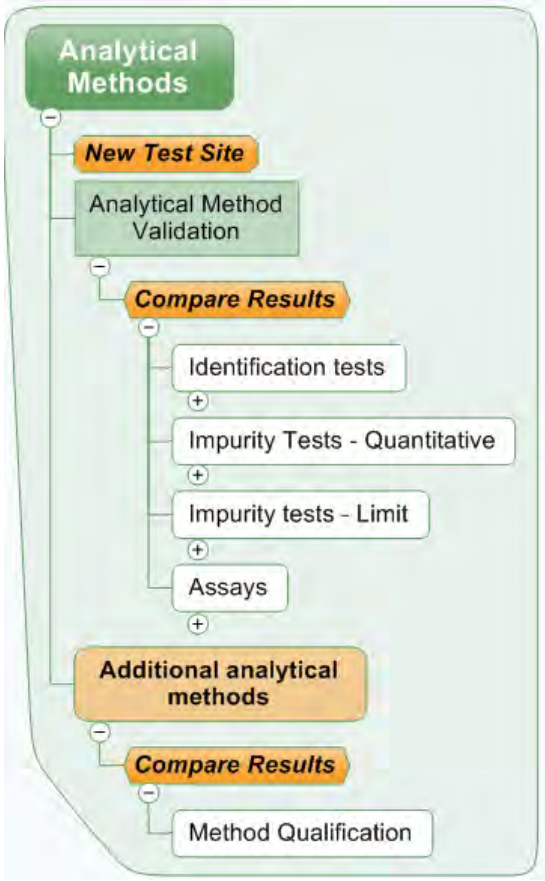
Starting material

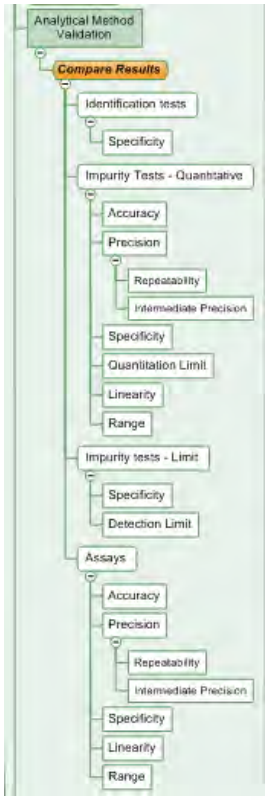
- Same where possible:
  - cell bank (allogeneic)
  - large tissue/cell donation
- Where starting availability is limited consider;
  - pooling
  - 'normal' donor
  - cadaveric
  - other (animal, cell line etc?)
- Shipping qualifications

Stability

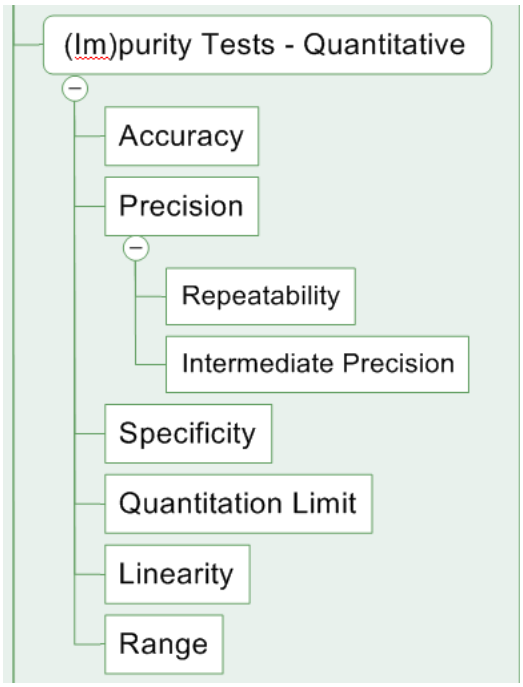


Methods



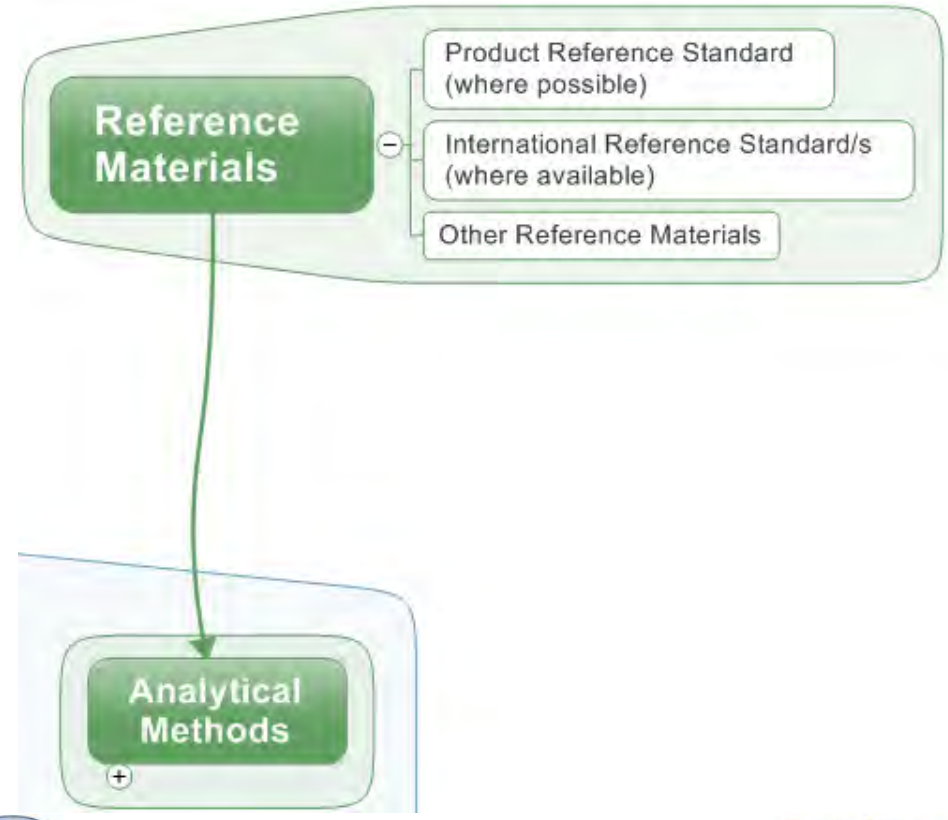


- Training



See ICH Q2

Don’t Forget Reference Materials

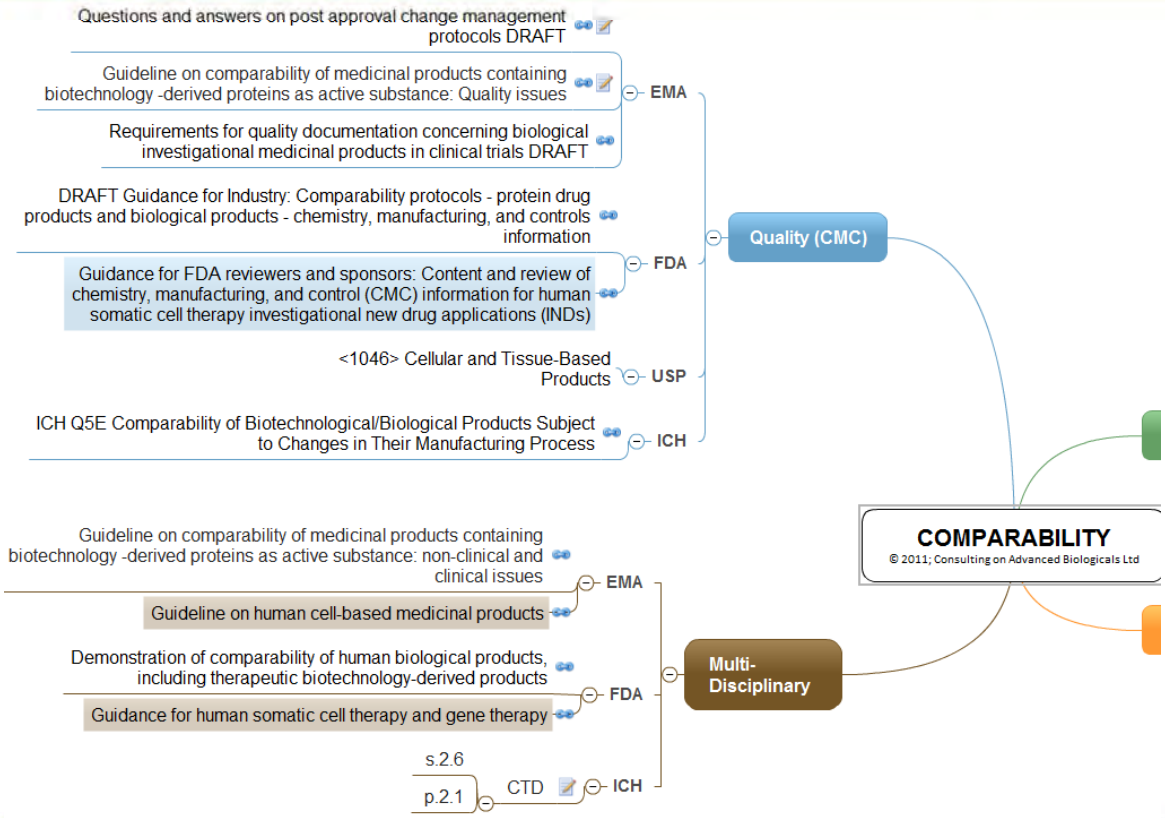


Conclusions

- Plan well
- The objective is to confirm the deliberately changed variable (new manufacturing site) can produce a comparable product
  - Keep all other controllable variables the same as far as possible
- Comparability cannot be demonstrated in most cases by release specifications alone
- Extended characterisation – orthogonal/additional methods and additional samples
- Consider whether the methods you have are sensitive to change.

Consulting on Advanced Biologicals

Comparability Guidelines



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