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Master Cell Bank Concerns

- **Master Cell Bank Concerns**
  - **Lack of identity of genetic components**
  - **Lack of confirmed absence of adventitious virus**
  - **Proof of MCB clonality**
  - **MCB inventory management**
- **Other Areas of Concern**
  - **Comparability testing to support changes**

Master Cell Bank Concerns

- **Lack of identity of genetic components**
  - Example: Elelyso (taliglucerase alfa):
    BLA information request letter, October 28, 2010

> You have provided nucleic acid sequencing data indicating that only (b) (4) of the sequenced clones had the expected deoxyribonucleic acid (DNA) sequence, with some of the changes in DNA sequence altering the protein sequence. You attributed this result to matrix effects and polymerase chain reaction (PCR) artifacts but provided no data to support this conclusion. Additionally, no information was provided demonstrating that the protein coding sequence is maintained during culture to the end of production.

- Suggests that the gene sequences in the MCB are not identical to the expression construct gene sequence, inconsistent with ICH Q5B
- Additional gene sequencing results for the MCB and end-of-production cells were requested, additional data to determine potential extent of genetic variations

Reference: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/022458Orig1s000Admincorres.pdf

Master Cell Bank Concerns

- **Lack of confirmed absence of adventitious virus**
  - Example: Vimizim (elosulfase alfa):
    BLA information request letter, August 02, 2013

[redacted] The master file you reference, (b) (4) does not provide sufficient information to assess the adequacy of virus testing of this human sourced component and your master cell bank has not been tested for the presence of any human viruses. This raises a concern that human virus may be present in your cell bank and this could impact the safety of your final drug product. Therefore, provide a risk assessment and relevant data (literature reference, etc.) on human virus infection and propagation in your CHO-K1 cell line. [redacted] Based on this information, you should provide a risk assessment and propose and justify a strategy to test your master cell bank for the most relevant human viruses, or justify why testing for the presence of human viruses is not necessary.

Reference: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125460Orig1s000AdminCorres.pdf

Master Cell Bank Concerns

- **Proof of MCB clonality**
  - MCB: Aliquot of a single pool of cells which generally has been prepared from the selected cell clone under defined conditions, dispensed into multiple containers and stored under defined conditions
  - MCB is used to derive all WCBs
  - Concern: Non-clonal cell bank can give rise to outgrowth of a subpopulation of cells that generate products with different CQAs

References: ICH Q5D (1997), EC GMP Annex 2 (2018), WHO Evaluation of Animal Cell Cultures as Substrates TR978 (2013), USP <1042> [Limited Dilution Cloning]

Master Cell Bank Concerns

- **Proof of MCB clonality**
  - US:
    - At IND Stage:
      - Reviewers do an initial assessment of information provided about the clonality of the MCB
      - If significant deficiencies are noted, then comments will be communicated.
      - Lack of clonality is not necessarily a hold issue.
    - At BLA Stage:
      - Adequate assurance of clonality should be provided
      - Having low assurance of clonality of MCB doesn't necessarily mean not approvable – but…
      - Control strategy (e.g., increased controls) to manage non-clonal MCB (or additional studies to confirm clonality) may be needed.

Reference: R. Novak, CDER, WCBP 2017

Master Cell Bank Concerns

- **Proof of MCB clonality**
  - Examples:
    - Unituxin (dinutuximab):
      CMC information request letter, August 06, 2014
    - Crysvita (burosumab-twza)
      PMR/PMC development template: product quality (CMC) – PMC#1, April 17, 2018
    - Zinplava (bezlotoxumab)
      Summary review, October 21, 2016
  - In each case, the manufacture was assigned a postmarketing commitment to complete clonality testing

References:

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125516Orig1s000Admincorres.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761068Orig1s000Admincorres.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/761046Orig1s000SumR.pdf

Master Cell Bank Concerns

- **MCB inventory management**
  - Acceptable cell bank inventory level
    - Anticipated utilization rate
  - Cell bank long-term storage stability
    - Provide available data in submissions supporting stability, as well as proposal for continued monitoring of banked cell stability
  - Contingency plan for cell bank (catastrophic event)
    - Split stocks and store at different locations

References: EC GMP Annex 2 (2018), ICH Q5D,

Other areas of concern

- **Comparability testing to support changes**
  - 3 steps to reduce residual uncertainty:
    1) Quality (analytical/functional),
    2) Nonclinical, and
    3) Clinical comparability
  - For process changes to a biologic/biopharmaceutical product, the demonstration of 'highly similar' via comparability testing:
    - Above 3 steps are optional
    - Begin with Quality comparability and continue based on residual uncertainty
  - For biosimilar product, the demonstration of 'highly similar' via comparability testing:
    - Above 3 steps are mandatory

References: ICH Q5E, CfPIE (2019)

Other areas of concern

- **Comparability testing to support changes**
  - More than just meets specs before and after change
    - Relevant, comprehensive physicochemical, biological, and functional assay characterization
      - Head-to-head comparison preferred
    - Accelerated and Stress stability slope comparison
      - Potential differences in molecular variant formation
    - Consistency batches
    - Historical data analysis (e.g., potential drift)
  - *During nonclinical and early clinical phases of development, comparability testing is generally not as extensive.*

References: ICH Q5E, CfPIE (2019)

Other areas of concern

- **Comparability testing to support changes**
  - For marketing submissions, consider comparability protocols (post-approval change management protocols)
  - Examples:
    - Qualification of new WCB
    - Qualification of new Reference Standard materials
    - Drug product manufacturing site change

References: ICH Q5E, CfPIE (2019)

Other areas of concern

- **Comparability testing to support changes**
  - HA comments - examples:
    - "…insufficient demonstration of comparability between commercial batches and batches used during clinical studies."
      Oxervate (cenegermin) EPAR, May 18, 2017
    - "A major objection was raised regarding comparability between the clinical material and the commercial material."
      Takhzyro (lanadelumab) EPAR, October 18, 2018
    - "A site-to-site comparability study was conducted…met all lot release specifications. However, the characterization of cell growth and transduction efficiency showed statistically significant differences. Thus, the products produced by the [two sites] are not considered comparable."
      Kymriah (tisagenlecleucel) SBA, August 30, 2017
    - "Demonstrated lack of analytical comparability between the materials manufactured using the previous [(b)(4)] and the proposed commercial [(b)(4)] is of concern because Phase 3 clinical studies were exclusively supported by [(b)(4)] materials."
      Andexxa (coagulation factor Xa (recombinant), inactivated-zhzo) BLA CRL, August 17, 2016

Thank You!