Biopharmaceutical Method Transfer as part of the Quality System.

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Experience

- Involved in method and process transfers for 25 years
- Bring perspective from both biopharmaceutical and device/diagnostic industries
- Experience with consent facility puts emphasis on Quality System perspective

Abbreviations/Definition

QS: Quality System
SU: Sending Unit
RU: Receiving Unit
ALCM: Analytical Lifecycle Management
Cpk: Process capability index
SPC: Statistical process control

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

For Today

- Some examples of transfer failures
- Then and now – changes in method transfer over many years
- Regulatory and industry expectations
- Fitting risk-based method transfer into larger QS
- Examples of how to efficiently fit method transfers into larger QS
  - *We are only covering transfer of non-compendial biopharmaceutical methods today.*
  - It is assumed that formal method transfers are required starting with validation of methods used in conjunction with pivotal clinical trials

Method Transfer Goals

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

➢ There are no clear detailed guidelines currently available!

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

Familiar Causes of Method Transfer Failures

- Method SOP unclear
- HPLC dead volumes different
- HPLC column heaters different
- HPLC backgrounds different
- Sample handling/training
- Use of “equivalent” items

Unexpected Causes for Transfer Failures

- Bias between spectrophotometers
- Wall voltage
- Lab elevation

➢ Not all problems can be predicted and many only show up over time!

Method Transfer Failures Have Led to:

- Increasing scrutiny of method transfers by industry and regulators
- Increasing challenge for companies:
  - Identifying/screening RU
  - Higher cost/resource requirements
  - Changing business plans to reduce/eliminate transfers
  - Developing early business strategy to comprehend where methods will be run
  - Addressing transfer failures

20th Century Method Transfer

- Transfers between companies less common
- Less common than today to transfer same method to several locations across the globe
- Less regulatory scrutiny
- Risk-based approach rarely used
- Post-transfer method monitoring inconsistent and frequently ineffective
- Acceptance criteria was commonly +/- 2 sd

+/- 2 sd Transfer Criteria Formerly Used

- Wide and easily met
- Rewards large sd:
  - Poor precision increases sd
  - A small number of data points increases sd
- Doesn't answer key question of required performance by SU and what is needed to meet required performance
  - ➢ No longer accepted by many regulators or people in industry
  - ➢ Not statistically valid

Regulatory Expectations for Method Transfers in 2016?

- Equivalency testing
- Use of 2-sided student t test (TOST)
- SU and RU +/- 1 sd
- Use more than one lot of material for transfer

➢ Not currently in any official regulatory guidance

+/- 1 sd /TOST Impact

- Expectations often established *separate* from risk-based approach
- High method failure rate
- Focuses on point-in-time transfer rather than long-term transfer impact
- Companies employing strategy different than regulator suggestion
  - Differences addressed as part of filings with associated risk of regulator acceptance
- Companies changing business strategies

Industry Practice

- Variable
- Perspective of integrating analytical transfers into larger QS:
  - Sometimes absent
  - Varies when applied

Method Transfer as Part of the QS

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Fitting Transfers into Larger QS cont.

- Interaction of analytical transfers is complex and touches on many parts of QS:
  - Documentation
  - Investigation/deviations
  - Quality Technical Agreements (QTAs)
  - Method validation
- Major interaction should occur with:
  - Risk management
  - Method monitoring

Risk-Based Approach to Method Transfers

One Potential Approach

- Utilize FMEA
- Principles are more important than particular application

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

- Risk Priority Number (RPN)
  - Risk
  - Probability
  - Detection

- RPN number drives categorization of risk which drives actions

Risk Magnitude is Product and Method Specific

Impacted by:

- Use of orthogonal methods
- Understanding product safety profile
- Etc.

➢ Beyond the scope of today's presentation

Risk Probability

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

- A lot is known about methods prior to transfer
- CPk is a useful tool as a step in determining probability of problems

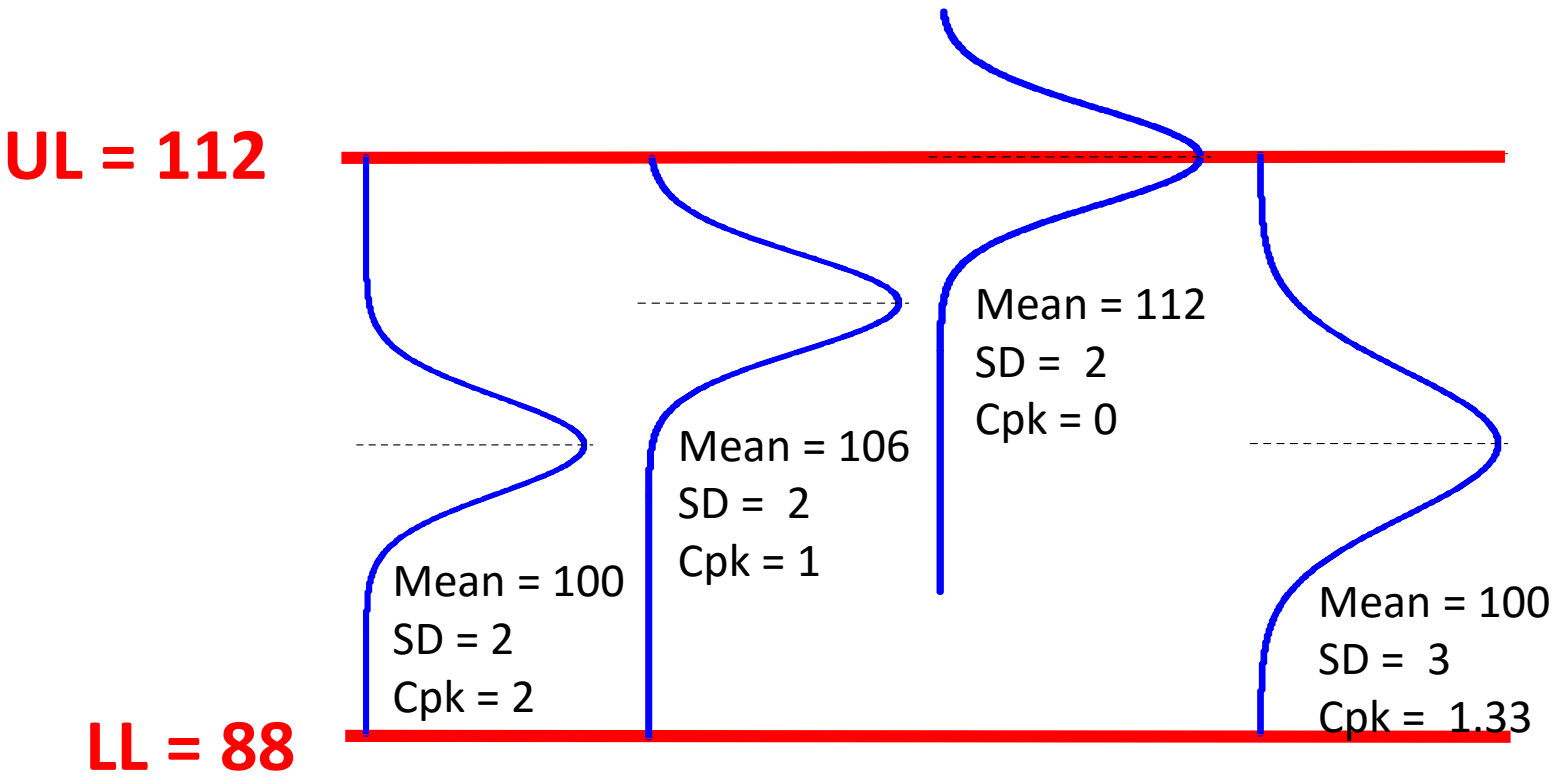
Information for Risk Assessmenbt

- Utilize current parameters being tracked by ALCM or other parts of QS
  - Right first time
  - Deviations
  - Investigations
- Process Cpk is important in understanding potential impact of analytical changes on the probability of an inappropriate measurement

Process/Method Performance

- Cpk is commonly used to monitor process performance reflecting specifications, analytical capability, and process output.
- SPC is commonly used to monitor methods to ensure control over a period of time
  - Method monitoring will be discussed as part of monitoring

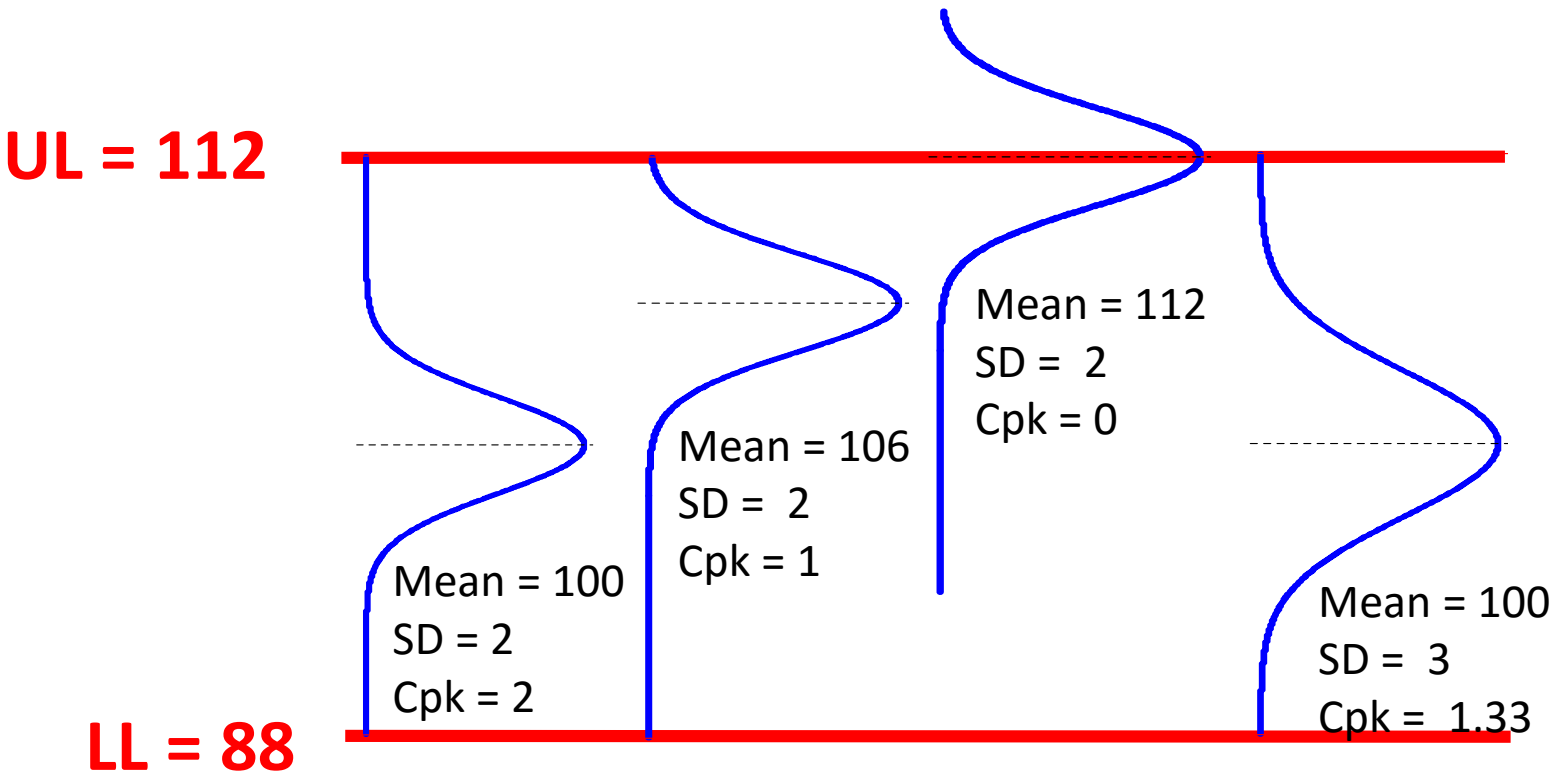
What is Cpk?


UL = 112
LL = 88
Mean = 100
SD = 2
Cpk = 2
Mean = 106
SD = 2
Cpk = 1
Mean = 112
SD = 2
Cpk = 0
Mean = 100
SD = 3
Cpk = 1.33

Can we Agree….

- Some methods can tolerate biases and/or bias changes better than other methods based on whether a change in precision or bias impacts decisions made from results?
- Should some methods or process be fixed prior to considering a transfer?

Cpk and Method Monitoring



Risk Imperative

Understanding that methods are differentially sensitive to change brings us into a risk-based approach to method transfers!

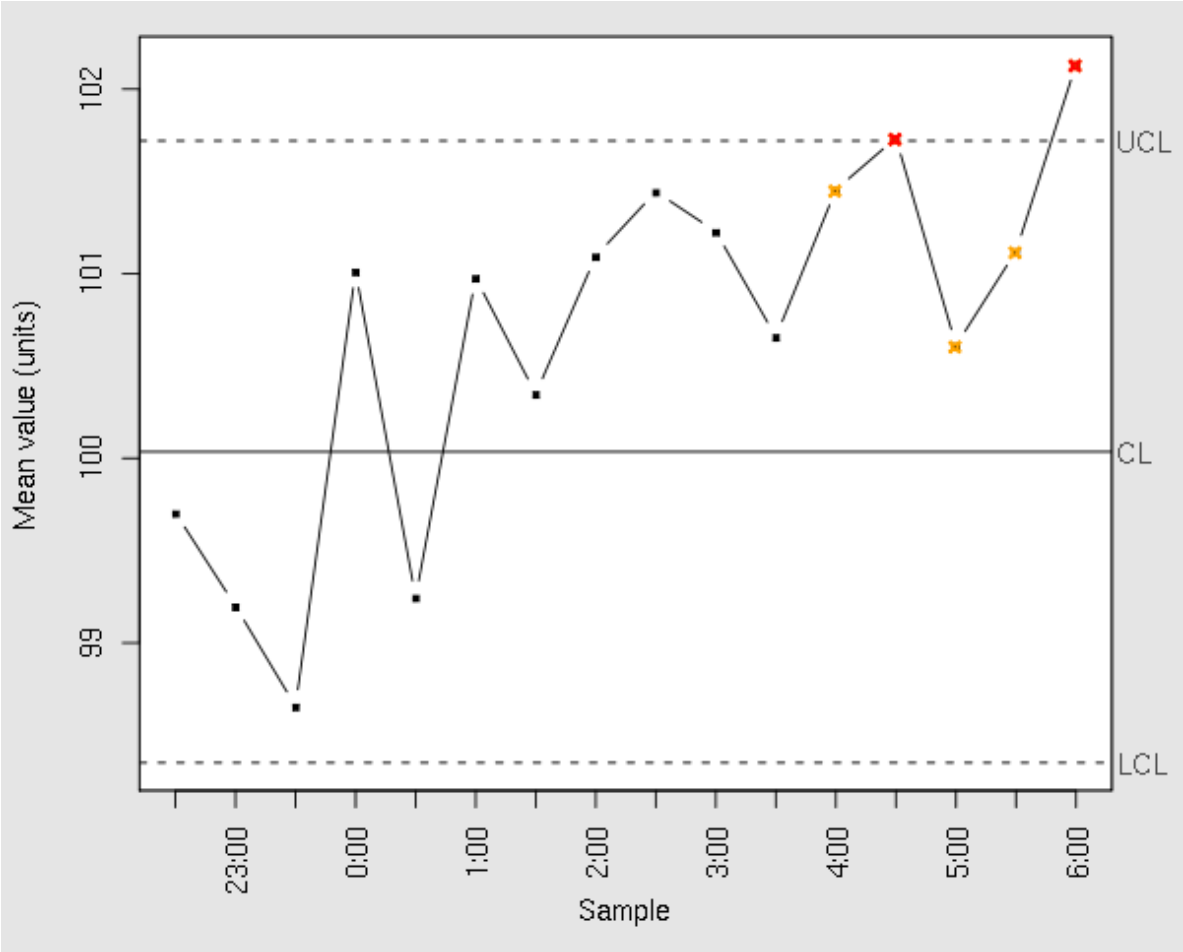
Detectability

- Detecting issues as part of method transfer protocol
- Detecting issues subsequent to transfer as *part of method monitoring*

Method Monitoring

- Deviation, investigation, and right first time history are important
- Method performance monitoring (e.g., SPC) is critical
  - Trends references/controls
  - Longer term measurement than system suitability limits
  - Provides real time method feedback
  - Repetitive problems should feed into method history and ALCM
  - Industry is increasingly using SPC

Control Charting For SPC



Application of SPC

- Utilize run rules
- Results outside of run rules require action
- Goal is to identify issues prior to failure

➢ Provides ongoing confidence in the method!

Method Monitoring at RU

- This is commonly overlooked when transfers are anticipated
- Method monitoring is a critical component of the method transfer risk profile
- Many companies don’t have procedures and/or experience in addressing transfer of method monitoring.

Method Monitoring at RU

- It may be necessary for RU to establish their own control range for controls/references
- It's important that monitoring at RU be similar to that at SU. For example, changing response to flags from 5 days to 3 months introduces quality and business risks
- A QTA between SU and RU should comprehend involvement of both SU and RU in method monitoring

Risk Management 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) impossible.
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 MAbs

Fitting Method Transfers into QS

- Need to align with existing procedures/practices as much as possible
- Need flexibility to adapt existing QS for method transfers

Proceduralized Transfer Requirements

- Checklist or risk matrix used to prepare for every transfer
- Useful for incorporating learnings into QS
  - FMEA should identify items but a documented matrix ensures a level of long-term consistency

Examples of Proceduralized Knowledge

List/risk matrix requiring evaluation of:

- SU vs RU training
- SU vs RU instruments
- SU vs RU lab environment
- RU verification of spreadsheet calculations
- RU data integrity management
  - This list can initially be established utilizing experienced people and then added to secure institutional learnings

Documentation of Transfer Strategy Into a Transfer Plan or Protocol

- Specifity is/is not included in transfer because…
- LOQ/LOD for analytes of interest is/is not included in transfer because (note, should indicate use/need of stressed material)…
- Linearity is/is not included in transfer because….

  - The entirety of method validation is usually not replicated at the RU

Using Multiple Lots for Transfer

- Question being answered must be clear!
- Has question already been addressed?
  - Specificity
  - LOD/LOQ
  - Linearity
- Inclusion of multiple lots can be problematic:
  - Availability
  - Can add noise to data

Feasibility Run

- Analogous to a process engineering run
- Useful in uncovering surprises that would result in transfer failure
- Unaware of any regulatory requirement or prohibition.
- Should align with approach for engineering runs
  - *It is not a substitute for a formal transfer and should not be used to generate specifications to make a transfer likely to pass.*

Transfer Protocol

- Needs to follow general documentation requirements described in QS (part of a larger transfer plan)
- Appropriate statistical analysis should be clearly documented
  - Some differences with SU QS may be required to best align with both SU and RU Quality Systems

Transfer Protocol Flexibility

Reference appropriate portions of QS noting any exceptions such as:

- Investigations will be documented per attachment A from SOP XXX. Section 1-4 of SOP XXX apply to the investigative process.
- Deviations must be documented in the report and signed off by (A, B, C) rather than following SOP YYY

Transfer Report

- Should provide clear summary of transfer and information related to transfer
- Report should reference appendices containing data that is consistent with SOP AAA
- It should be clear what approval of report means and reference appropriate QS control:
  - Data shows acceptable performance by RU
  - *OK for RU to initiate testing?*

What if You are Working with a Maturing QS?

- Risk-based approach still appropriate but will need to be situation-dependent (no one size fits all)
- Risk analysis may result in:
  - Tighter transfer acceptance criteria
  - Changes in method monitoring
  - A temporary mitigation strategy along with a longer-term CAPA

The Future: Analytical Target Profile?

From USP Stimuli Article:

"In this Stimuli article, the USP Validation and Verification Expert Panel discusses how the modern concept of a lifecycle model, which is based on process validation and described in ICH guidelines Q8, Q9, and Q10, can be applied to analytical procedures. The Expert Panel proposes that the traditional approaches to validation, transfer, and verification should be integrated into the analytical procedure lifecycle process rather than being viewed as separate entities. As a starting point or "predefined objective" according to ICH Q8, the requirements for a measurement of a critical quality attribute are established in the Analytical Target Profile.

Analytical Target Profile Consistent with FDA Guidance?

- 2015 FDA Guidance: “Analytical Procedures and Methods Validation for Drugs and Biologics Guidance for Industry”.
- “Transfer studies usually involve two or more laboratories or sites 469 (originating lab and receiving labs) executing the preapproved transfer protocol. A sufficient 470 number of representative test articles (e.g., same lot(s) of drug substance or drug product) are 471 used by the originating and receiving laboratories. The comparative studies are performed to 472 evaluate accuracy and precision, especially with regard to assessment of interlaboratory 473 variability.”

Wrap Up

- A risk-based approach to method transfer is appropriate
- Use of method transfers should be integrated into the Quality System by utilizing as many common components as Possible
- A successful transfer consists of point-in-time data from transfer protocol as well as implementation of appropriate method monitoring to ensure long-term sucess

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