
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

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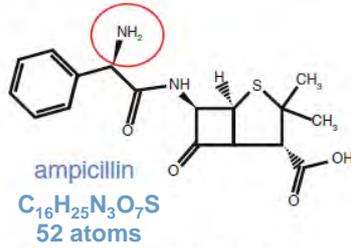
Biologicals are Complex

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

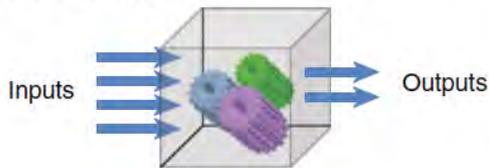
b Chemically synthesized drug

Defined process-structure-function

- Complete knowledge of chemistry and physics



- Knowledge and measurement of all relevant inputs and outputs



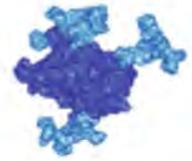
- One, defined active ingredient linked unambiguously via its identity to the safety and efficacy (S&E) profile



c Biologic

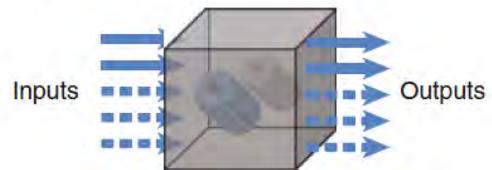
Correlated process-structure-function

- Partial knowledge of biology and chemistry



Erythropoietin
 >4000 atoms

- Impossible to identify or measure all inputs and outputs



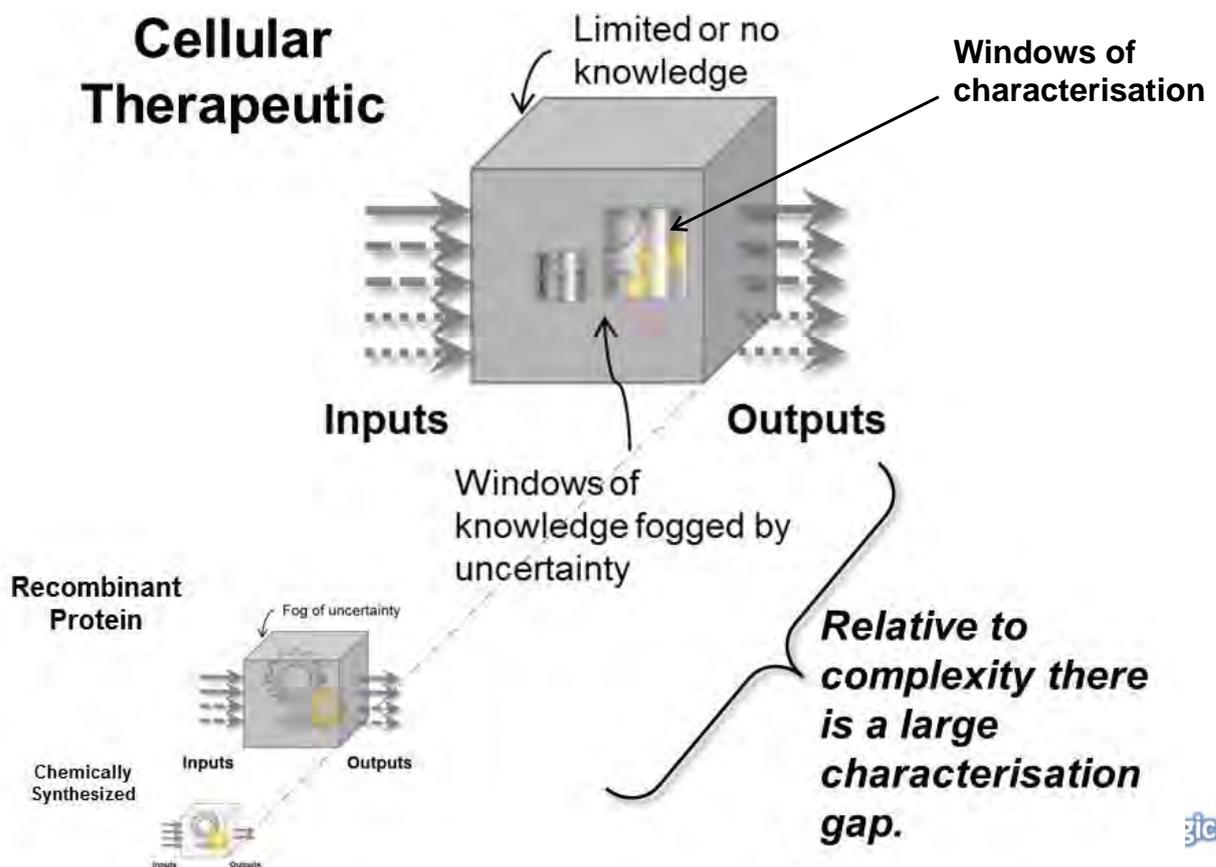
- Heterogeneous, partially defined active ingredient correlated to the safety and efficacy profile – contingent on process consistency



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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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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

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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.

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Why Meeting Current Specifications is NOT Sufficient!

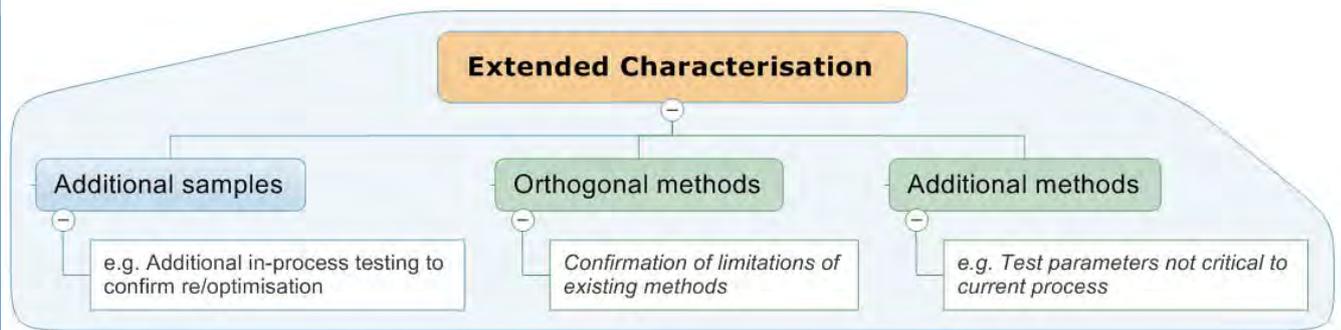
- Characterisation of the product and process identifies test methods that are useful as IPC/release specifications.
 - Some of these will hopefully be CQA
- Manufacturing experience (and other factors) are used to set specifications for a stable qualified process.
- Changing that process means the validity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

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Extended Characterisation



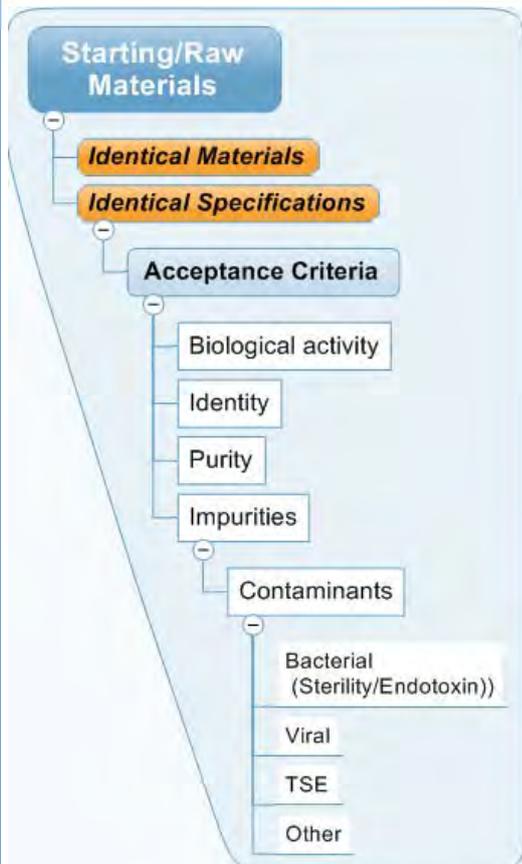
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Starting and Raw Materials

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



General

- Same materials (same batch)
- Same specifications

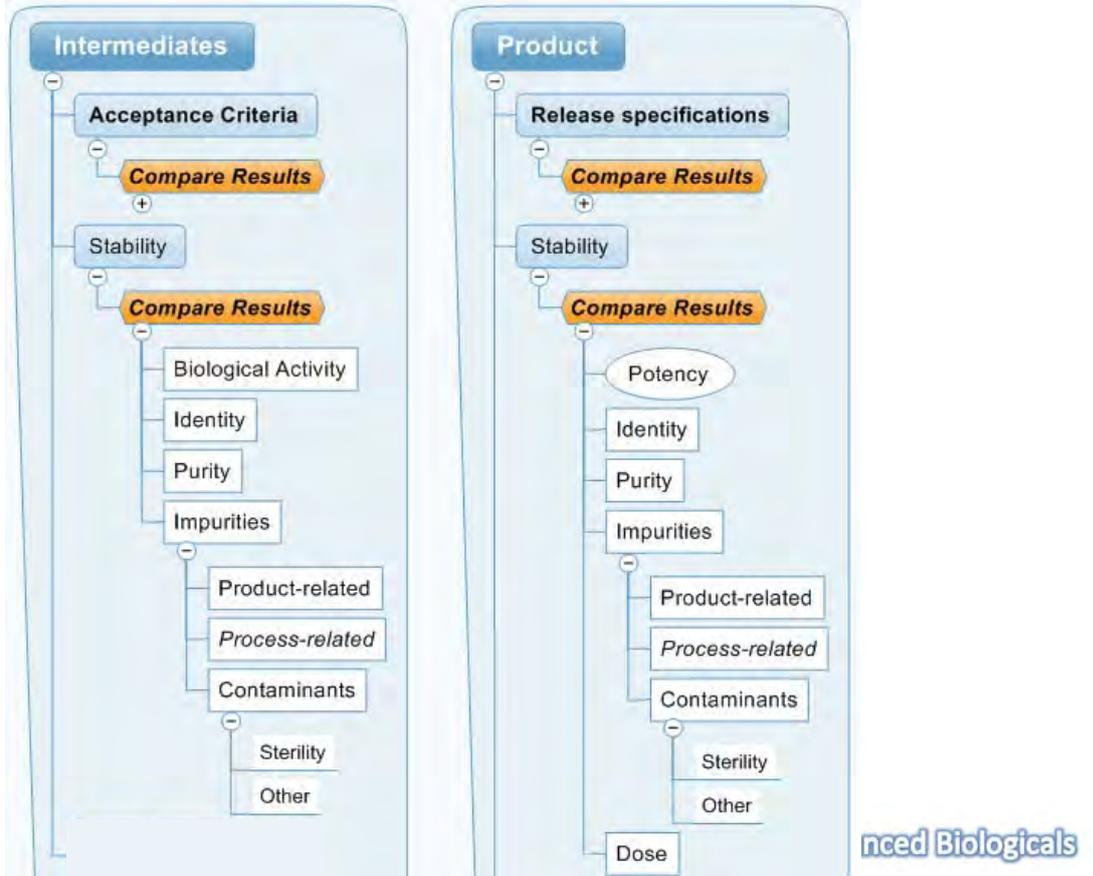
Starting material

- 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

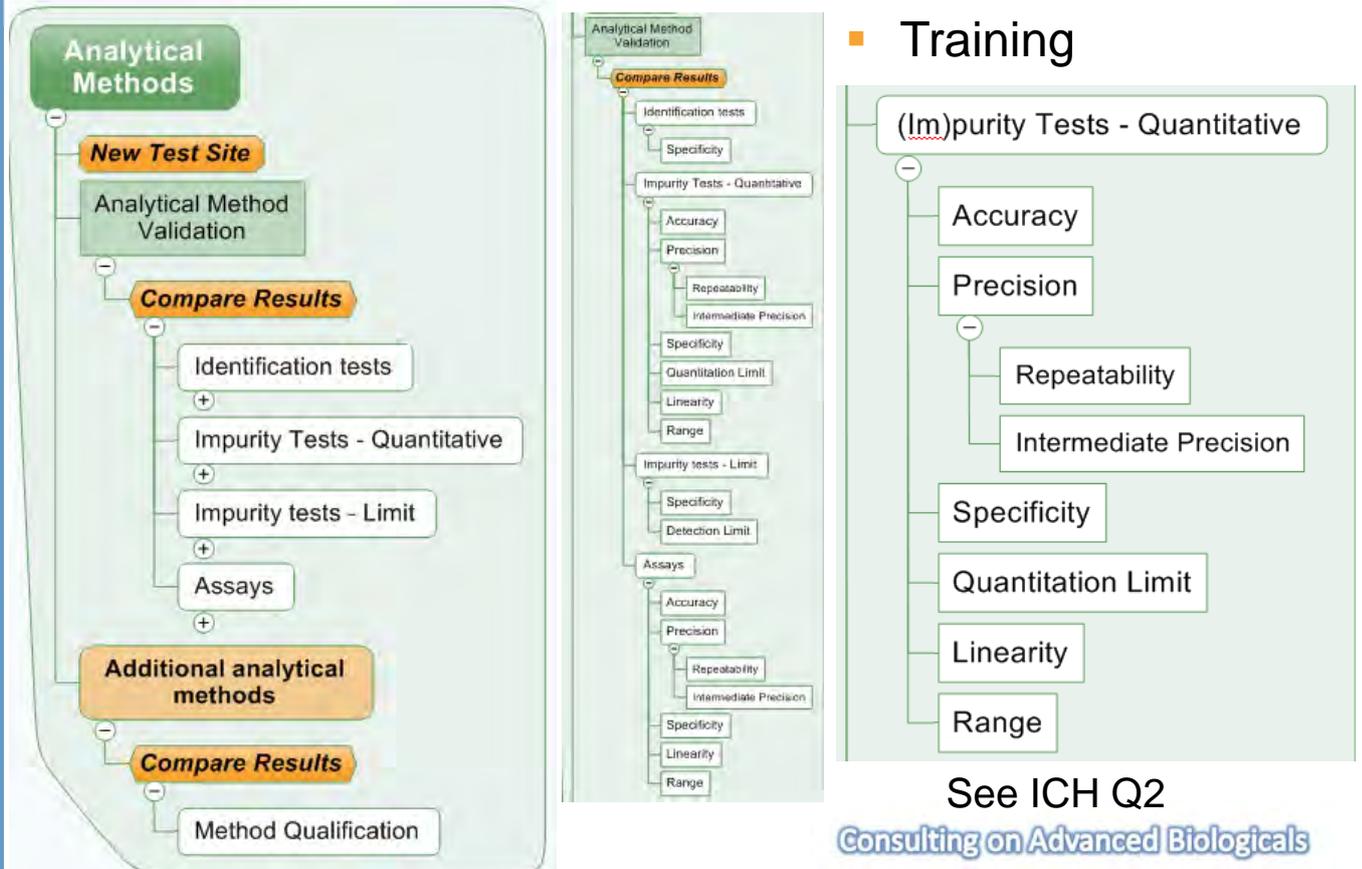
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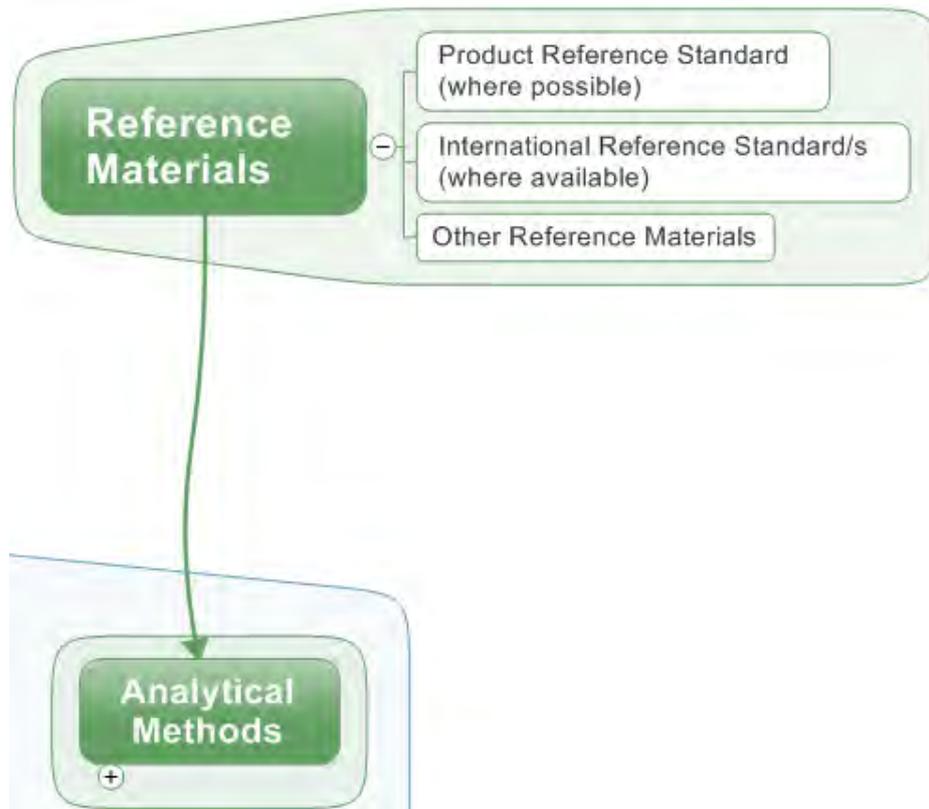
Stability



Methods



Don't Forget Reference Materials



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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.

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Comparability Guidelines

Questions and answers on post approval change management protocols DRAFT

Guideline on comparability of medicinal products containing biotechnology-derived proteins as active substance: Quality issues

Requirements for quality documentation concerning biological investigational medicinal products in clinical trials DRAFT

DRAFT Guidance for Industry: Comparability protocols - protein drug products and biological products - chemistry, manufacturing, and controls information

Guidance for FDA reviewers and sponsors: Content and review of chemistry, manufacturing, and control (CMC) information for human somatic cell therapy investigational new drug applications (INDs)

<1046> Cellular and Tissue-Based Products

ICH Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process

Quality (CMC)

Guideline on comparability of medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues

Guideline on human cell-based medicinal products

Demonstration of comparability of human biological products, including therapeutic biotechnology-derived products

Guidance for human somatic cell therapy and gene therapy

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p.2.1

CTD

Multi-Disciplinary

COMPARABILITY

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