Regulatory Implications of Allogeneic Cell Banking Strategy

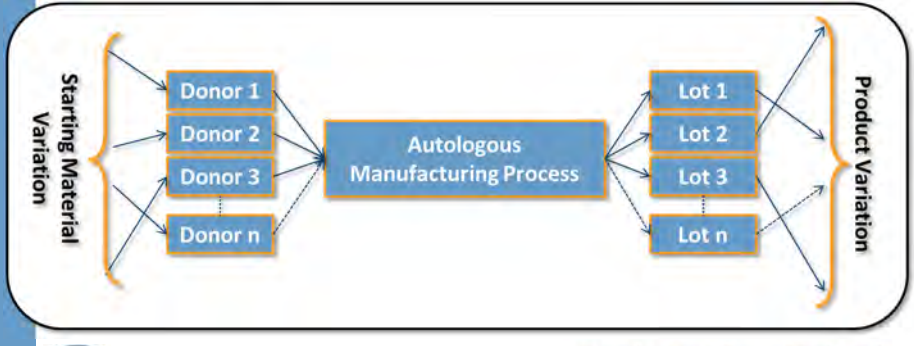
Christopher A Bravery

cbravery@advbiols.com

Process Extremes: Autologous

- Starting material variable
- Process variable
- Large number of batches means overall variability established by MAA/BLA

→ **Highly variable product**



Process Extremes: Biotech Model

- SM variation minimised
- Process variable
- *Product variability mostly due to process*
- Relatively small number of batches, but variability minimised

Note: biotech MCB normally single-cell cloned continuous cell lines (e.g. CHO)

Allogeneic: Not usually like biotech

- Individual banks not normally single-cell cloned
- Cell banks will differ and often will not last entire product lifecycle.
- Relatively small number of batches means overall variability may not be well established by MAA/BLA

Note: Comparability between cell banks is challenging!

Why does this matter?

- Comparability between cell banks (donors) is not a trivial task
- It is unlikely that a new cell bank can be introduced (post-MAA/BLA) without agency approval;
  - EMA: Variation
  - FDA: Supplement
- While both agencies have a system for pre-agree comparability protocols it seems unlikely these will be allowable, at least in the near-term.
- Current EMA thinking is that a new cell bank (donor) will require some sort of clinical qualification.

Why does this matter? #2 EMA Example

- Prepare new cell bank, undertake safety and comparability testing etc
  - Estimate a minimum of 6 months work (assuming clinical data is not necessary)
- A type II (most biological product variations) variation is a 60 day procedure
  - Add pre and post paperwork and it takes a minimum of 4 months before the change can be applied.
  - If questions arise the procedure could take longer.
- Overall time to implement change approximately 1 year!
  - Could be much longer if clinical data is needed
- Overall cost for new CB easily $1M when safety testing and comparability work and agency fees combined.

What's the message?

- The regulatory burden will be much higher than biotech unless your CB is large enough to last the entire product life-cycle (as is the case with biotech).
- The more new CB's needed over the product life-cycle, the greater the regulatory burden and costs.
- If your cell bank will only supply enough material for around 2-3 years THIS IS A PROBLEM!

Some Solutions

- Could combine donors to make larger bank
  - US: CFR 1271.220(b) excludes pooling of donors
  - EU: only asks clear strategy to maintain traceability (Directive 2009/120/EC Annex I: Part IV; 3.3.2.1(b))
  - Increases safety risks
- Include more than one cell bank in clinical development
  - Increases risk of failure if cell banks are not equivalent
  - Early phase trials may not be adequately powered to identify differences
  - But if enough banks can be qualified during development then no new banks would be needed after MAA/BLA
  - If you use only one CB in development you will not know the impact on product variability.
  - Assumes cell bank stability is >20-30 years

Conclusions

- Cell banks are used to reduce the variability of the starting material, which is usually the greatest source of variability for biological products.
  - Biotech; single cell clone
  - single MCB for entire product life-cycle.
- Most allogeneic products can not follow this approach
  - Single cell cloning isn't usually appropriate/possible
  - A single donor cannot supply the entire product life-cycle
  - New cell banks (donors) need to be introduced from time to time
- Each cell bank is likely to require clinical qualification
- It is important to develop a strategy to deal with this early on.