

# Analytical Method Performance Monitoring

Ruojia Li

Bristol-Myers Squibb

4<sup>th</sup> Statistical and Data Management Approaches  
for Biotechnology Drug Development

October 30 - November 1, 2017

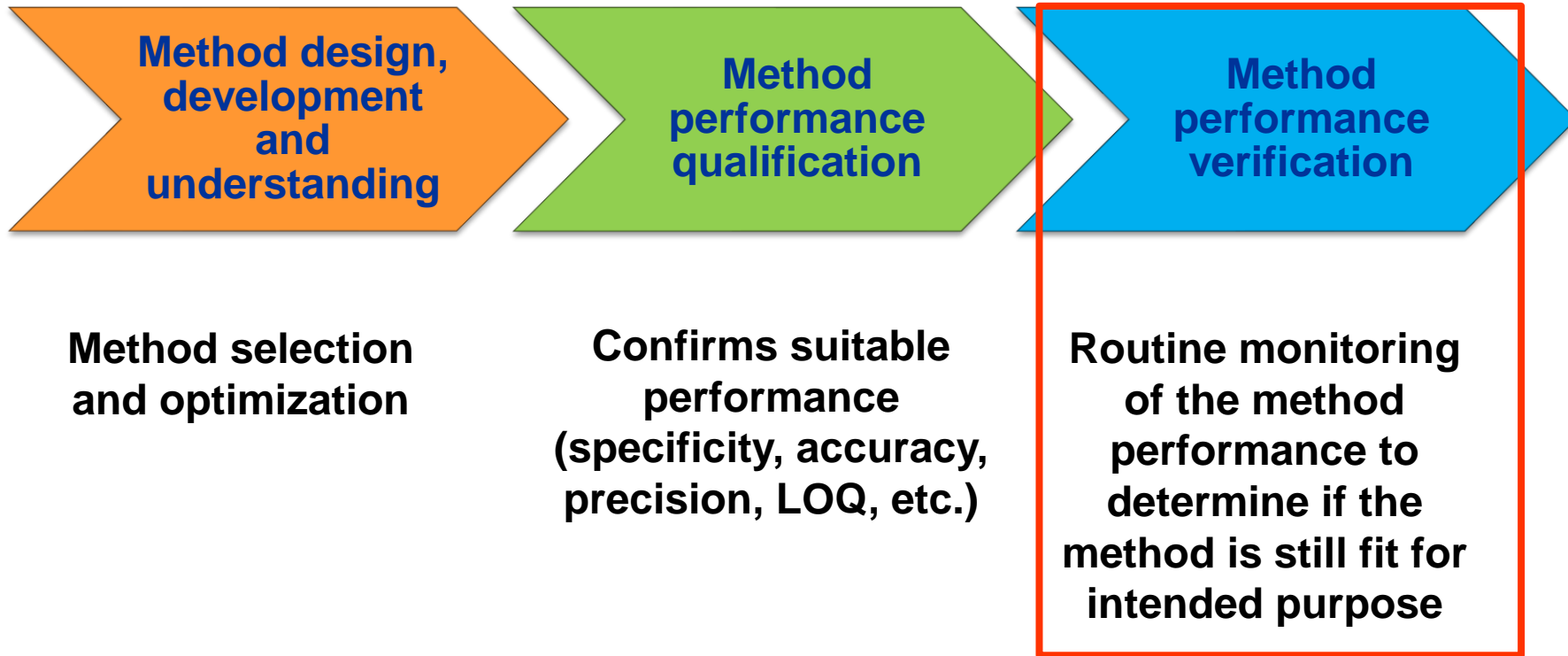
# Outline

---

- **Purpose of method performance monitoring**
- **Fundamentals of method performance monitoring**
- **Examples of method performance monitoring approach and outputs**
- **Summary**

# Analytical Method Lifecycle

---



# Purpose of Method Performance Monitoring

---

- **Meet regulatory expectations**
- **Understand long-term method performance**
  - **Provides more reliable estimate than method validation**
- **Confirms analytical method consistent performance and control across laboratories**
- **Proactively identify method performance variations**
- **Troubleshooting and continuous improvement**
- **Provide useful real time data for product related investigations (e.g., OOS, stability)**
  - **Enable partitioning variation between method and process**

# Fundamentals of Method Performance Monitoring

- **Appropriate monitoring attributes (what)**
  - What measures the method performance?
  - What are our major concerns on the attributes?
- **Meaningful data evaluation approach (how)**
  - Appropriate statistical analysis approach
  - Proper control limits and trending rules
- **User-friendly data analysis tool**
- **Data management system**
  - Harmonized data entry format across laboratories
  - Universal data access across the network, including CRO and stakeholders
  - Data integrity, GMP requirements

# Method Performance Monitoring Data to be Collected

Data	Examples	Purpose
Reference standard and / or quality control (QC) results	<p><b>Potency methods:</b> QC relative potency</p> <p><b>Impurity methods:</b> %Recovery of the control(s)</p> <p><b>Separation methods:</b> Monomer, HMW, LMW, main peak, acidic/basic group %area of the reference material</p>	Key attributes that measure the performance of the analytical method
Assay system suitability results	Reference standard curve $R^2$ , QC/reference parallelism measurements, %CV of the OD values, main peak pl values	Understand assay invalid rate, failure mode and potential impacting factors.
Other relevant information	Site, date, analyst, instrument, reagent, notebook reference	Provide useful information for troubleshooting and method improvement

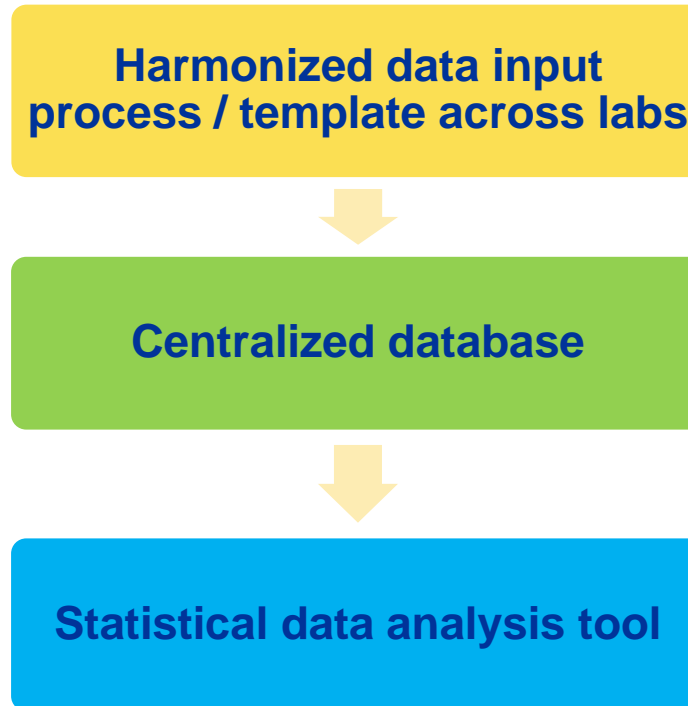


# Method Performance Monitoring Data Evaluation and Summary Tools

<b>Data Analysis Tool / Outcome</b>	<b>What does it do?</b>
<b>Shewhart individuals chart / Levey-Jennings</b>	<b>Data visualization</b>
<b>Simple summary statistics (N, mean, SD) for the key attributes</b>	<b>Provide reliable estimate of assay performance</b>
<b>Assay invalid rate summary</b>	<b>Understand assay invalid rate and failure mode. Provide useful information for troubleshooting and method improvement.</b>
<b>More sensitive control chart (e.g., CUSUM)</b>	<b>Address specific concerns on small shift. Can also be used for assessing reference standard stability</b>

# Method Performance Monitoring Work Flow

---



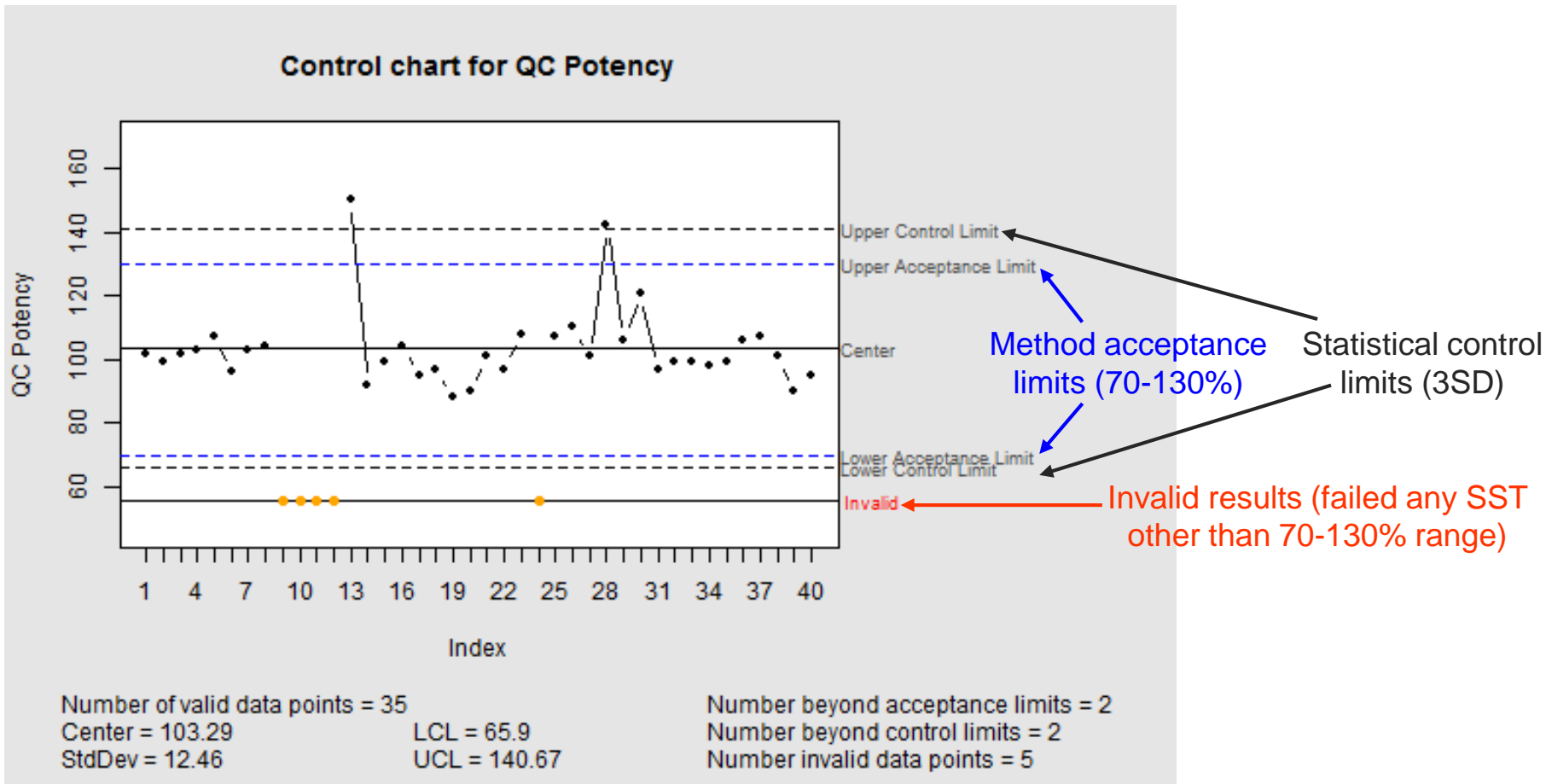
**Centralized group to perform formal data analysis  
and report results**

---

# Examples of Method Performance Monitoring Outputs

# Example Output - Shewhart Chart

## Plot of QC potency results



# Example Output - Simple Statistics

## Summary of valid QC potency results

N	Mean	SD
35	103	12

- Summarize all valid QC potency results (including the ones that failed the method acceptance range for QC potency but passed all other system suitability criteria)
- The SD of long-term QC potency results provides a reliable estimate of assay precision
- The results can help determine meaningful acceptance criteria for method transfer, bridging studies etc.

# Example Output - Assay Invalid Rate Summary

## System suitability failure summary

SST Parameter	Invalid Count	Invalid Rate
Ratio of Slopes	1	3%
Ratio of Upper Asymptotes	0	0%
Difference of Lower Asymptotes	0	0%
Model Lack-of-Fit	0	0%
A-D	1	3%
R2 of regression	2	5%
QC potency (%)	4	10%
Relative Confidence Interval Width (%)	1	3%
Total	7	18%

Total # of assays 40

Help understand assay invalid rate and failure mode.

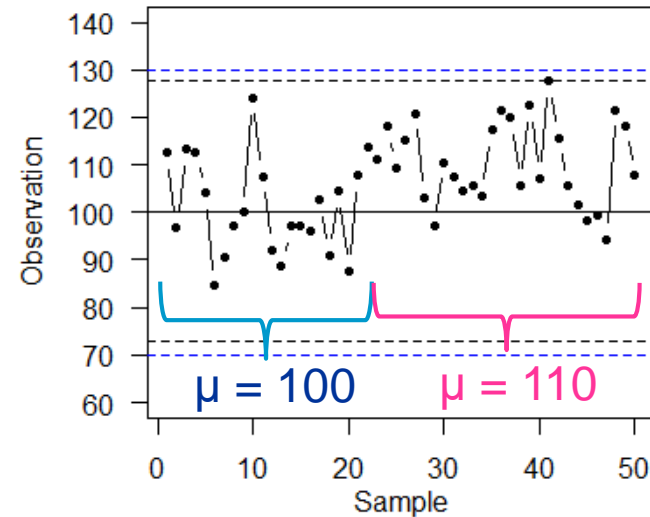
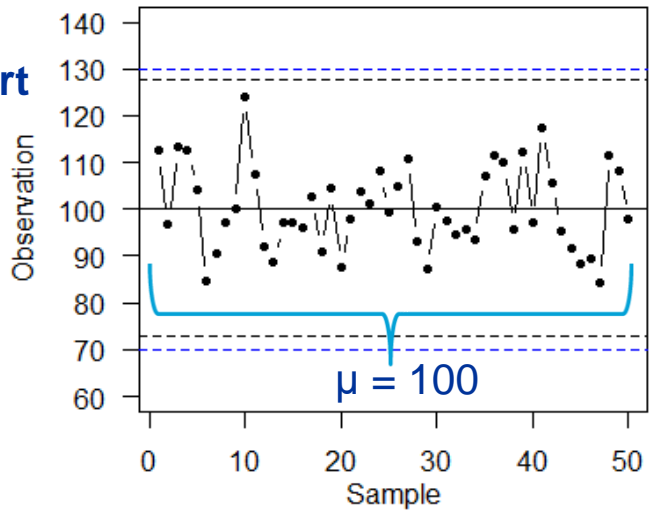
Provide useful information for troubleshooting and method improvement

# Example Output - CUSUM Charts

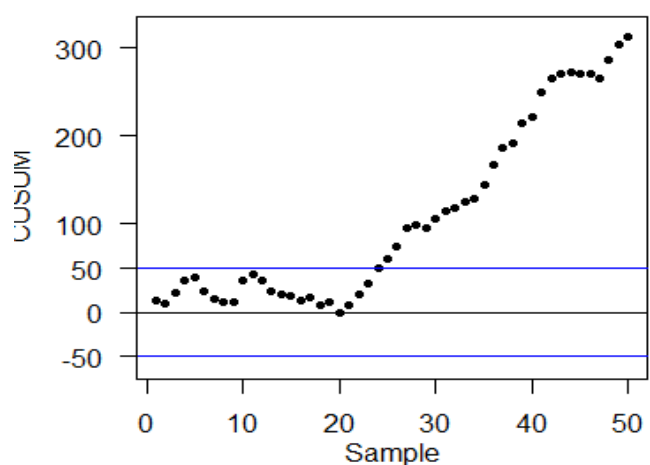
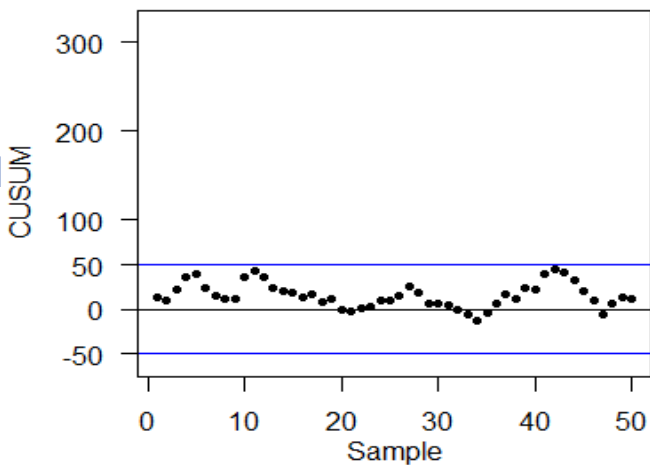
No shift

Mean shifted by 1 SD after the 20<sup>th</sup> observation

Shewhart chart



CUSUM chart

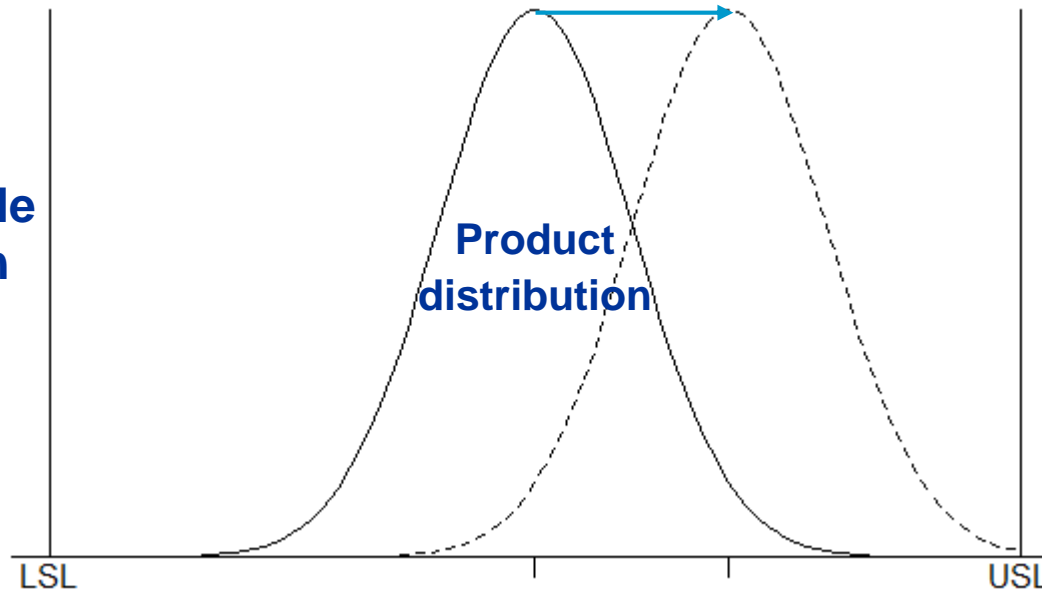


# CUSUM Control Chart Set Up

- The CUSUM chart parameters are selected depend on the size of the shift to be detected and desirable ARL
- An “out-of-control” shift is determined based on subject area knowledge and risk assessment such as impact on specification and other critical attributes

Allowable mean shift due to reference standard shift

**Example:  
Define allowable  
shift based on  
specification**



# Summary

---

- **Method performance monitoring is an integral part of the analytical method lifecycle**
- **A feasible method monitoring program requires harmonized data input template and trending analysis approach, as well as good data management.**
- **Implementation of method monitoring tool needs close collaboration across various functions.**

# Acknowledgement

---

**Yishu Xue**

**Dan (Cassie) Liu**

**Olga Karagiozova**

**Lei Zhang**

**Lisa Lundberg**

**Deepti Ahuja**

**Sanjana Kirloskar**

**Colleen Quinn**

**Cathy Zhu**

**Monica Nelson**

**Scott Umlauf**

**Tara Stauffer**

**Isam Qahwash**

**Darren Kamikura**

**Rachel Li**

**Madesh Belakavadi**

**Philip Ng**

**Eric Payne**

**Marcel Zocher**

**Tapan Das**