SESSION 4: NEXT STEPS

Moderator: Sheng Lin-Gibson, NIST

- Meeting summary
- Key concepts / outline for whitepaper
- Other businesses

https://www.surveymonkey.com/r/CCW_idea_box

Workshop Goals	Actions and potential solutions
Raise awareness of the importance and challenges associated with cell counting measurements	• Whitepaper • Additional NIST-FDA workshops
Develop and document best practices for cell counting	• Whitepaper • Develop methods of general use through appropriate forums
Discuss options to address measurement challenges through collaborative studies (NIIMBL)	• Send R&D topics to NIIMBL/TAC for funding to advance biomanufacturing
Workshop outcomes to support the development of international standards and more specific measurement challenges	• Cell counting serves as a use case for upcoming ISO standard effort for cell characterization

Recap

- Overarching theme: Counting is important
- Many use cases, important considerations, lessons learned, opportunities/new technologies
- FDA does not require prescriptive methods:
  - fit for purpose
  - system suitability
- Example of measurement assurance strategies for cell counting

Terminology

- What is required during qualification, validation, and verification

Fit for purpose

- I would like to count AA cells in media/matrix BB using CC methods for DD purpose

AA	BB	CC	CC
MSC	Universal	Manual	Release
iPSC	media	Automated	Dose
Car-T	Cryo-	Impedance	In process
…	preservant	Imaging	Compability
	…	Flow	R&D
		…	…

- What is good enough – how to set specification using meaningful parameters

Various approaches

- General framework vs. individualized methods
- total cell count → → various stages of cell health
- Improving the quality of “gold standard” methods → → new counting technologies

3. ACCURACY

The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional **true value** or an **accepted reference value** and the value found.

This is sometimes termed trueness.

Ref: VALIDATION OF ANALYTICAL PROCEDURES: TEXT AND METHODOLOGY Q2(R1)

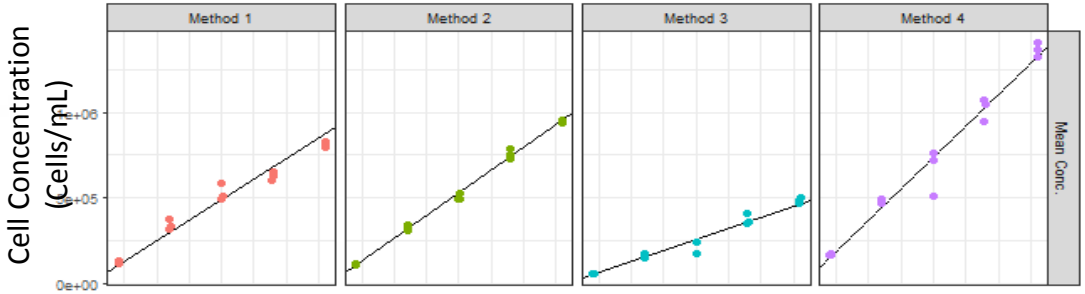
Role of reference material/reference standards

- Beads and their roles in calibration, comparability
- Cells RM as an in process control, proficiency testing
- Opportunities for new, better reference materials/what is NIST doing

Evaluating the quality of cell counting methods in the absence of a ground truth

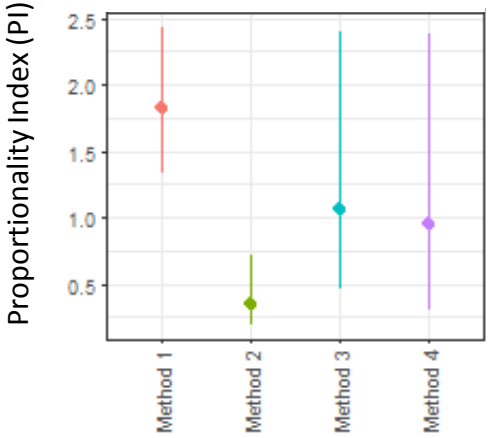
ISO/WD 20391-2 [Under development: 20.60]
Biotechnology -- Cell Counting -- Part 2: Experimental design and statistical analysis to quantify counting method performance

Cell Counting Results for 4 methods



- Comparability between methods
- Accuracy
- Precision
- Linearity (proportionality)
- Reproducibility

Proportionality



Tools to get to “good enough”

- Strategies for better measurements
- Education materials
- Reference materials/reference standards
- Bioprocessing control (equipment, reagent, etc.)
- Competency
- Method standards

What works well?

(ripe for standardization / best practices / SOP)

What are ongoing efforts

- Methods and funding to keep the discussions going
- NIST certified beads consortium

- ISO Cell Counting Part 1– definitions and general considerations
- ISO Cell Counting Part 2 – method to evaluate the quality of cell counting

What is needed?

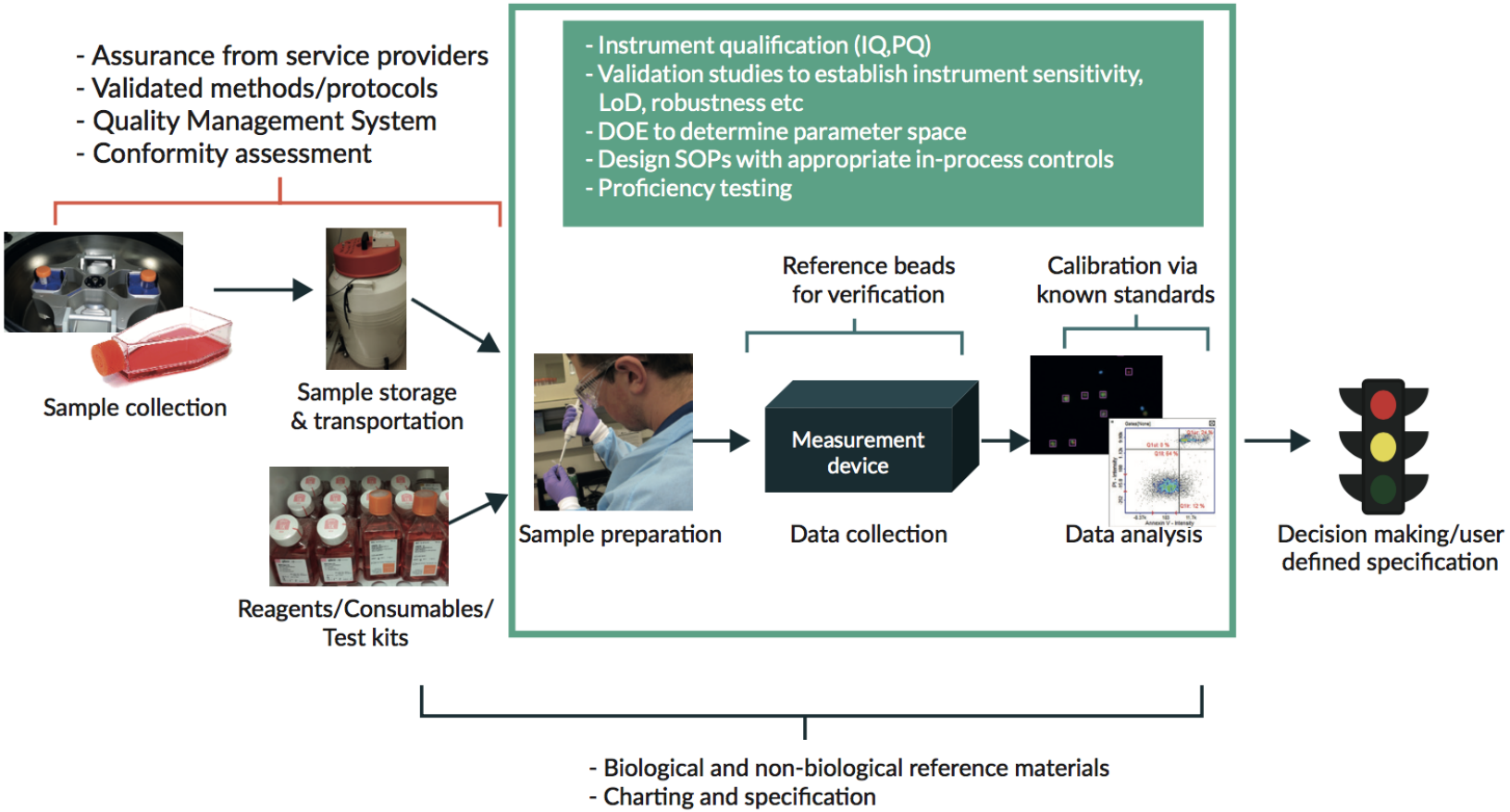
(common understanding, methods, guidance, etc.)

- Deep dive on several case studies
- Best practices
- Spike in or other methods
- Minimum information for a specific method to provide confidence
- Inter-laboratory study / formation of consortium

Additional Topics for NIST-FDA workshop

FIGURE 2

An example of a generalized cell counting process that involves an automated imaging device, and where potential controls and standards for managing and minimizing sources of variability could be used.



The central green box contains 3 steps of a typical measurement process; other aspects such as the composition of donor samples, reagent sourcing, and sample handling may contribute additional variability to the cell counting process

Lin-Gibson, et al. Bioinsights 2016.

Working with NIST

Laboratory collaborations via joint studies, CRADA, consortium, post-doctoral opportunities, etc.

Participate in NIST workshops

Participate in standards development efforts, including inter-laboratory studies

Learn more @ www.nist.gov or search NIST Advanced Therapies

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Outline of a whitepaper

- Brief recap of workshop
- Key concepts
  - What works well
  - What is ongoing
    - ISO Cell Counting Part 1– definitions and general considerations
    - ISO Cell Counting Part 2 – method to evaluate the quality of cell counting
  - What is needed
    - Gaps in current guidance (communication, technical, guidance?)
    - Additional tools to improve measurement assurance

TC276 cell characterization standard effort

based on outcomes of Jan2017 US-Japan Workshop

Cell characterization "umbrella" standard – to enable common understanding

Cell characterization measurement process standard

By attribute	By technique	By purpose	By cell type
Cell counting 1 & 2	Flow Cytometry	Cell therapy products	??
Viability ??	Imaging	Gene therapy products	??
...	...	Drug discovery	

Cell Counting Standards are under development; all others are listed as examples