U.S. FOOD & DRUG ADMINISTRATION

Regulatory Science Considerations for Cell Counting

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Cell Counting is Crucial for Products in Multiple FDA Centers

- CBER: many cell-based products, cell-based assays
- CDER: stem-cell based screening assays for drug development, cell-based production of biologics
- CDRH: devices for counting cells, diagnostics
- CVM: many cell-based products
- CFSAN: presence of cells in certain products

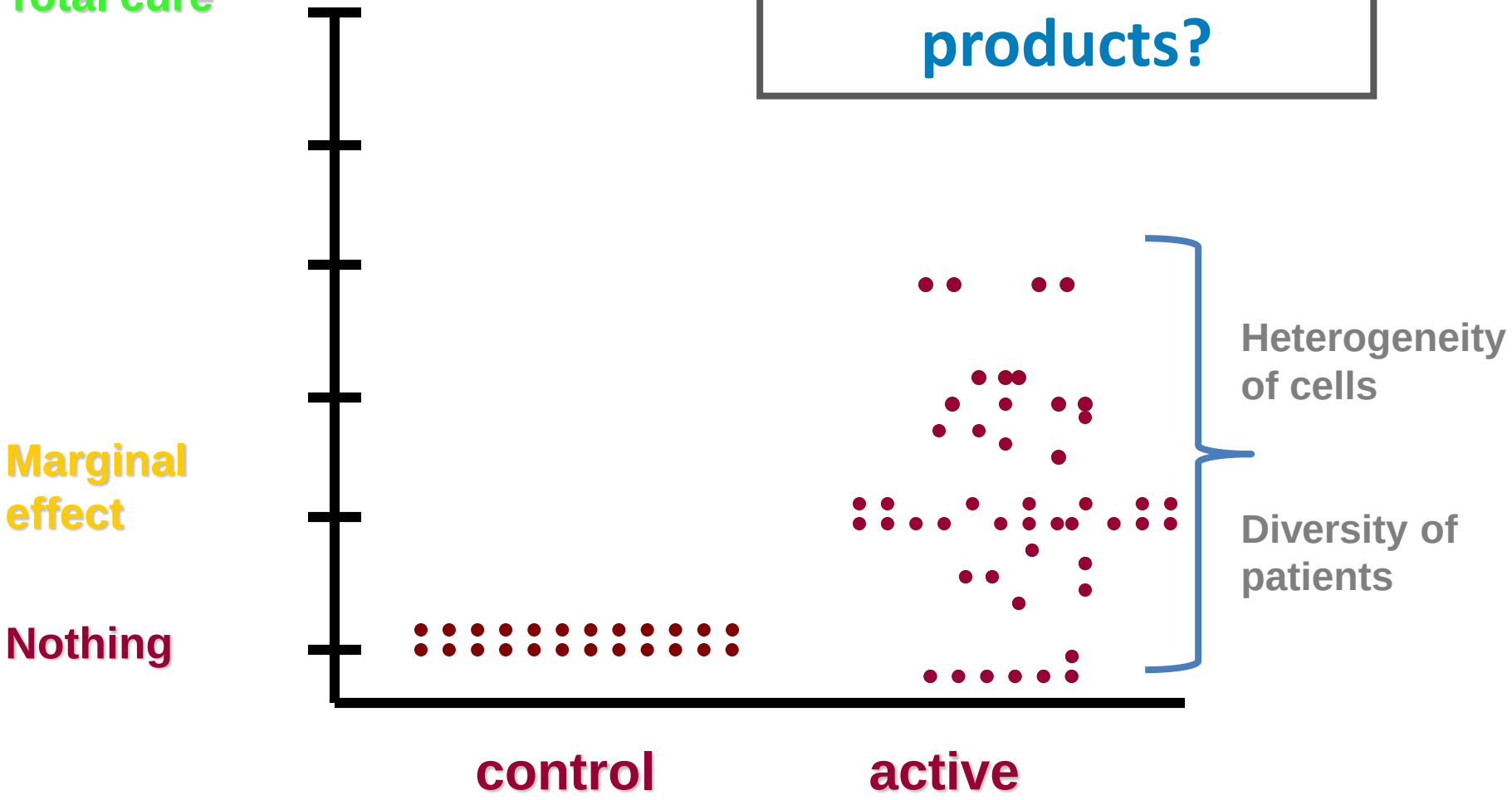
- My examples: CBER- regulated cell-based products
  - Generally applicable to other FDA-regulated products

Regulatory Considerations for All Biologics

- Safety, efficacy, purity, potency, identity, quality
- Oversight of both product and process
- Quality control of source materials, intermediates, and product
- Reproducibility of lots
- Comparability after manufacturing change

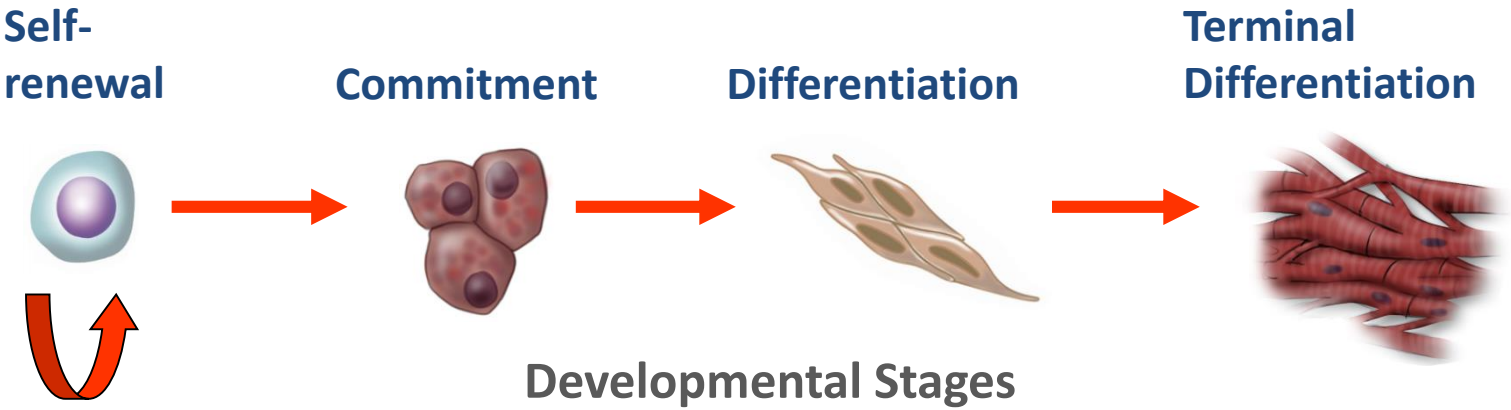
Reliable cell count is crucial to all of these!

What do you measure to identify the effective products?



Slide courtesy of Malcolm Moos

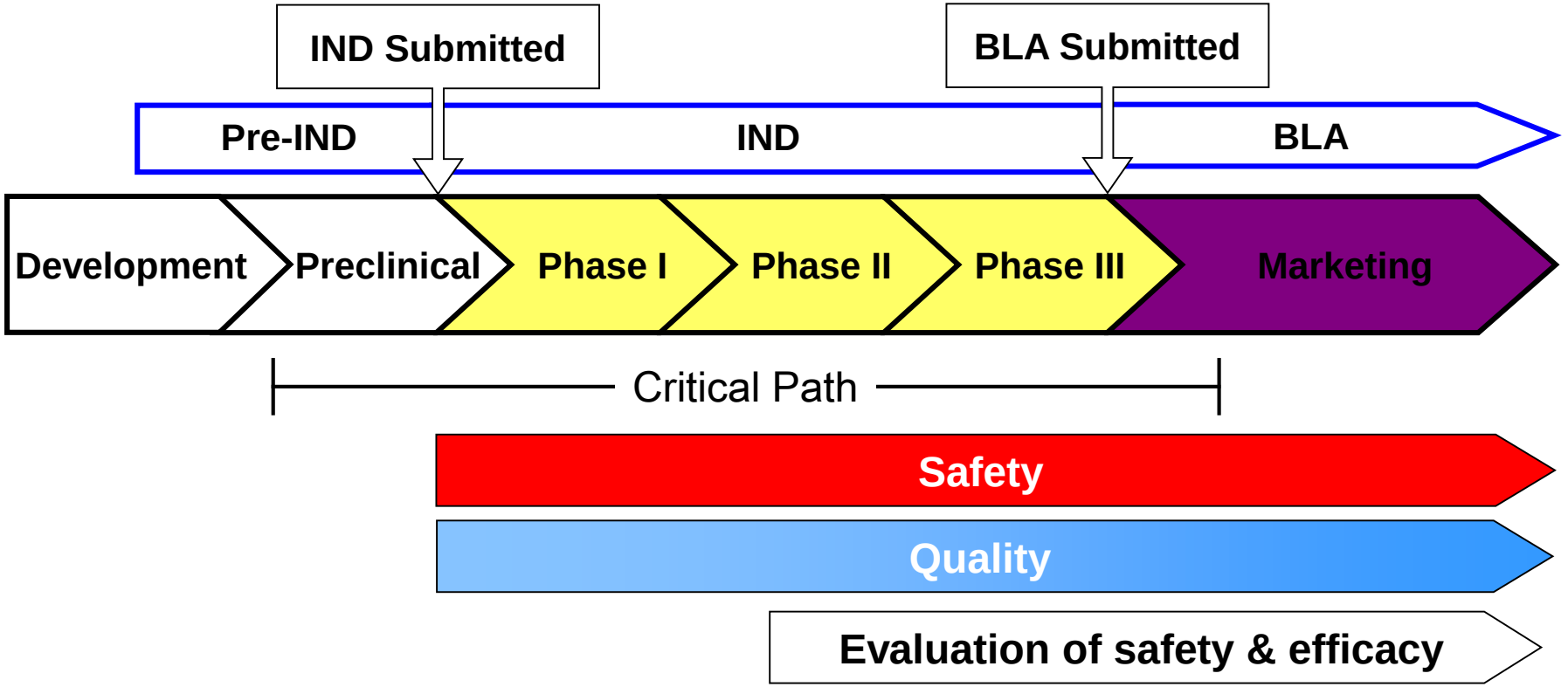
How Can We Help Fulfill the Tremendous Promise?



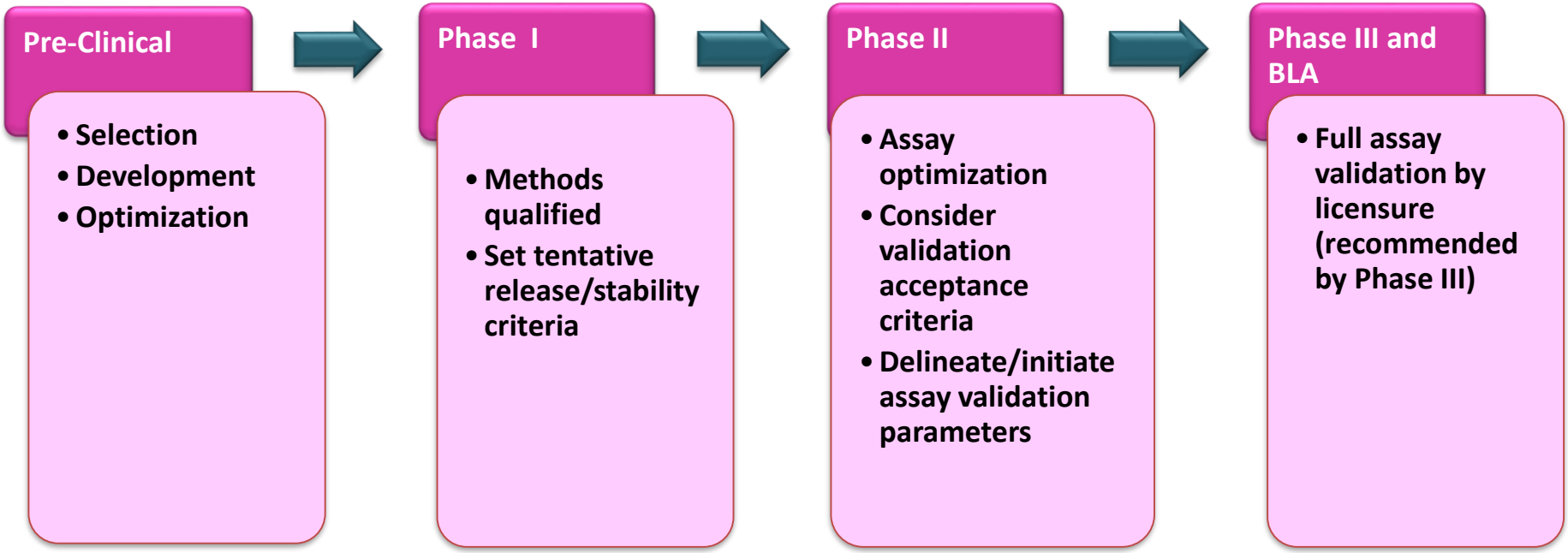
Can we develop ways to identify Quality Attributes that predict safety and effectiveness?

(Purity, Identity, Potency)

Counting is Crucial During All Stages of Cell-based Product Development



Analytical Method Development



Assay Qualification: Determining if an assay is suitable for its intended purpose

Assay Validation: Assuring that the assay is suitable to its intended purpose on a routine basis

Cell Product Characterization

- **Cell count/viability**
- Purity
  - Free of extraneous materials
- Identity
  - Specific test to distinguish it from others
- Potency
  - Assay for biological function

- Sponsor determined methods
- **Cell count crucial for many of these parameters**
- **Preclinical safety studies and clinical dose based on these tests**
- **Viability recommendation: 70%**
  - **When are you counting?**
  - **Thawed or "recovered"?**

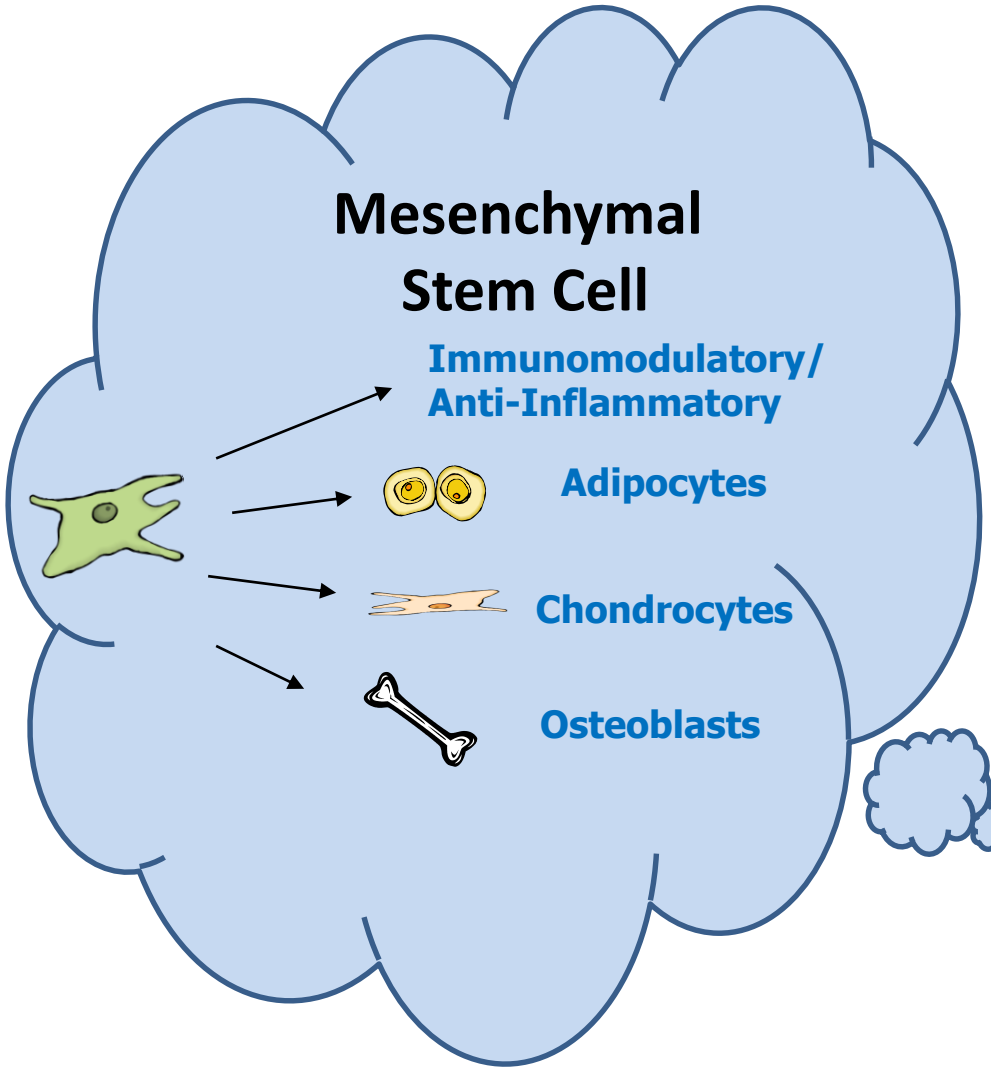
Additional Considerations for Cell-based Products

- Counting often established for one product by one manufacturer in one site
- Other considerations
  - Multiple clinical sites
  - Multiple manufacturing sites
  - Technology Transfer (new site, scale out, etc.)
  - Influence of cell delivery method
  - Automated QC methods
- Standards (written, physical) would be beneficial

Validation Considerations

- Useful references
  - Analytical Procedures and Methods Validation for Drugs and Biologics. Guidance for Industry 2015.
    - For INDs, sufficient information is required at each phase of an investigation to ensure proper identity, quality, purity, strength, and/or potency. The amount of information on analytical procedures and methods suitability will vary with the phase of the investigation.
  - ICH VALIDATION OF ANALYTICAL PROCEDURES: TEXT AND METHODOLOGY Q2(R1)
- Examples for cell counting
  - Robustness/ruggedness
    - Capacity to remain unaffected by small, deliberate variations in method to indicate reliability during normal use
  - Linearity
    - Dilution series and curve fitting (R2) over range tested
  - Accuracy
    - Variability (%CV) across replicate samples, multiple dilutions, (different methods)
  - Range
    - Cell dilutions that are accurate and precise
  - Intermediate precision
    - Different lots, different operators, different days
  - Precision: repeatability
    - Identical cell lots in same laboratories, same operators, same apparatus, short time frame
  - LOD
    - Lowest cell density detected in serial dilutions
  - LOQ
    - Lowest cell density that is accurate and precise

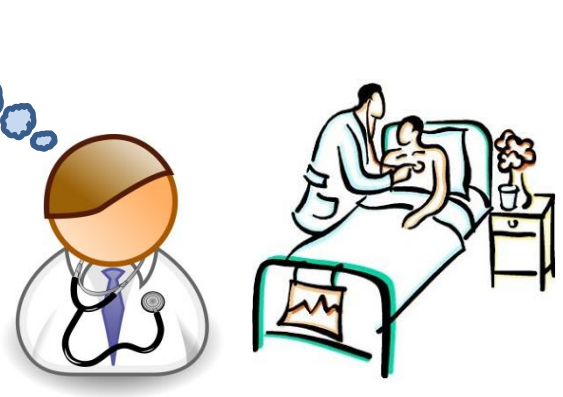
MSCs and Product Characterization



?

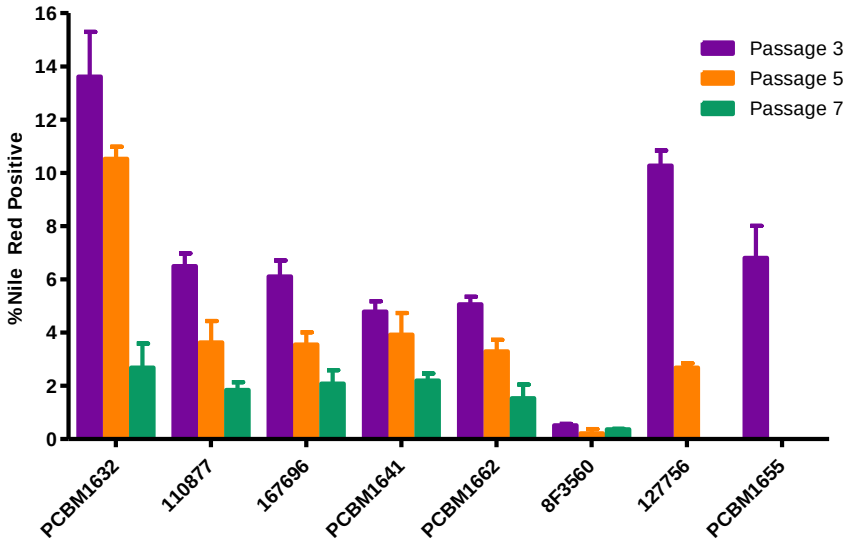
Manufactured
MSC

Adherent in culture
CD73+, 90+, 105+
Lymphocyte marker negative



Heterogeneity of Cells

- Total count of cells may not = total biological activity
  - Not all CD34+ cells are long-term HSCs!
  - Not all MSCs have the same biological activities



MSC Adipogenic Activity Decreases with Tissue Culture Passage: Donor Differences

Lo Surdo JL et al., *Cytotherapy, 2013.*

Benefits of Standards

(Written, Physical)

- Confidence/comparison
- Basic and Translational Research
  - Academic labs
  - R&D labs
  - Within context of one sponsor
  - Within community of developers
- Facilitate development of safe and effective cell-based products
  - Precise and Accurate Cell Counts

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OCTGT Learn Webinar Series:

http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

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