Risk-Based Approach to Method Transfer

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Today’s Discussion

• Background
• FMEA perspective on method transfer
• Application examples
• Wrap-up

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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

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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

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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.

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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.”

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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

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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

- UL = 112
- LL = 88

- Mean = 100, SD = 2, Cpk = 1
- Mean = 106, SD = 2, Cpk = 0
- Mean = 112, SD = 2

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Comparison of Analytical Results

Acceptance Specifications are 8 – 12

Site 1

Site 2

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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

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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

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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

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Method Monitoring

• Mitigates risks associated with issues missed with point-in-time transfer protocol
• Can be applied based on knowledge rather than taking a one-size fits all approach:
  – Allows changes as more knowledge is gained
  – Can allow focus on problems
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 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 specification
• Risk matrix
• Addressing one-off issues

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# Risk Management Leads to Appropriate Level of Work

<table>
<thead>
<tr>
<th>Transfer A</th>
<th>Transfer B</th>
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<tbody>
<tr>
<td>Process and method Cpk excellent (3.5).</td>
<td>Process and method Cpk poor (0.9).</td>
</tr>
<tr>
<td>Good history transferring between labs.</td>
<td>No or poor history transferring between labs.</td>
</tr>
<tr>
<td>Method has established references (WRS), method monitoring (SPC), and ALCM.</td>
<td>No established reference and limited history makes effective method monitoring (SPC) difficult.</td>
</tr>
<tr>
<td>Easy HPLC method that is shoot and dilute</td>
<td>Complex ELISA.</td>
</tr>
<tr>
<td>Part of platform system that both SU and RU are familiar with</td>
<td>Enzyme assay for SU and RU that have previously only worked with MAbs</td>
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## Risk-Based Approach to Method Specificity

<table>
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<tr>
<th>Question</th>
<th>Analysis</th>
<th>Comment</th>
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| How likely is the method transfer to impact specificity?                | - Method is unchanged and matrix is unchanged.  
- Robustness as part of method validation showed excellent specificity even for grossly adulterated matrix.  
- Shipping/sample analysis studies have demonstrated that neither shipping or sample handling at RU impacts samples | The risk of method transfer impacting method specificity is low                                                                                                                                                                                                 |
| Would a change in method specificity at the RU be detected?             | - Process and method monitoring will detect meaningful changes in analytical results due to specificity.  
- Ongoing monitoring of working reference standard provides linkage to previous analytical performance  
- Ongoing ALCM activities currently in place at SU will be applied at RU | A meaningful change in method specificity is likely to be detected preventing use of problematic results.                                                                                                                                                          |

**Conclusion:** 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.

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Method Transfer as Part of the QS

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Wrap Up

• A risk-based approach to method transfer is appropriate
• A successful transfer consists of point-in-time data from transfer protocol as well as implementation of appropriate method monitoring to ensure long-term success
• The method transfer/monitoring process can be incorporated into the ALCM
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