

# What follows:

- Jeff Staecker slides from CMC Forum CASSS CMC Strategy Forum “Methods on the Move: Addressing Method Transfer Challenges for the Biopharmaceutical Industry” held on 23 January 2017 in Washington, DC.
- Article summarizing forum that includes talks from regulators and industry can be found at:

*<https://bioprocessintl.com/business/cmc-forums/methods-on-the-move-addressing-method-transfer-challenges-for-the-biopharmaceutical-industry/>*

# **Risk-Based Approach to Method Transfer**

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# Today's Discussion

- Background
- FMEA perspective on method transfer
- Application examples
- Wrap-up for risk-based approach to method transfer
- Some highlights from Jan 23 CASSS CMC Forum on method transfer

# Abbreviations/Definition

**QS:** Quality System

**SU:** Sending Unit

**RU:** Receiving Unit

**ALCM:** Analytical Lifecycle Management

**Cpk:** Process capability index

**SPC:** Statistical process control

**FMEA:** Failure Mode and Effects Analysis

**Method Transfer Failure:** *Any appreciable immediate or long-term problem linked to RU results different than expected SU results*

# Method Transfer Goals

- Meet financial goals
- Ensure that safety/efficacy not compromised
- Assure that method validation applies to RU
- Regulatory compliance

# Changes

“Changes lead to differences. The differences may or may not be measurable and the changes may or may not be meaningful”

- Method transfers are a change that will result in “differences”
- Method transfer processes should be designed to detect and prevent meaningful adverse changes

# Transfer Failures

Failure manifests during/soon after transfer:

- Often have high visibility and commitment to fix by both SU and RU
- Easier to address since labs, people, and materials are still available

Failure manifests months to years post-transfer:

- Lower visibility and expectation that RU figure things out can be high
- Comparison to original method execution by SU may be impossible
- Detection in the absence of effective method monitoring can be quite difficult

# Method Problems Identified During Method Transfer

- HPLC dead volumes different
- HPLC column heaters different
- HPLC backgrounds different
- Use of “equivalent” items
- Bias between spectrophotometers



# Variable Conditions that Lead to Method Transfer Problems

- Focus/training
- Wall voltage
- Elevation
- Relative humidity
- Ambient temperature
- Solar Radiation
- Shipping/handling
  - Many transfer problems can be missed if method transfer is dependent on “point-in-time” transfer data

# ICH Q9

“In addition, the importance of quality systems has been recognized in the pharmaceutical industry and it is becoming evident that quality risk management is a valuable component of an effective quality system.”

# Common FMEA Parameters Driving RPN

- Risk Priority Number (RPN) a multiple of:
  - Impact (severity)
  - Probability
  - Detection

# Risk Impact (Severity)

Impacted by:

- Use of orthogonal methods
- Understanding product safety profile
- Product supply

➤ *Risk Magnitude is Product and Method Specific*

# Risk Probability

ICH Q9 “The evaluation of the risk to quality should be based on scientific knowledge....”

- A lot is often known about methods and processes prior to transfer
- Process Cpk is a useful tool as a step in determining potential impact of method performance due to transfer

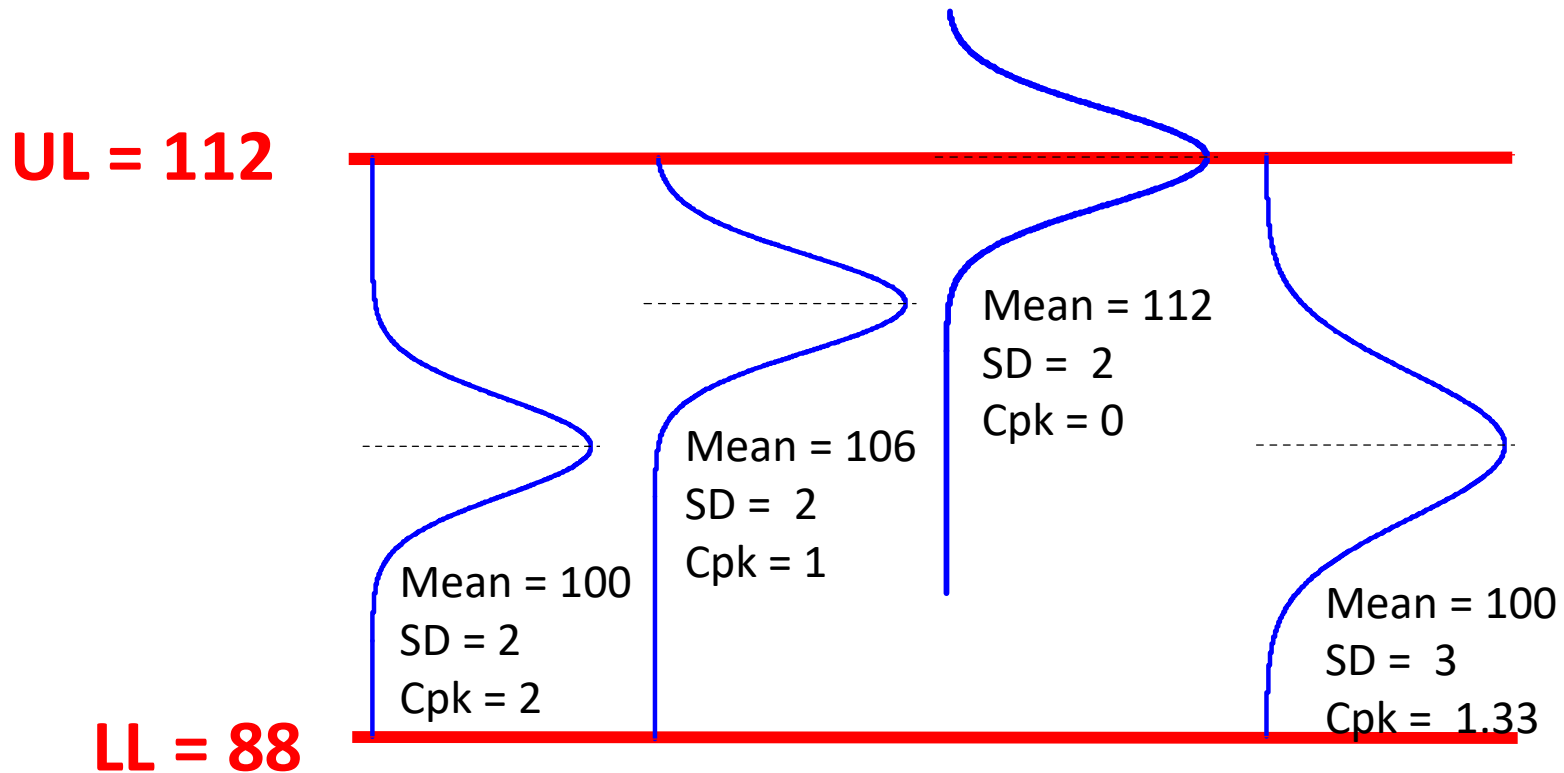
# Process Performance

- Cpk is commonly used to monitor process performance reflecting specifications, analytical capability, and process output.
- Cpk can help determine whether method transfer changes (bias/precision) pose a risk to product quality

# CpK

- Higher numbers better
- Driven by:
  - Specifications/limits
  - Variability
  - How centered the process mean is

# Transfer Risk based on Cpk

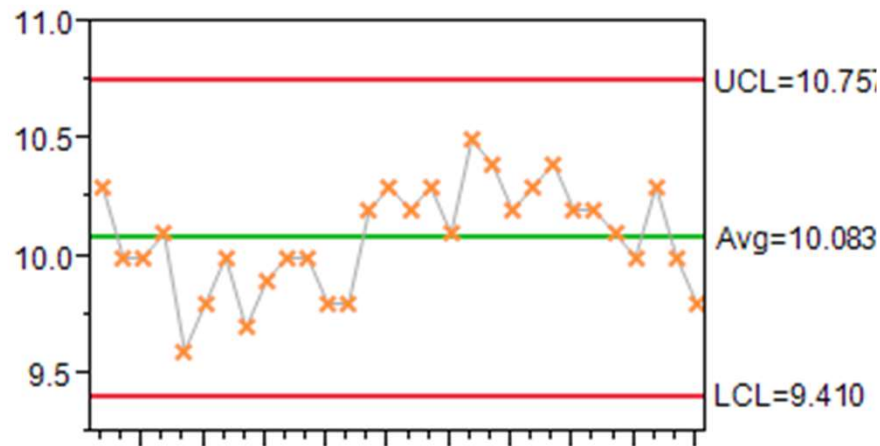




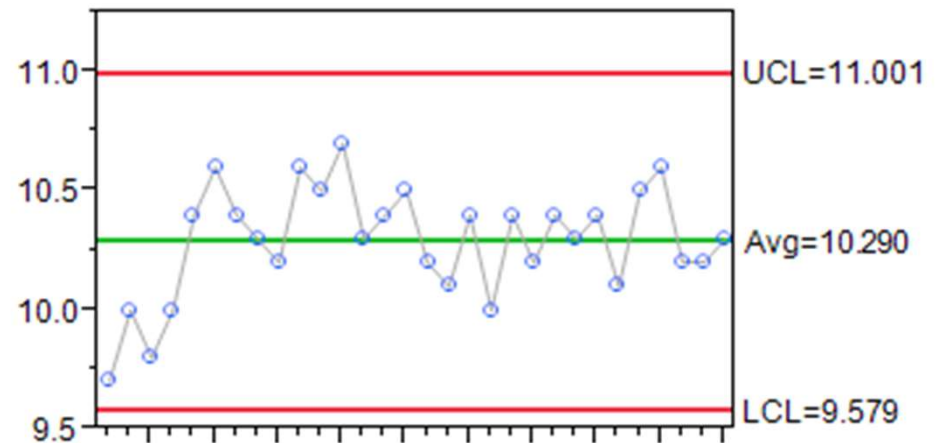
# Comparison of Analytical Results

Acceptance Specifications are 8 – 12

Site 1



Site 2



# Taking Cpk Risk-Based Approach:

- Risk-based criteria (e.g., probability of false positive or false negatives) can be established for method transfers based on process and analytical knowledge
- Methods associated with well-controlled processes have less transfer-associated risk
- Risk-based approaches should be pro-active rather than retrospective
- Product specifications can't be continually tightened to reflect process capability

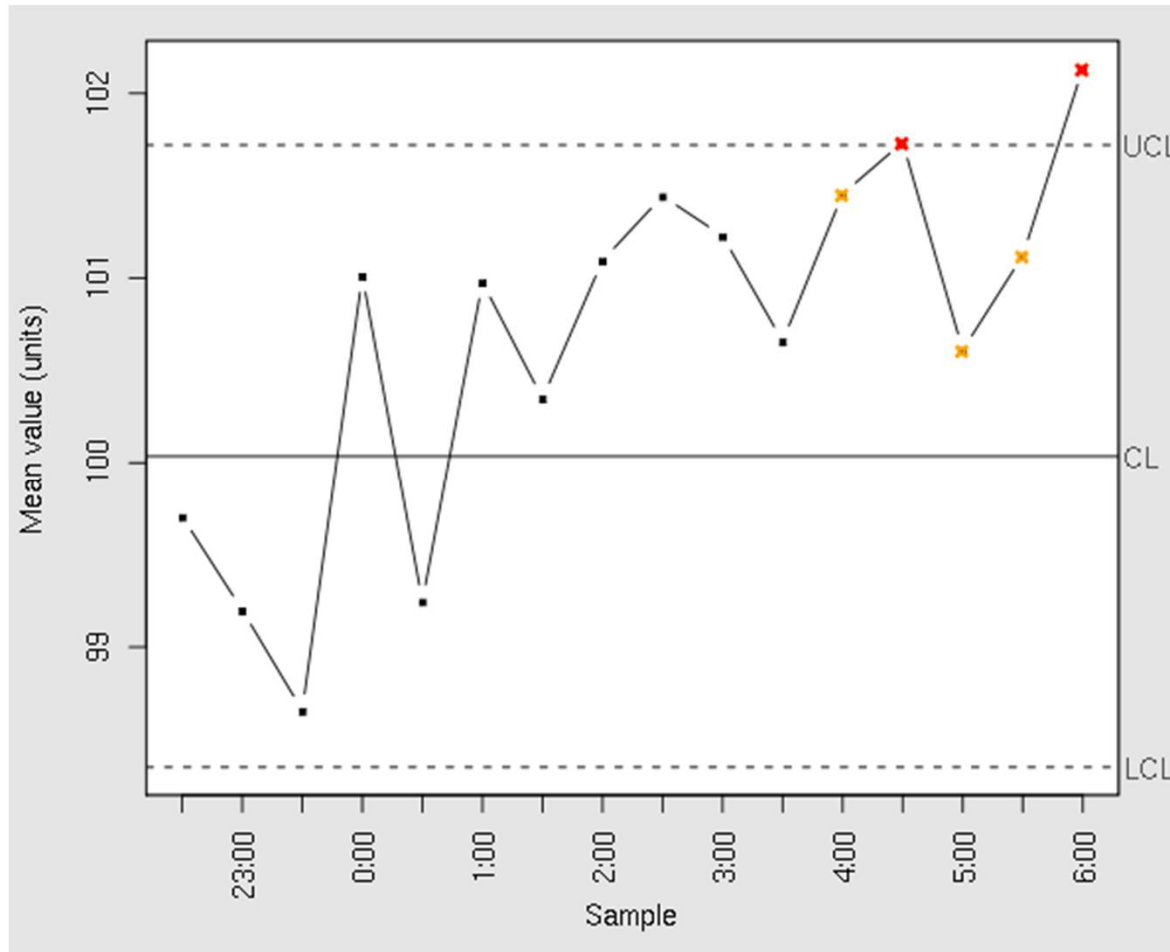
# Detectability

- Method monitoring to detect method transfer issues is often not part of the method transfer process
- Detecting issues subsequent to transfer as *part of method monitoring can be a potent mitigation to method transfer risks*

# Method Monitoring

- Deviation, investigation, system suitability criteria, and right first time history are important
- Method performance monitoring (e.g., SPC) can be critical
  - Trends references/controls
  - Can provide a longer term perspective than simple system suitability limits
  - Can provide real time method feedback
  - Repetitive problems should feed into method history and ALCM
  - SPC is a proven Quality tool

# Control Charting For SPC



# Method Monitoring at RU

- Provides potent mitigation for method transfer risks
- It may be necessary for RU to establish their own control range for controls/references
- Common references (e.g., WRS) and controls can be critical to effective long-term method monitoring
- Performed by some companies but usually not part of method transfer submissions

# Applications of Risk-Based Approach

- Establishing transfer specification
- Risk matrix
- Addressing one-off issues

# Risk Matrix Leads to Appropriate Level of Work

Transfer A	Transfer B
Process and method Cpk excellent (3.5).	Process and method Cpk poor (0.9).
Good history transferring between labs.	No or poor history transferring between labs
Method has established references (WRS), method monitoring (SPC), and ALCM.	No established reference and limited history makes effective method monitoring (SPC) difficult.
Easy HPLC method that is shoot and dilute	Complex ELISA.
Part of platform system that both SU and RU are familiar with	Enzyme assay for SU and RU that have previously only worked with MAb



# Risk-Based Approach to Method Specificity

Question	Analysis	Comment
How likely is the method transfer to impact specificity?	<ul style="list-style-type: none"> <li>Method is unchanged and matrix is unchanged.</li> <li>Robustness as part of method validation showed excellent specificity even for grossly adulterated matrix.</li> <li>Shipping/sample analysis studies have demonstrated that neither shipping or sample handling at RU impacts samples</li> </ul>	The risk of method transfer impacting method specificity is low
Would a change in method specificity at the RU be detected?	<ul style="list-style-type: none"> <li>Process and method monitoring will detect meaningful changes in analytical results due to specificity.</li> <li>Ongoing monitoring of working reference standard provides linkage to previous analytical performance</li> <li>Ongoing ALCM activities currently in place at SU will be applied at RU</li> </ul>	A meaningful change in method specificity is likely to be detected preventing use of problematic results.
<p><b>Conclusion:</b> Additional method specificity studies such as looking at 3 lots of material during method transfer is unnecessary. The inclusion of additional lots has the potential to introduce a small amount of noise making statistical comparison of SU and RU results more challenging. No additional method specificity studies will be undertaken and a single lot of material will be used for method transfer.</p>		

# Method Transfer as Part of the QS



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# Questions?

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