Reference Standards: Regulatory Requirements

Christopher A Bravery
cbravery@advbiols.com

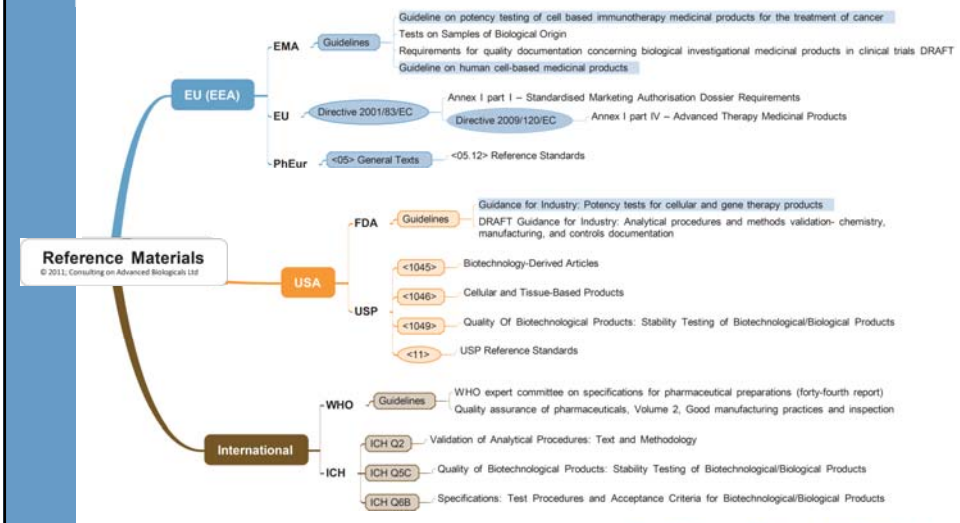
Introduction

- Types of reference standards and materials
- Why do we need them?
- Regulatory expectations

Types of Reference Material

- International biological Reference Standards
  - WHO (NIBSC); e.g. epoeitin, filgrastim (G-CSF).
  - Not available for many biologics
  - Not available for ANY cell therapy products; nor likely to be in foreseeable future.
- In-house Primary Reference Material (active substance)
  - Prepared by manufacturer from early batch
  - Well characterised
  - Calibrated against International reference standard, if available.
- Other reference materials

Regulatory Expectations

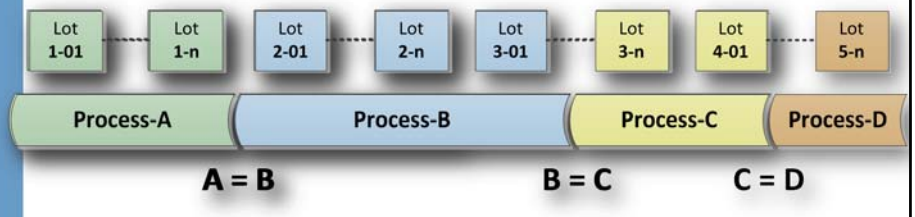


See our web-tools: www.advbiols.com/resources

Why use reference material?

- Change is inevitable
  - Change in materials
  - Change in process
  - Change in analytical methods

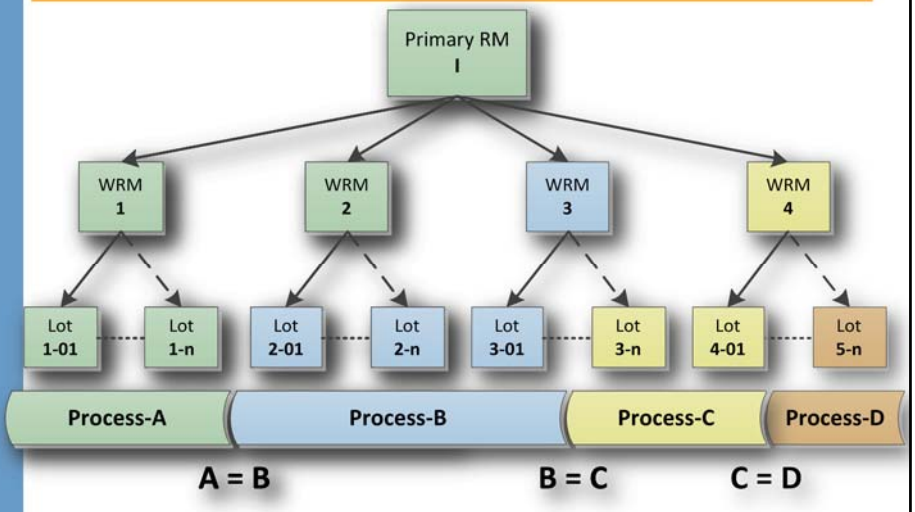
BUT, Does A = D ?



5

Consulting on Advanced Biologicals

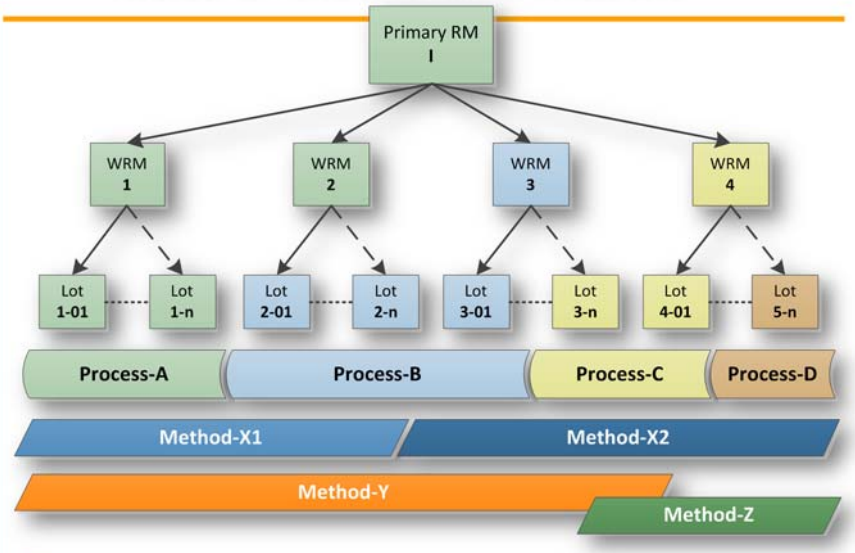
In-house Reference Material



6

Consulting on Advanced Biologicals

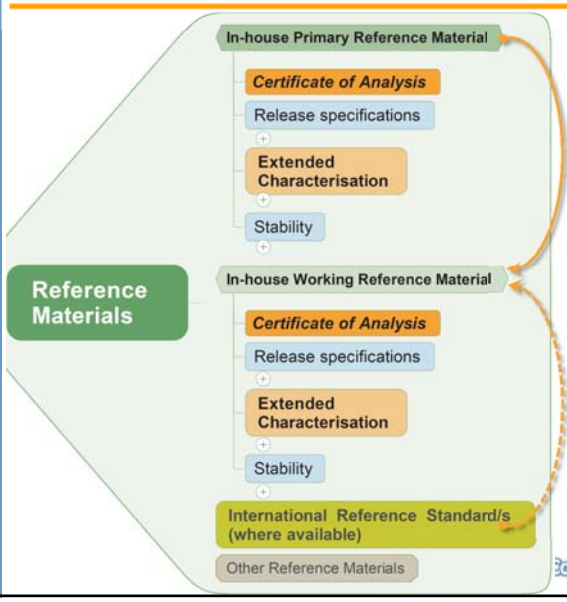
Uses of Reference Materials



7

Consulting on Advanced Biologicals

Preparing Reference Materials



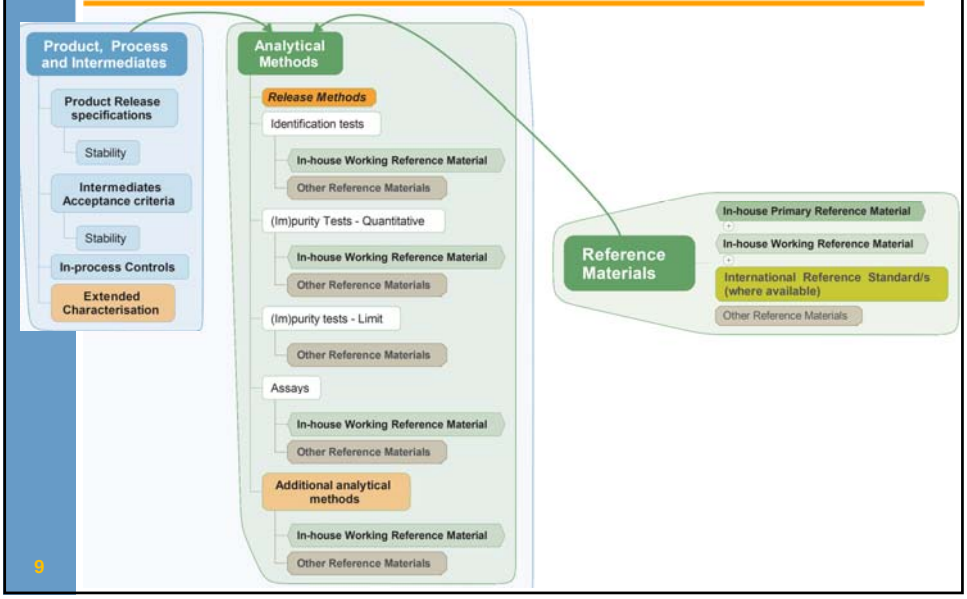
The Working Reference Material is qualified against the Primary Reference Material

Where available the in-house Reference Material is calibrated against a Reference Standard

8

Consulting on Advanced Biologicals

Using Reference Materials



Challenges for cell-based Reference Materials

- RM would need to be cryopreserved or lyophilised
  - OK when product is frozen
  - May cause issues for fresh products (altered characteristics)
- Difficult to set aside large batches as RM, especially for autologous
  - Use normal or cadaveric donors
  - Pool material
- Might be possible to use cell line with uniform reliable response in particular assay/s that can be related to product.

If in-house cell Reference Material not possible

- It may be necessary to develop different reference materials for different tests – but understand the limitations.
- Alternative reference materials appropriate to assay, e.g
  - Potency might rely on release of cytokine, or might be based on gene expression – use reference cytokine or prepare cDNA reference material.
  - Identity/Purity might rely on surface marker – use beads coated in surface marker protein
- Think outside the box.

Note: These are not recommendations, merely speculation on possible solutions.
It is recommended to discuss with regulators, since experience is limited at this time.

Conclusions

- The use of Reference Materials is a central concept in medicines regulation.
  - ICH, FDA, EMA, USP, PhEur, WHO
- Living cells pose significant problems for the development of in-house product Reference Material
- Routine use of Reference Material complements trending and supports comparability
- Its good practice to have 'relevant' positive controls in all analytical methods: where a cellular reference material cannot be developed, alternative reference materials need to be identified and qualified.
- The sooner the better since changes are ubiquitous during development.