Regulatory Implications of Allogeneic Cell Banking Strategy

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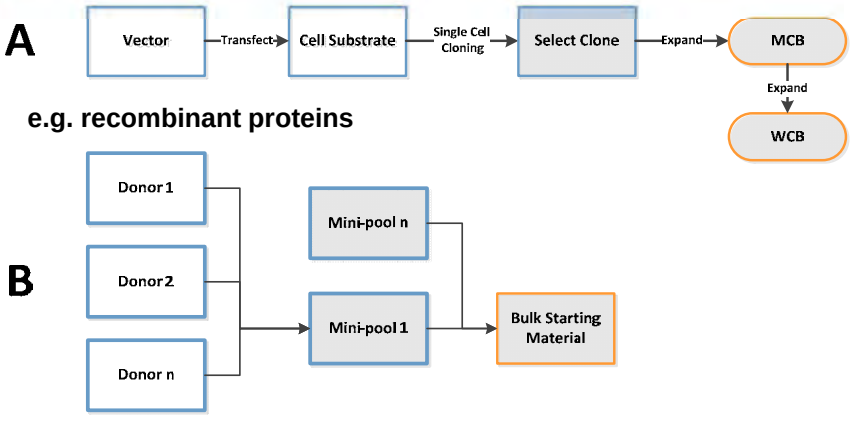
Introduction

- General concepts in control of biological starting materials
- Why are off-the-shelf CBMP different to biotech?
- What's the impact?
- Possible strategies
- Conclusions

Biological Starting Materials

- Biological starting materials (and raw materials) are generally a source of variability
  - Often difficult to define their quality, e.g. plasma
  - Donor variability (human, animal, plant, etc)
    - Genetic, environmental, nutrition/health status, age, sex etc etc.
- Controlling this variability helps control the overall variability of the process and resulting product.
- Two broad strategies are used for biological medicinal products depending on their nature and source:

Approaches to control biologics starting material variability



Control of Starting Materials:
Off-the-shelf (allogeneic) products

- Donor usually 'normal' (can choose); cellular active substance more likely to be clearly defined.
- Acceptance criteria can be defined
- Pooling unlikely to be suitable:
  - 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))
  - Risk probably outweighs benefits in most cases anyhow
- Isolate, *in vitro* expand and bank (donor) SM
  - Limits to expansion for most cells, except some stem cells
  - risks of DNA damage/cell changes etc
- Consequently cell bank generally of limited capacity
  - Except some stem cells
  - Will **need to be renewed from time to time**

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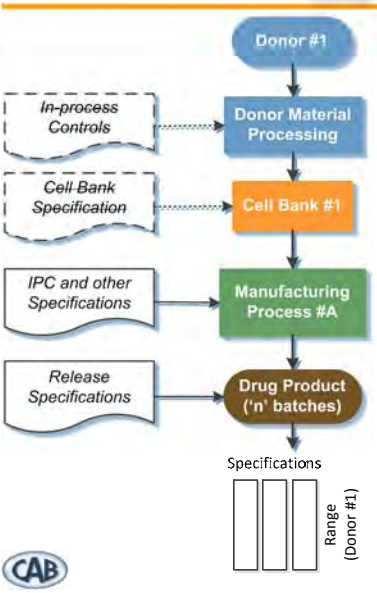
Single MCB that can last product life-cycle



- If only a single MCB is prepared it is not possible to define specifications for the manufacture of future cell banks.
- The resulting DP specifications reflect only a single donor and may differ with a different donor
- Later selecting a new donor that results in a comparable MCB and DP may therefore be difficult

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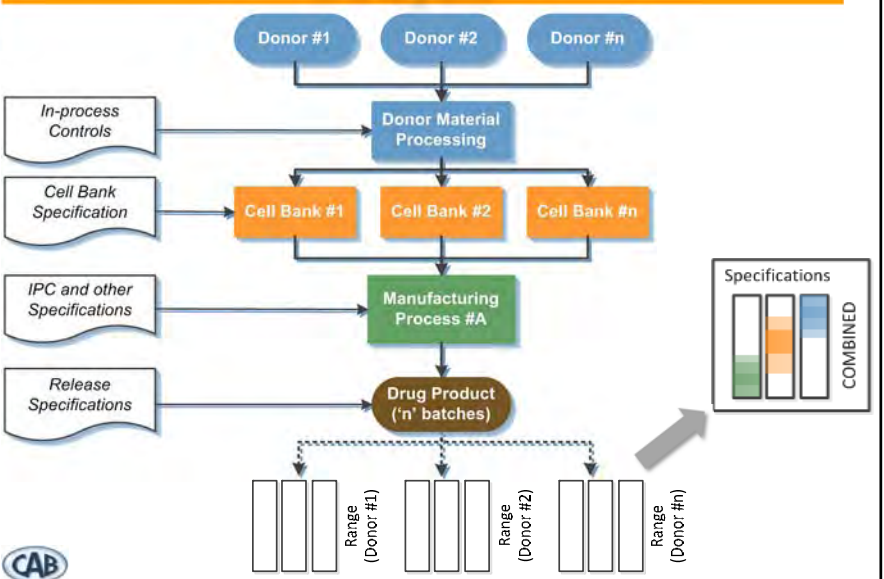
Is it risky to assume my MCB can last the entire product life-cycle?

- Although it is known that biotech cell substrates are stable for at least 20-30 years, these are continuous cell lines, not primary cells.
- There may be plenty of evidence that different cells are stable for decades, some even used clinically but;
- It will not be known for sure that the MCB you prepare is still capable of making your product in 30 years.
  - It might deteriorate
  - It could also be subject to catastrophic loss
    - back-up locations important

Multiple MCB required over product life-cycle



What does this mean?

- You need enough manufacturing experience with enough MCB to capture the variability due to the process and the donor.
- You also need enough clinical experience with different MCB to confirm they have equivalent safety and efficacy.
  - More than one MCB for pivotal studies
  - Probably even where release testing doesn't identify obvious differences because:
    - These are highly complex products, and
    - The critical quality parameters may not have (probably have not) all been identified

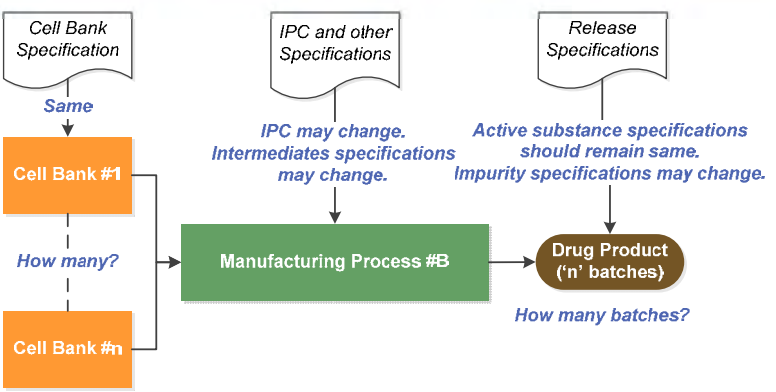
Why does this matter?

- 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 pre-approval;
  - EMA: Variation
  - FDA: Supplement
- While both agencies have a system for pre-agreed 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.

Implications following market authorization

- Prepare new cell bank, undertake safety and comparability testing etc
  - Estimate a minimum of 6 months work (assuming clinical data is not necessary)
- In EU, 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 MCB easily $1M when safety testing and comparability work and agency fees combined.

Adds complexity to comparability following other process changes



Considerations for Clinical Development

- Early phase trials may not be adequately powered to identify differences in MCB
- Including more than one cell bank in clinical development:
  - Might increase the risk of study failure if MCB are not equivalent
    - Possible need to increase patient numbers
  - True clinical comparability would not be feasible
- But if enough banks can be qualified during development then no new banks would be needed after MAA/BLA
  - Assuming they are stable for product life-cycle

Possible (untested) Strategies to consider

- Prepare a number of research MCB for characterisation but omit viral testing (expensive)
  - Additional data to support MCB specifications and general characterisation information
  - Make batches of product to understand impact of donor variability on product specifications
    - Also worth doing before viral testing for clinical banks
    - Issue: using untested MCB in GMP facility
    - May need 'model' process outside of GMP
- Select small number of MCB for clinical development
  - Perhaps covering extremes of specification
    - May increase risk of clinical failure
    - Good nonclinical models might help reduce risk

Conclusions #1

- Cell banks are used to reduce the variability of the starting material, which is usually the greatest source of variability for biological products.
- For allogeneic CBMP each cell bank is likely to require some sort of clinical qualification
- It is important to develop a strategy to deal with this early on.

Conclusions #2

- The regulatory burden will be much higher than biotech unless your MCB is large enough to last the entire product life-cycle (as is the case with biotech).
  - The more new MCB 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 or less; THIS IS A PROBLEM!