
Quality Considerations for Technology Transfer

Christopher A Bravery

cbravery@advbiols.com

1



Consulting on Advanced Biologicals

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

2



Consulting on Advanced Biologicals

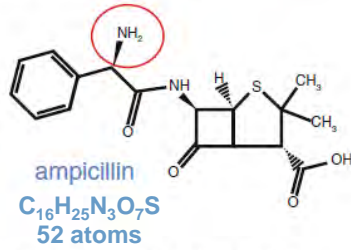
Biologicals are Complex

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

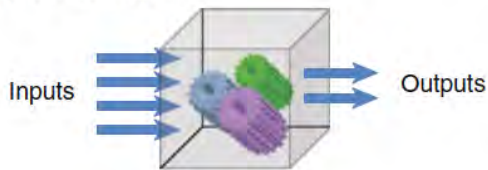
b Chemically synthesized drug

Defined process-structure-function

- Complete knowledge of chemistry and physics



- Knowledge and measurement of all relevant inputs and outputs



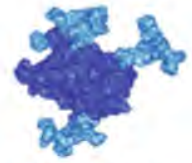
- One, defined active ingredient linked unambiguously via its identity to the safety and efficacy (S&E) profile



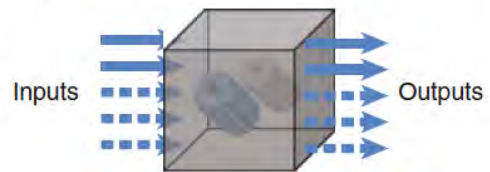
c Biologic

Correlated process-structure-function

- Partial knowledge of biology and chemistry



- Impossible to identify or measure all inputs and outputs



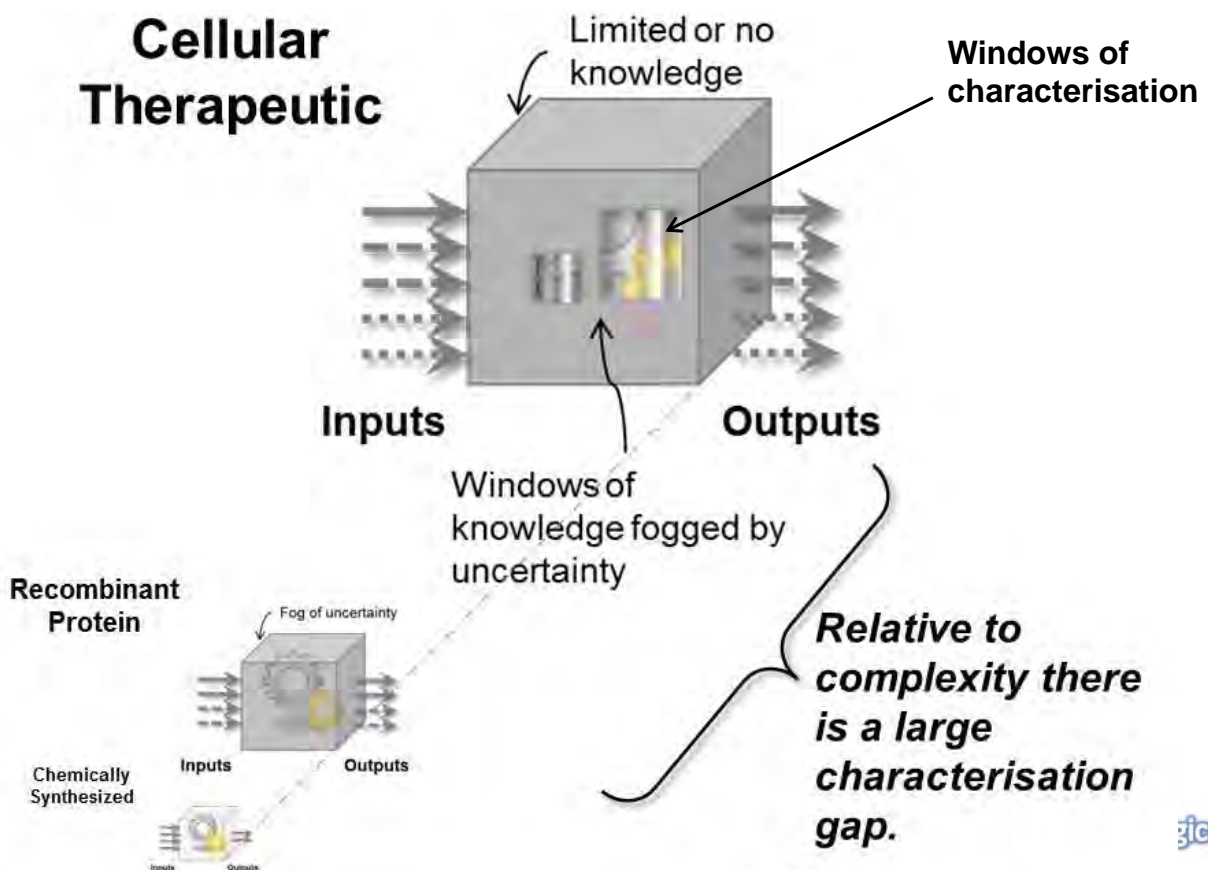
- Heterogeneous, partially defined active ingredient correlated to the safety and efficacy profile – contingent on process consistency



3

Cell Therapy Products even more so

Cellular Therapeutic



4

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

5



Consulting on Advanced Biologicals

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

6



Consulting on Advanced Biologicals

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.

7



Consulting on Advanced Biologicals

Why Meeting Current Specifications is NOT Sufficient!

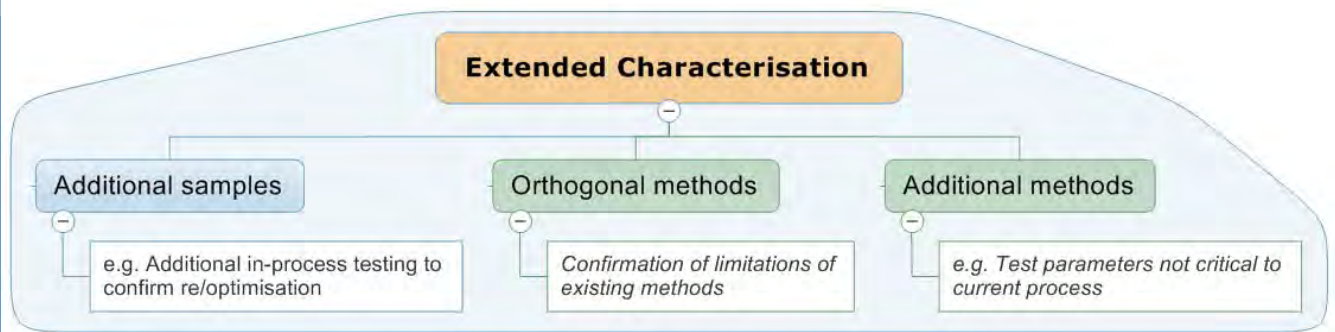
- Characterisation of the product and process identifies test methods that are useful as IPC/release specifications.
 - Some of these will hopefully be CQA
- Manufacturing experience (and other factors) are used to set specifications for a stable qualified process.
- Changing that process means the validity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

8



Consulting on Advanced Biologicals

Extended Characterisation



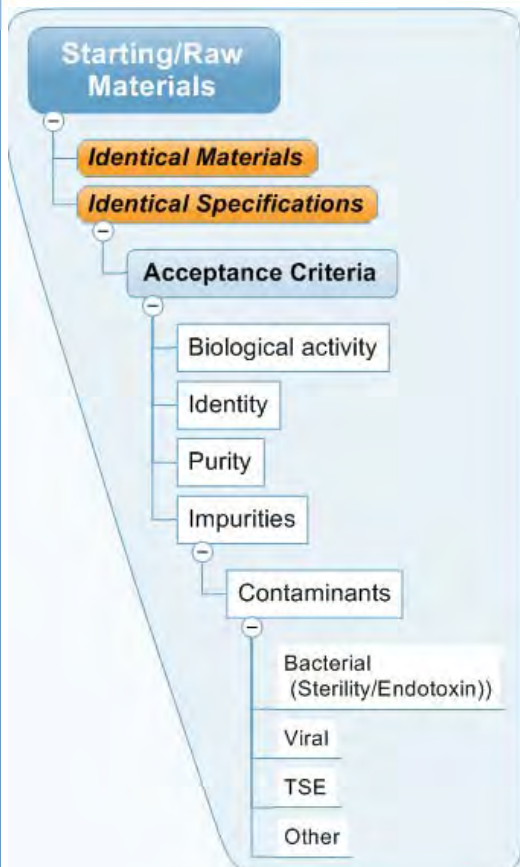
9



Consulting on Advanced Biologicals

Starting and Raw Materials

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



General

- Same materials (same batch)
- Same specifications

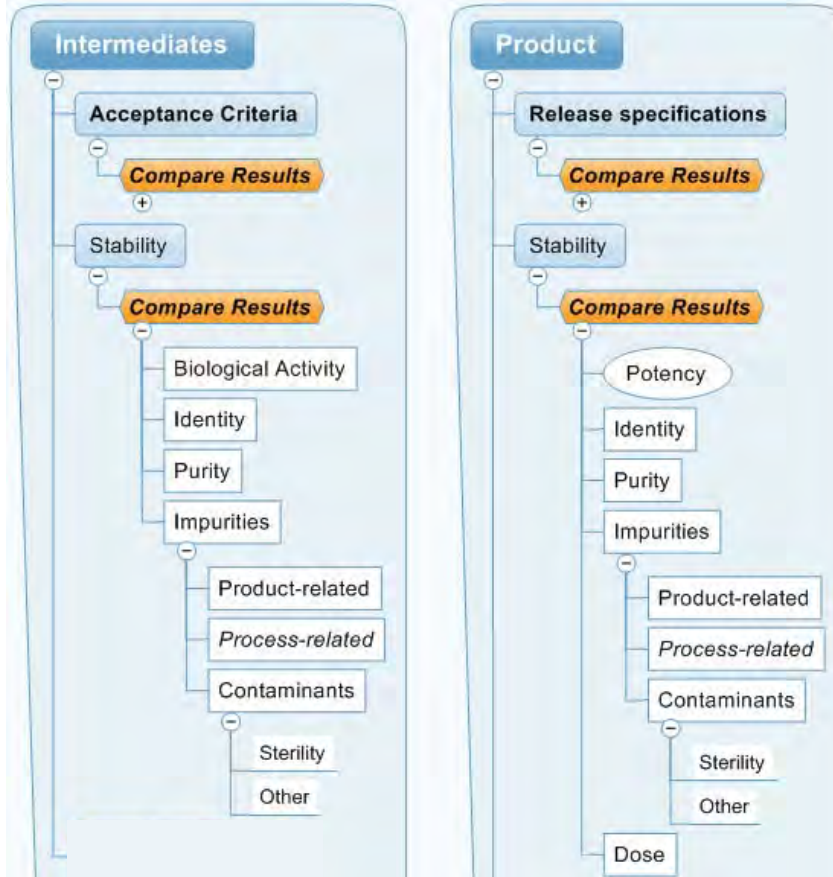
Starting material

- 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

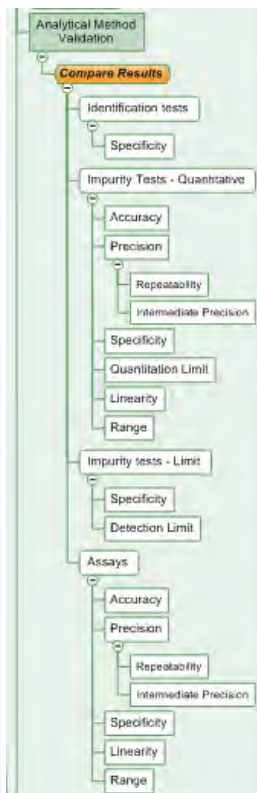
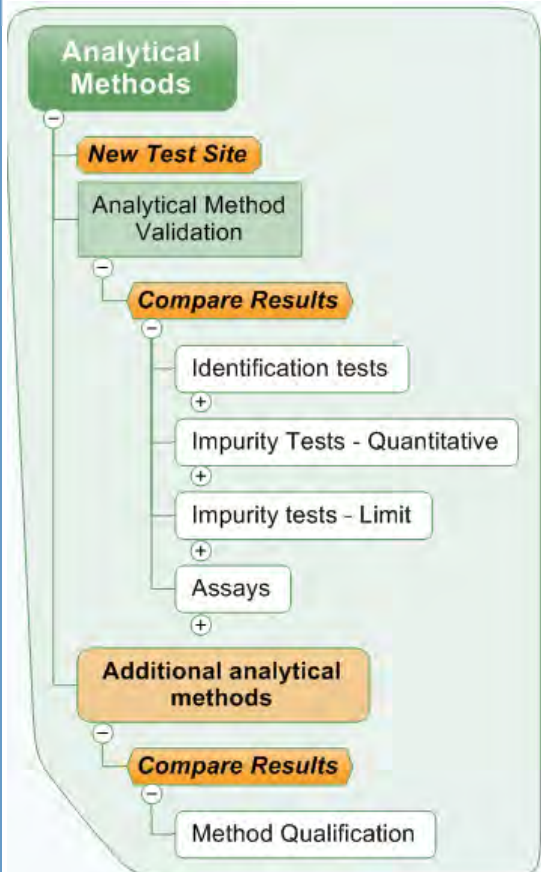
Consulting on Advanced Biologicals

10

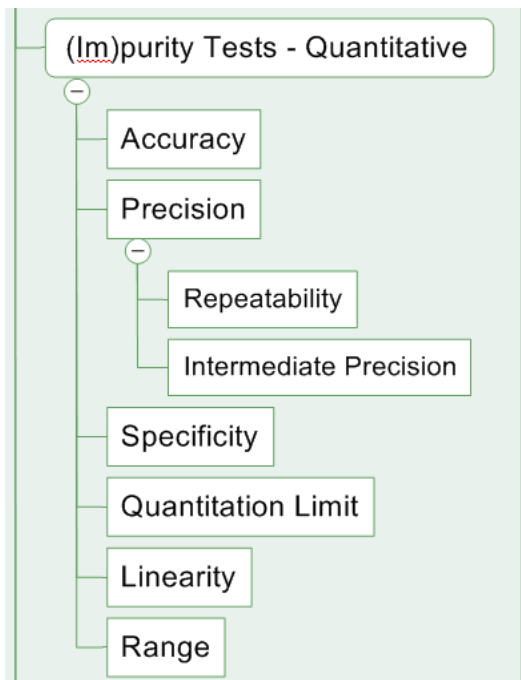
Stability



Methods

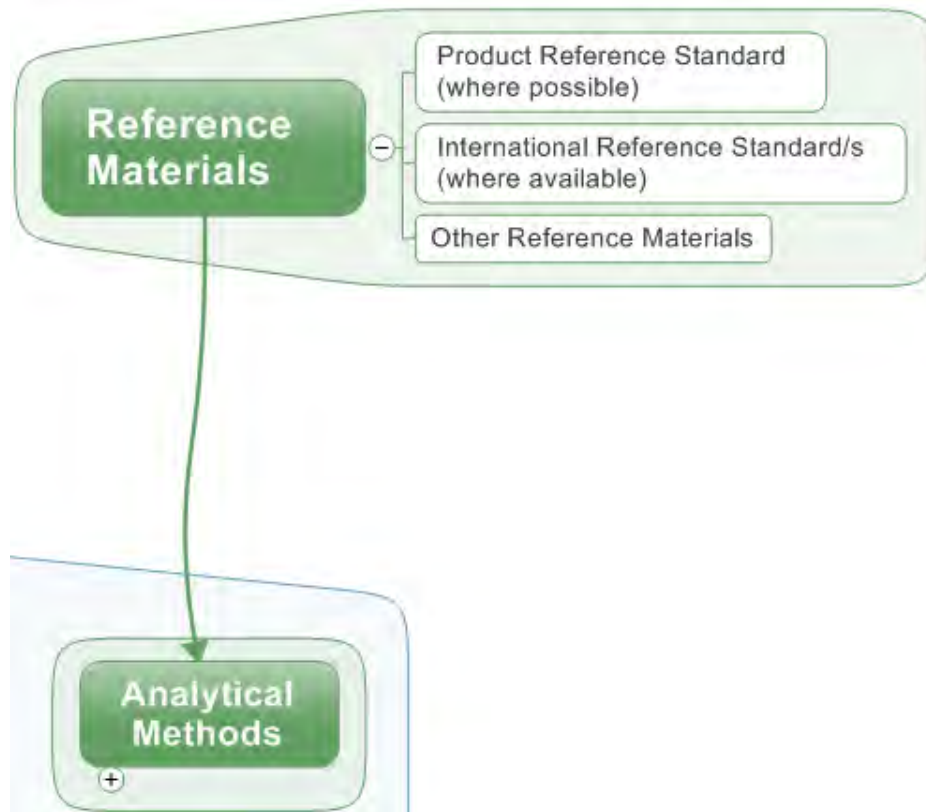


Training



See ICH Q2
Consulting on Advanced Biologicals

Don't Forget Reference Materials



13



Consulting on Advanced Biologicals

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.

14



Consulting on Advanced Biologicals

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)

EMA

FDA

USP

ICH

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

s.2.6

p.2.1

CTD

ICH

Multi-Disciplinary

COMPARABILITY

© 2011; Consulting on Advanced Biologicals Ltd