Reference Standards: Regulatory Requirements

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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. epoetin, 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**
Why use reference material?

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

BUT, Does $A = D$?

In-house Reference Material
Uses of 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.

Preparing Reference Materials
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.