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TILTING AT CLONES: A REGULATORY PERSPECTIVE ON THE IMPORTANCE OF "CLONALITY" OF MAMMALIAN CELL BANKS

Disclaimer

This presentation should not be used in place of regulations, published FDA guidances or discussions with the Agency.

Introduction

- This talk will address:
  - The background and context of clonality or “clonality”
  - What guidances say (and don’t)
  - Industry perspective
  - How reviewers review and assess the assurance of clonality
  - Management of cell lines that have low assurance

    OR

    Are demonstrably non-clonal

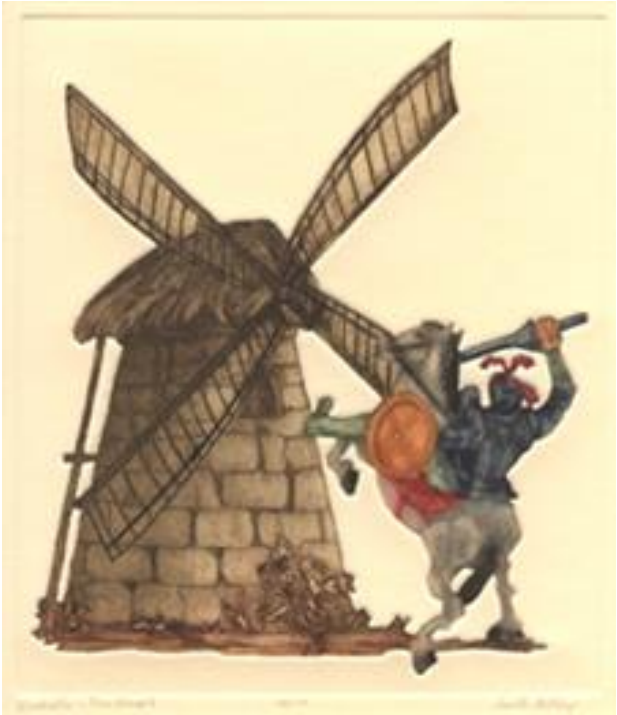

Figure from Georgetown Library website, drawing by Lucille Gilling

Basis for the Expectation of Clonality

- Regulatory basis:
  - No single document explicitly states that cell banks must be monoclonal (impossible to be 100%!);
  - Expectation that clonal cell lines are developed is described in ICH Q5D and EMA/CHMP.
  - "*…the cell substrate … has been cloned from a single cell progenitor*"
  - *"The cell substrate …should be a stable and continuous monoclonal cell line…"*
- Scientific basis:
  - To minimize the heterogeneity within the master cell bank (MCB) to allow for a consistent manufacture of a product.
  - When cell banks are non-clonal, every potential change made to the upstream process (raw materials, process parameters, manufacturing site, etc.) presents the potential to put selective pressure on the cultures, which **may** result in changes

Adapted from R. Novak, CASSS Strategy Forum, Jan 2017

Consistent with ICH Q11 Principles

- "A **control strategy** is a planned set of controls, derived from current product and process understanding, that assures process performance and product quality"
- "The use of upstream controls should be based on an evaluation and understanding of the sources of variability of a CQA".
- Understanding your cell line (including its "clonality") is necessary for process development and establishing a meaningful control strategy

Industry Perspective

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Industry view on the relative importance of "clonality" of biopharmaceutical-producing cell lines

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Industry Perspective

"Therefore, referring to …the "clonality" of a manufacturing cell bank is misleading…. a more accurate description would be that these cell lines can have a high probability of being clonally-derived"

"We agree that the clonal derivation of a production cell line is one factor with potential impact, but it is only one of many factors. "

"Further, we believe that regulatory emphasis should be primarily placed on ensuring product quality of the material actually administered to patients, and on ensuring process consistency and implementing appropriate control strategies through the life cycle of the products."

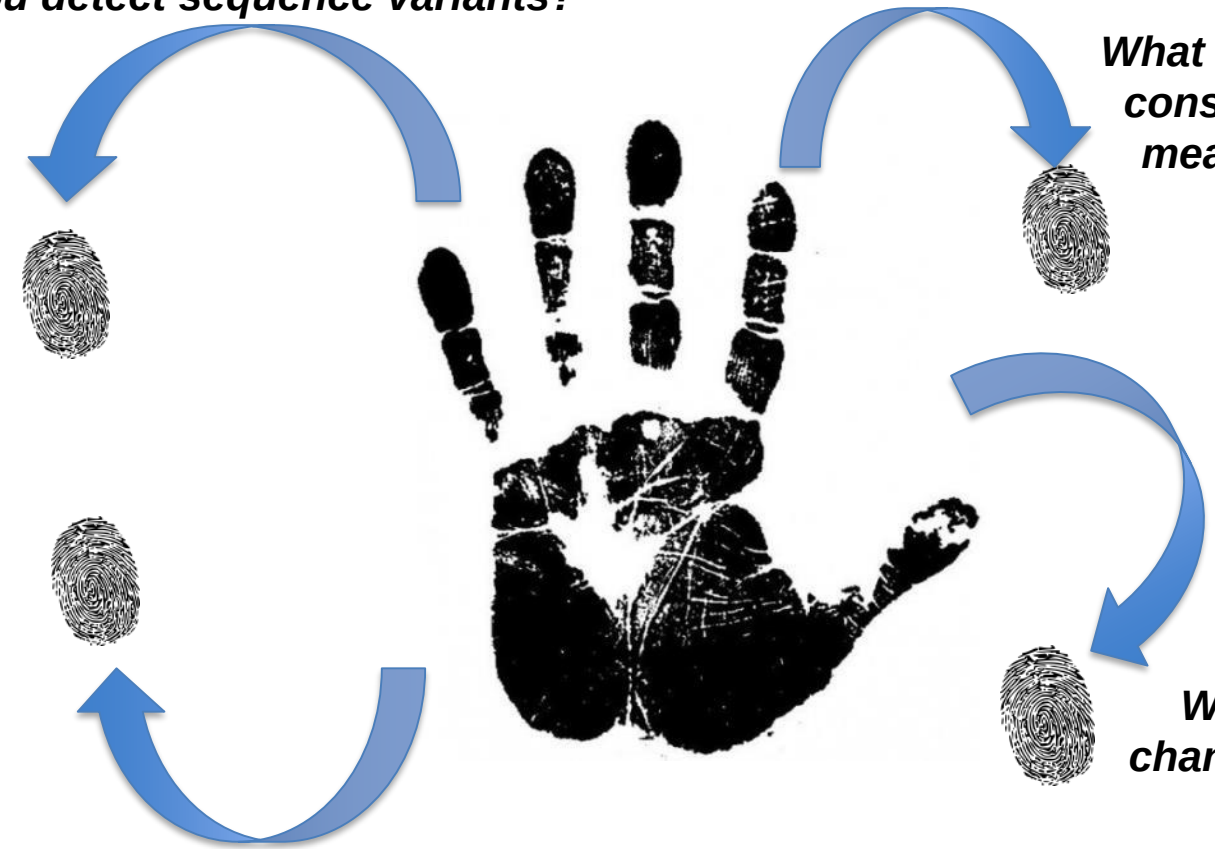
Mutual Understanding (And Agreement)

- Goal is to supply an effective product to patients (not a MCB)
- There is a continuum of probability and no firm threshold
- The cells we used to make biologics have their own nuances
  - Complexity (both product and the cells)
  - Cultures (heterogeneous)
  - Genetic and phenotypic drift (uncontrolled)
  - The same genetic plasticity that allows for these cells to be used to make biologics also makes the cell susceptible to selective pressure
- Assurance of clonality is ***only a part*** of the overall control strategy
  - Process consistency
  - Product quality
- ***How can one implement "appropriate control strategies through the life cycle" without an understanding of the risk?***

Thumbprints of Clonality on your Control Strategy

Could you detect sequence variants?

What tests of process consistency do you measure (or not?)



What CQAs are changing without us knowing?

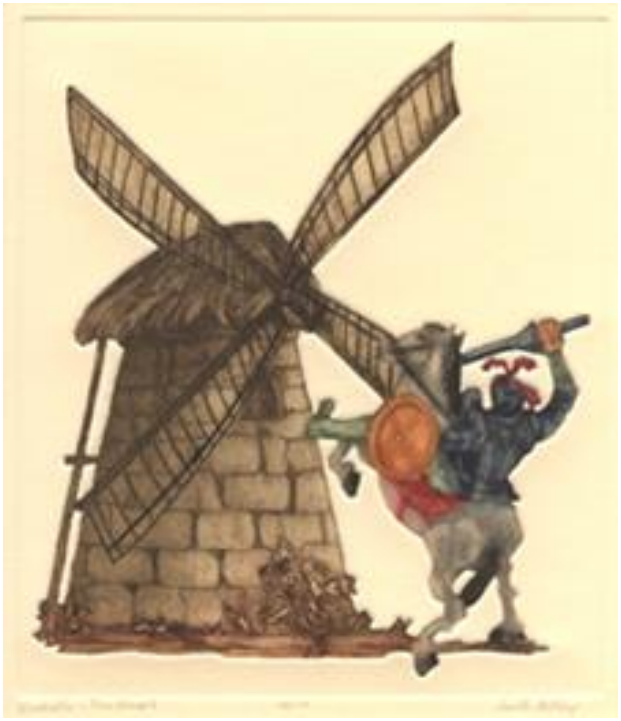
What's the qualification strategy for a new WCB?

It's about Patients and Risk

- Best to start with a "high" probability
- Starting with a cell line that has a high probability of being monoclonal **reduces** residual uncertainty (i.e, risk) when it comes to making changes to the manufacturing process.
- Studies done that support both validation and development activities are a brief snapshot
- A sufficient control strategy will be required for licensure (less up front work may result in more data later)

It can, (has, and will) Happen…

- Problems with cell culture, due to unexpected selective pressure, can lead to possible disruptions in manufacturing
  - The leading indicators may be missed
  - Won't find things you are not looking for
  - Quality system may not be able to identify change
  - Difficult to identify *what is new?* vs. *what is different?*
- Challenge is always centered on patient impact (reproducible supply or drug, i.e., no shortage)



Clonality

HOW DOES THE PRODUCT QUALITY REVIEWER APPROACH THE REVIEW?

Cell Line Development

- INDs are typically submitted to the Agency after MCB has already been developed
- The MCB may not be “fully” characterized at this time
- Focus of IND is safety
- Information submitted at the time of IND should provide enough understanding of the creation of the cell bank
  - Safety testing for adventitious agents per ICH Q5D
  - Information on the parental cell line history
  - Adaptation to serum-free conditions (if applicable)
  - How the cloning process was performed (Limiting Dilution Cloning, FACS, ClonePix, Clone Select, etc.)
  - How the final clone was expanded, assessed and selected (did you adapt to serum free conditions after cloning?)

Probability vs Assurance

- The use of “assurance” and “probability” in the context of review of a cell banks’ clonality reflects the following meaning:
  - **Probability** refers to a *numerical calculation* provided by the sponsor (e.g., Poisson distribution)
  - **Assurance** refers to an *assessment* of all the information provided, including probability calculations and supplemental data/information.

How is the final assessment of the adequacy of clonality determined?

- 3 Aspects inform the final decision:
  - Probability
    - What do you expect?
    - (Numerical, and generally provided by the sponsor)
  - Assurance
    - Probability + *Any Other Data?*
  - Final Control Strategy (CS)
    - The decision/recommendation
- One influences the understanding, sufficiency and evaluation of the next

Reviewer Considerations for Clonality at the IND stage

- At the IND stage, reviewers will do a initial assessment of the information provided about the clonality of the MCB. If potential concerns of “clonality” are noted, then a comment **may** be provided
- Lack of assurance of clonality is **not** typically a hold issue.
- Lack of assurance of clonality **will** influence the assessment of the control strategy at licensure

What is "Acceptable" Probability?

- There is not a firm numerical threshold for probability
- The probability of clonality must be calculated prospectively, no back-calculating (something did not grow ≠ nothing was there)
- Typically, two rounds of LD at the appropriate dilution level is acceptable
- Adaptation to serum-free conditions should be performed ***prior*** to cloning step. If adaptation occurs post-cloning, additional cloning steps are needed.
  - Serum added as part of expanding single-cell clones will not require additional rounds of cloning.
- Other techniques including FACS and ClonePix can provide high probability of clonality when performed using the correct procedures and parameters (alone or in combination)
- Imaging techniques could be used to supplement data from LD, FACS or ClonePix

What is “Acceptable” Assurance?

- If there is “acceptable” probability of clonality then additional assurance is not typically necessary or requested
- The additional data provided for assurance will not definitively prove clonality but rather provide supporting evidence
- Agency is open to proposal for different types of data (all about reducing risk)
- The type of data used to support clonality is dependent on the way the cells were cloned.
  - Dilution and characterization of individual subclones from the MCB
  - FISH could be an appropriate (but not for those cloned using site-specific integration).

Acceptability is dependent on adequacy final control strategy:

- High probability ⟹ Acceptable (no additional CS modification)
- Low probability + High Assurance ⟹ Acceptable (no additional CS modification)
- Low probability + Little Assurance + Augmented CS ⟹ Acceptable

Adapted from R. Novak, CASSS Strategy Forum, Jan 2017

Considerations at the BLA stage

- Adequate assurance of clonality should be provided at the time of the BLA submission.
- Supplemental data may be requested during the course of the BLA review
- A final determination of “low assurance” of clonality of the MCB at the time of licensure does ***not*** necessarily preclude approvability of the application.
- Augmentation of the control strategy, and/or a PMC could be an acceptable approach to managing a non-clonal MCB for licensure.

Augmentation of the Control Strategy

- Changes made to the control strategy for managing a potential non-clonal cell line will be product and application dependent (based on what we know we know, and what we know we don't)
- Some strategies that **have been** implemented:
  - Adding additional specifications (LC-MS/MS for Sequence Variants, Glycosylation despite not impacting MOA, etc.)
  - Assessment of limits of in vitro cell age
  - Establishing additional critical process parameters (growth parameters escalated to CPP)
  - Trending and Statistical Process Control
  - Additional risk assessment for changes in critical raw materials (media, components, etc.)
  - Tighter controls for re-qualification of a new WCB

Adapted from R. Novak, CASSS Strategy Forum, Jan 2017

Non-clonal Lines Post-Licensure

- Sponsors should consult the Agency as soon as possible if evidence of a non-clonal MCB becomes apparent.
- Sponsors should establish a plan to demonstrate the adequacy of the control strategy including a sub-clone analysis assessing the affect of different clonal populations on CQAs and process attributes.
    - We acknowledge accumulating this type of data may be time consuming
- In the interim, the sponsor should develop a plan to keep manufacturing an appropriate product
    - the use of statistical process controls to evaluate drift in the product
    - establishing additional critical process parameters
    - additional characterization for each lot of drug substance manufactured

Should I Reclone the MCB instead?

- Recloning of the MCB introduces its own substantial risk and this risk increases further along in development
- We do not necessarily advise to reclone the MCB late in development; introduction of a more robust control strategy may be more suitable (and preferable) approach.
  - May become difficult to link pre-clinical lots with clinical/commercial lots
  - Loss of development data
  - Issues with comparability

Conclusions

- The general expectation is that MCBs are created in way that provides sufficient probability of clonality
- The probability informs the assurance which informs the control strategy for a product.
- Lack of assurance of clonality does not necessarily result in INDs being placed on hold or preclude approvability of BLA
- Reviewers will look at the totality of the evidence to determine whether sufficient information has provided adequate assurance of clonality
- To address a low probability and assurance of clonality, the control strategy can be supplemented to manage a non-clonal MCBs to support licensure.

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