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# 5 Years of Real-Time Release Testing Data – Experiences on a high-volume product

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# Product and process introduction

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- Indication diabetes (DPP4 Inhibitor)
- Solid oral dosage form
  - Tablet
  - 3 strengths which are weight-multiples
  - ~ 30% active by weight
- Direct compression process with taste-masking overcoat
  
- Initial approval 2006
  - FDA, EMEA
  - Subsequent approval in > 60 markets world-wide
- Developed into high volume product ( > 250 batches annually)



# Product attributes that support RTRT

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- Simple direct compression process with good development history of uniformity
  - Relatively high active content (~30%)
- Very good stability
- No degradates
- BCS class I with well understood disintegration/dissolution behavior



# Merck Fully Supports QbD

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- Merck has embraced QbD as a strategic initiative on how we develop and manufacture products
  - QbD provides a consistent framework for developing high quality products that provide benefits to our patients and meet our customer's needs
  - QbD promotes systematic, scientific and risk-based approaches to product and process development
- Merck is executing a company-wide QbD strategy and playbook
- All of Merck's development programs now follow the QbD approach
  - Work processes are established to realize Merck's QbD strategy

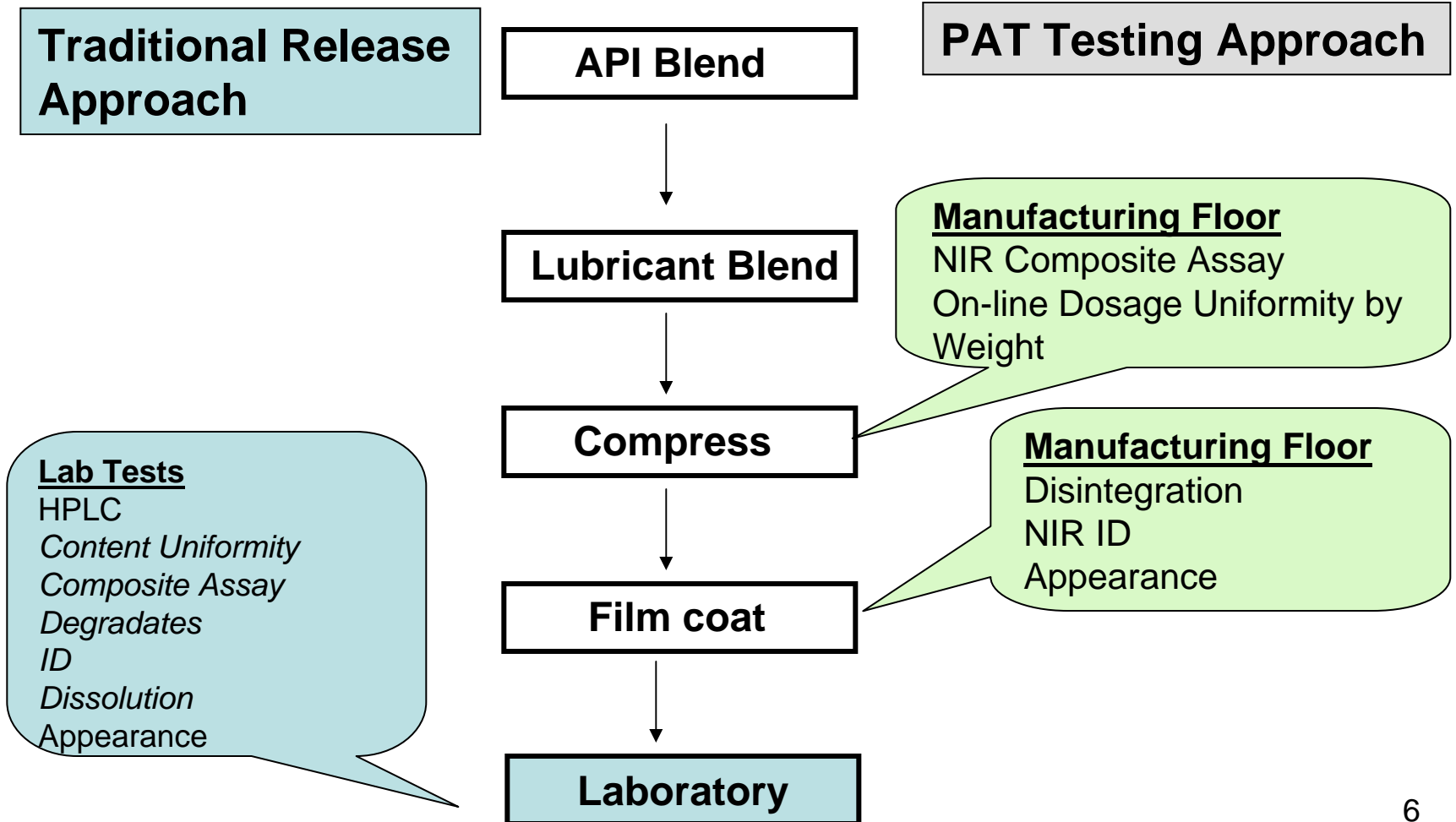


# Product attributes that support RTRT

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- This product was Merck's first venture into QbD principles in 2005-2006
  - Participation in FDA QbD pilot program
- “Quality by Design (QbD)” approaches used in
  - Development including
    - “Design Space”
    - Systematic assessment of control strategy elements
      - Analytical/testing
      - Process equipment
      - Procedures
  - Manufacturing
    - Implementation of control strategy
    - Process monitoring plan
    - Ongoing improvement/learning
- QbD elements covered in this presentation
  - Control strategy (RTRT approach)
  - Process Monitoring plan

# Control Strategy for Product – Real-Time Release Testing for Product Release





# Sampling Plan for CU and Assay

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- Core tablets are obtained every 15 minutes from the tablet press via automated sampling system
  - The number of tablets tested varies by dose and batch factors
- Tablet weight data
  - Between 240-690 tablets analyzed (distributed by location and side-of-press)
- Samples for NIR analysis
  - 3 tablet per “time location” per side (station) of the tablet press
  - Typical number of tablets for 100mg dose is 72 tablets tested by NIR
    - 36 tablets for side 1, 36 tablets for side 2
    - This corresponds to 12 locations (with 3 replicates)
    - 12 locations x 15 minutes = 3 hours of compression



# Release calculations

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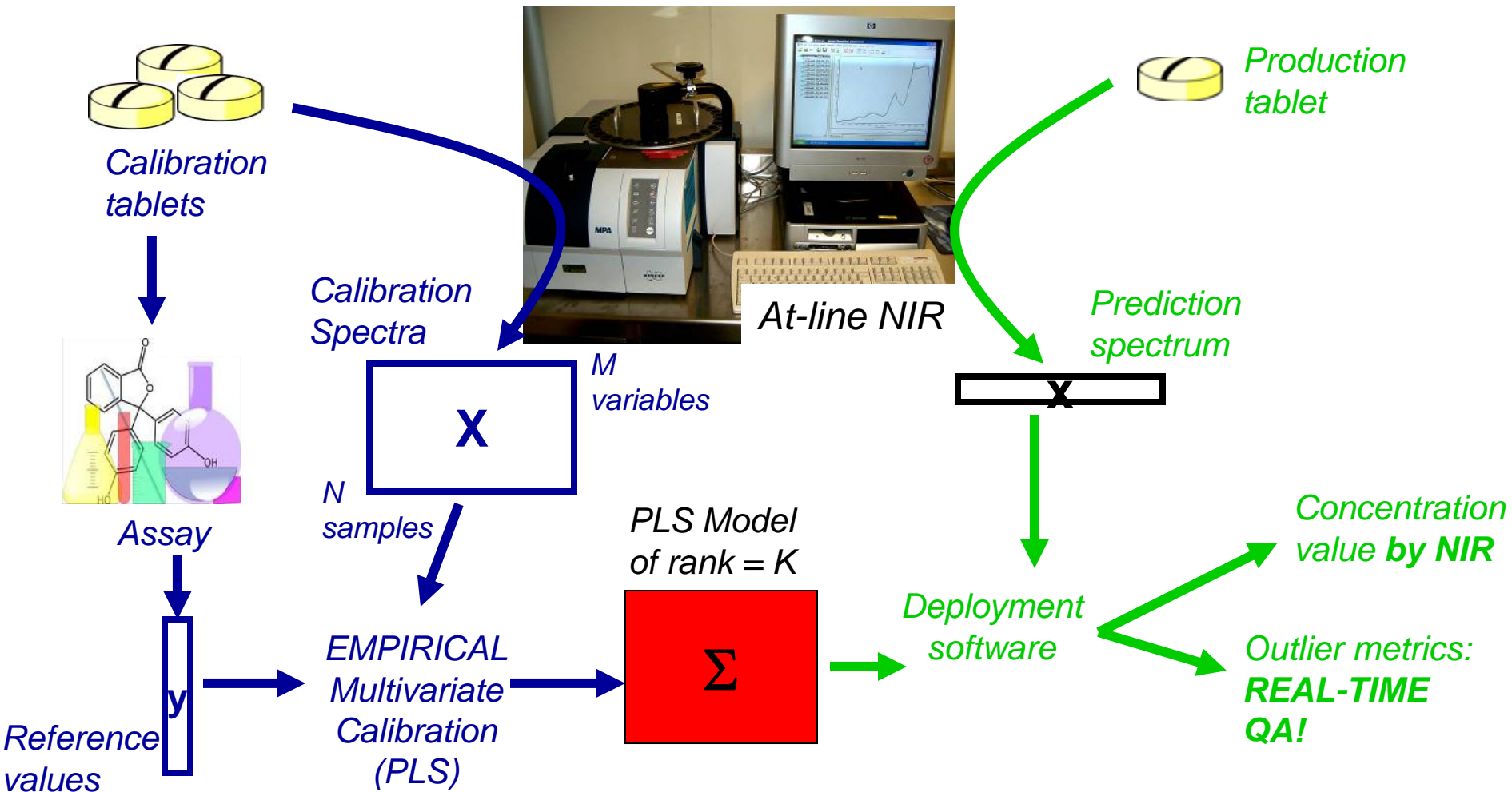
- Composite Assay
  - Each NIR result is in concentration units (mg/g of sitagliptin)
  - NIR results are averaged
  - Composite Assay (%LC) is calculated using **average NIR mg/g** and **average tablet weight**
  - Specification 95-105%
- Content Uniformity
  - Use weight uniformity instead of content uniformity (relatively high drug load)
  - Specifications based on large n counting test



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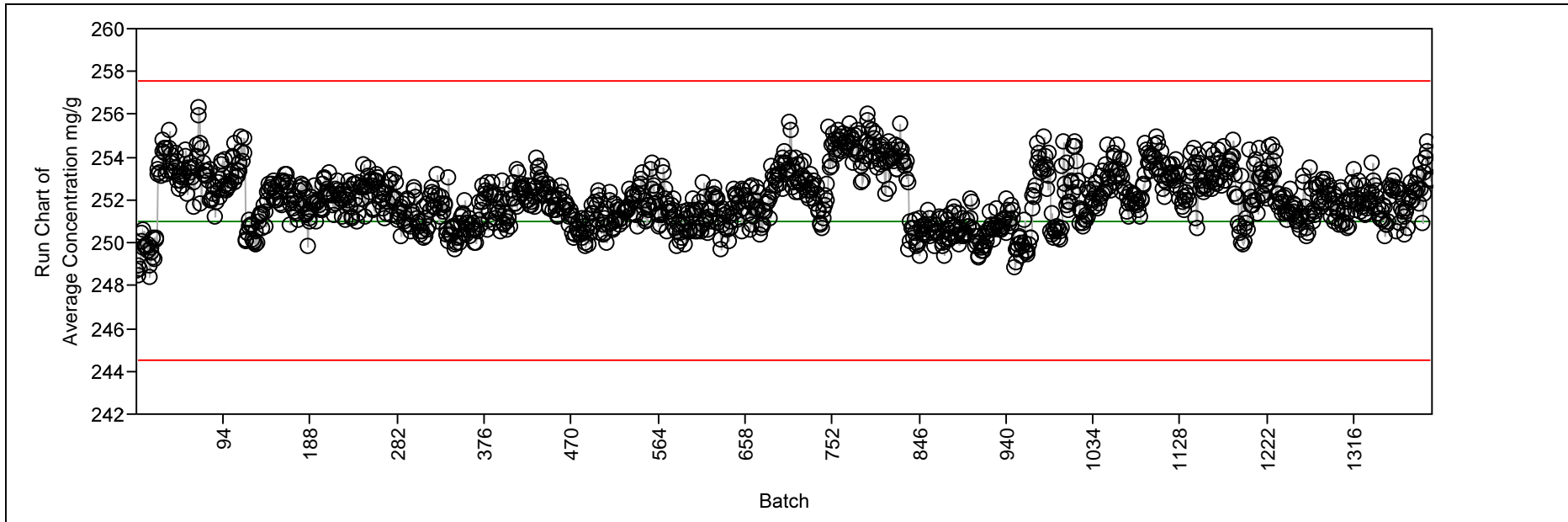
# NIR results for active concentration/assay

# PAT CALIBRATION & DEPLOYMENT



*EMPIRICAL multivariate calibration → REQUIRES real-time outlier monitoring!*

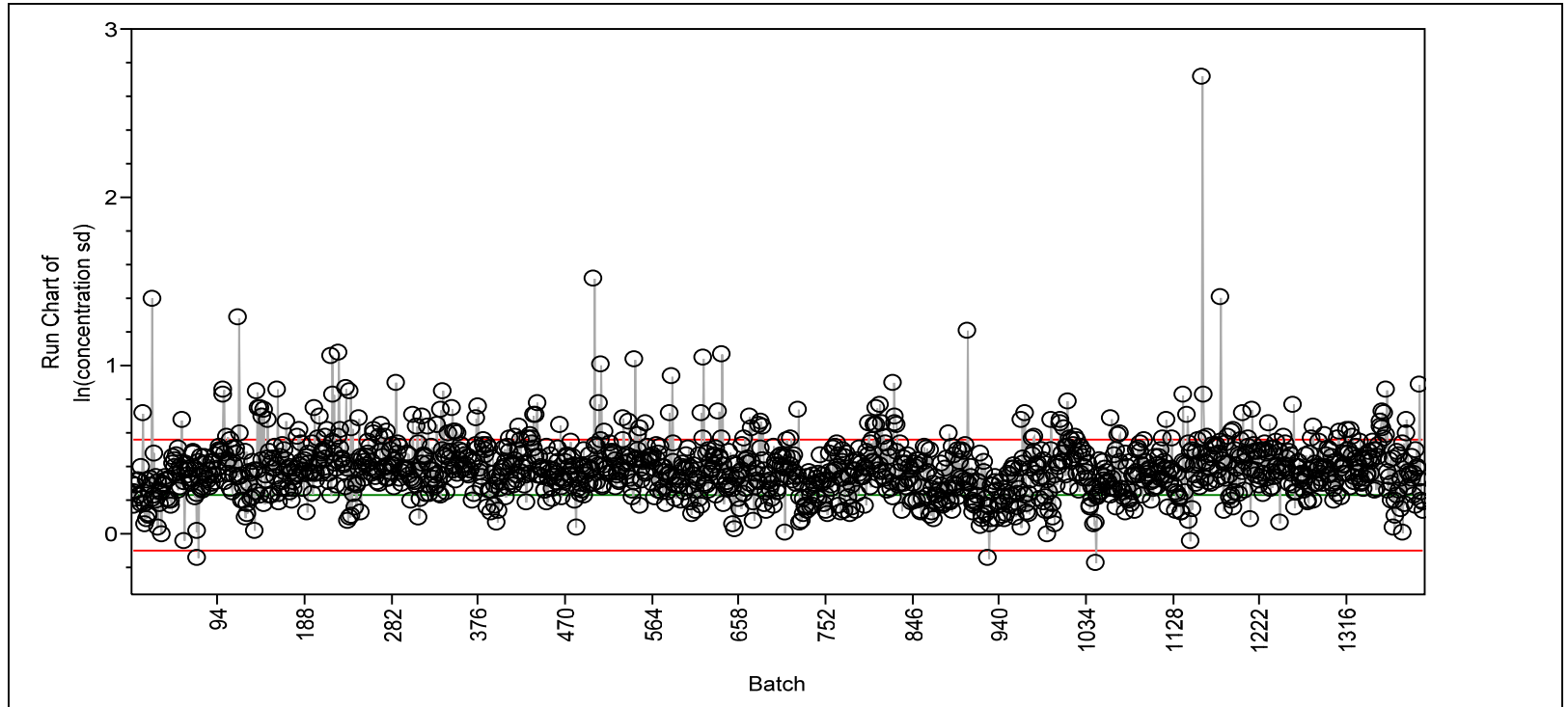
# Concentration Data - History



- Average Concentration by batch (mg/g)
- 1,399 Batches plotted (representing nearly five years of production)
- Original average and control limits shown – these were set by first 30 batches produced.



# Standard Deviation of Concentration Data by Batch

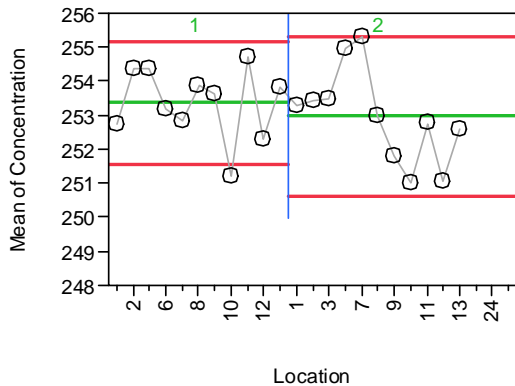


- Run chart of standard deviations provides evidence that
  - original limits based on first 30 batches was a slight underestimation
  - the limits later needed revising.
- Since that time, the variation has remained relatively stable over the 5 years of trending.

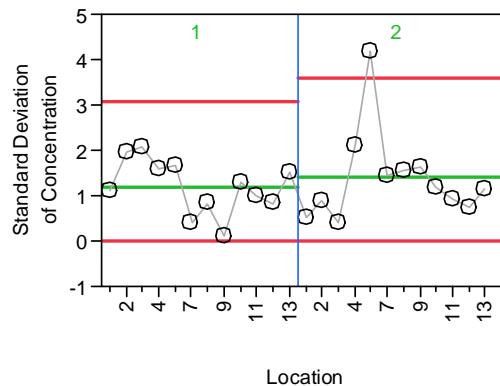
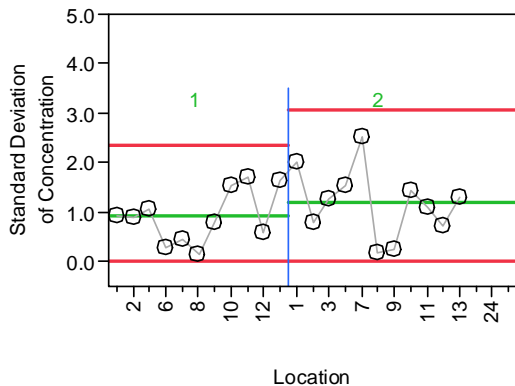
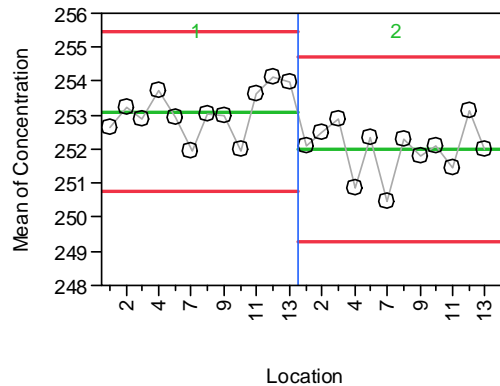


# Within Batch Concentration Trending

## Early Batch



## Recent Batch



With over 1,000 batches between these two batches and nearly 5 years of production, the consistency of concentration values is excellent.



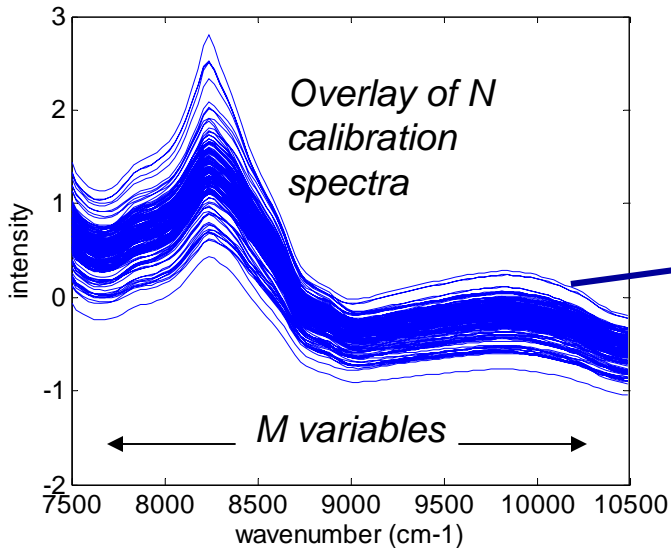
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# NIR Spectral Outlier limits

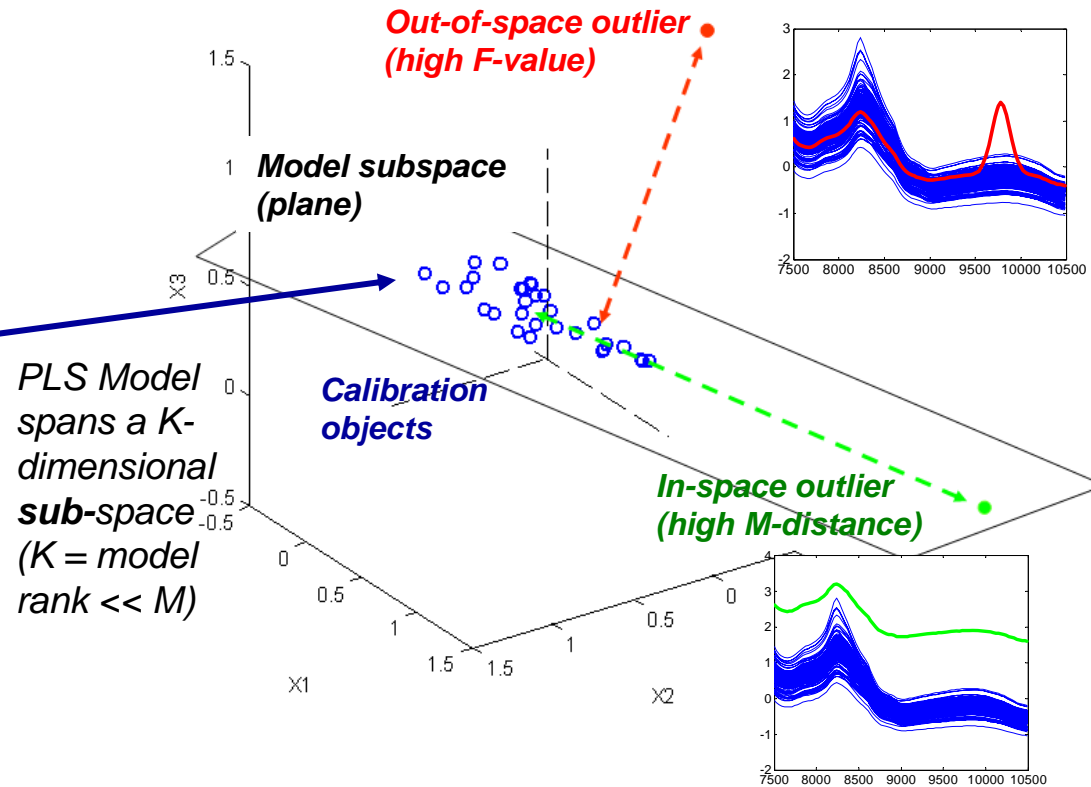
5 years of data to “fill the theoretical distribution”

# Multivariate Outlier Metrics

Each of the  $N$  calibration spectra is.....



.....a point in  $M$ -dimensional space



- Monitoring of metrics is imperative: **REAL-TIME NIR QA !**
- Two metrics reflect **different** NIR failure modes  $\rightarrow$  both must be monitored!

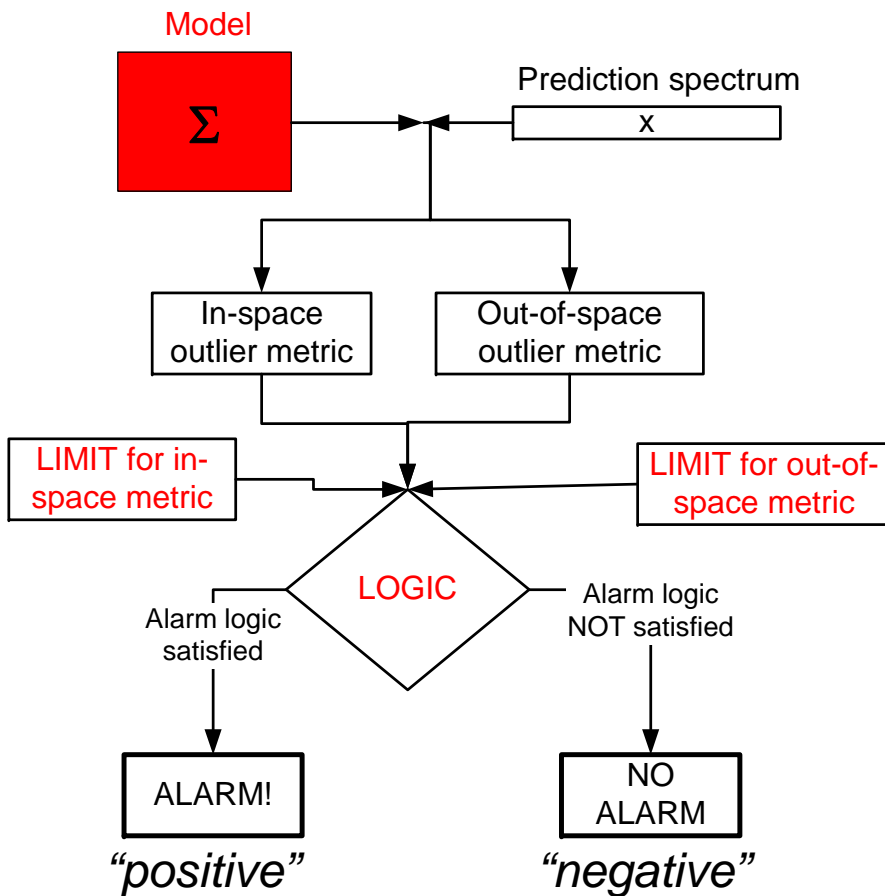
- Calibration spectra define “normality”
- Any **new** spectrum can be abnormal in 2 ways:
  1. in-space, and
  2. out-of-space

# Outlier Alarm System, and Limits

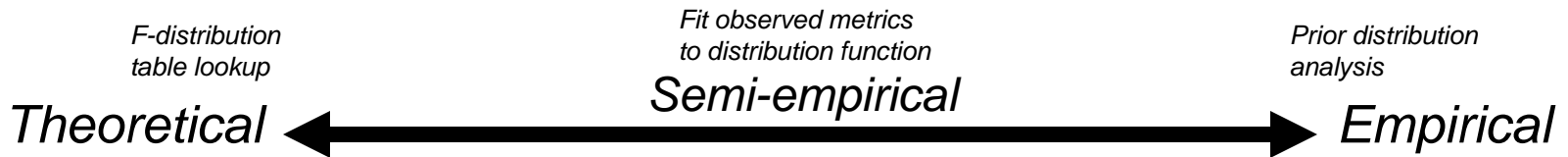
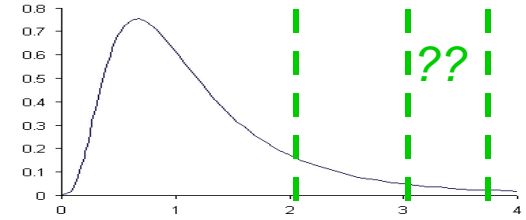
*Metrics are the central element of a larger “Outlier alarm system”*

*Other critical elements:*

- **Model:** is often the same PLS model that is used to generate assay results (does **not** need to be)
- **Limits:** the primary means to adjust **sensitivity and specificity** of the alarm
- **Logic:** how the results are used to determine “alarm” vs. “no alarm”



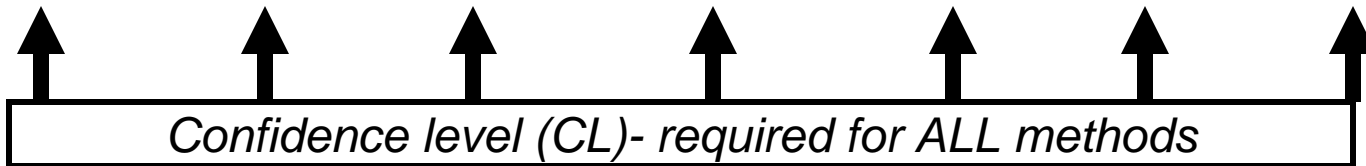
# Determining Alarm Limits: The Continuum of Methods



- *easy: requires only model **properties***
- *does not require “model experience”, BUT...*
- *requires assumption regarding distribution of metric values (F-dist)*

This method uses *theoretical* method based on *calibration* model properties (N,M,K) only

- *requires analysis of historical metric values, **and** software flexibility*
- *can only apply to “experienced” models, BUT...*
- *no distributional assumptions required*
- *takes advantage of experience*

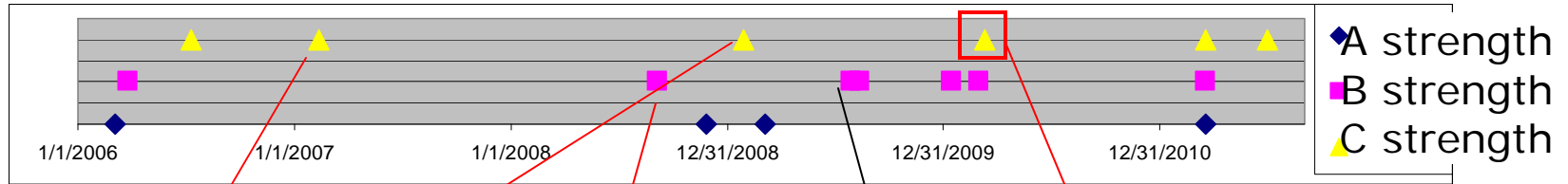


**CL** Should be *risk*-based, reflecting acceptable risks of both:

- **false positive:** annoying alarms
- **false negative:** undetected PAT issue



# PAT Method Events



MAR, JUL 06: 3 NIR models put into service

A and B model updates

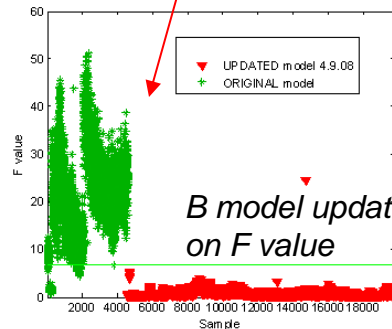
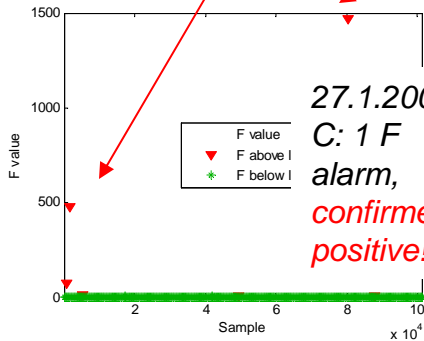
29.7.2009  
B: 6 MD alarms over 2 weeks, all negatives

B: 3 separate MD alarms, all confirmed positives!

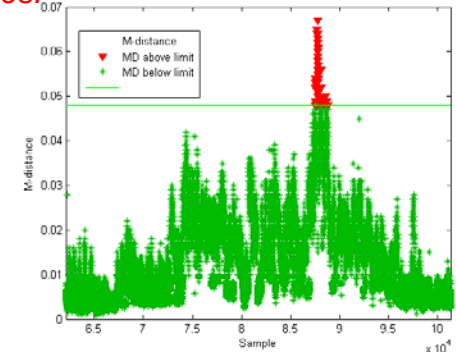
18.3.2011 (all): new MD limits set using 95% CL

30.6.2011  
C: model update

12.2.2007  
C: 2 F alarms, confirmed positives!



B model update effect on F value



10.3.2010 C 132 MD alarms over 8 batches! All negatives!

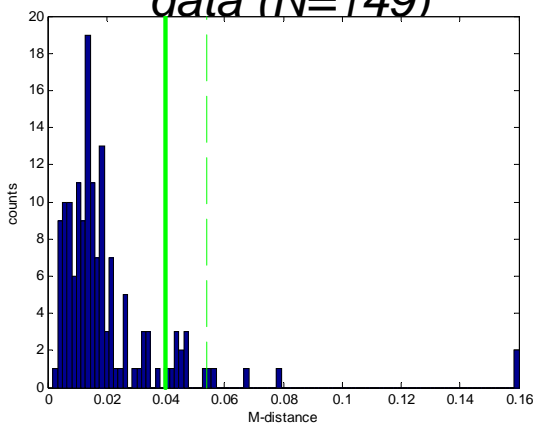
- C model generated useful metrics right away; A and B models did so after a model update
- Since 2006, only 6 confirmed positive tablets (out of >120k!)
  - all of which were flagged by the outlier detector!
  - none of which resulted in tablet quality issues!
- However, 132 false alarms for C model in 2010

→ Investigation of outlier metric limits (too "tight"???)

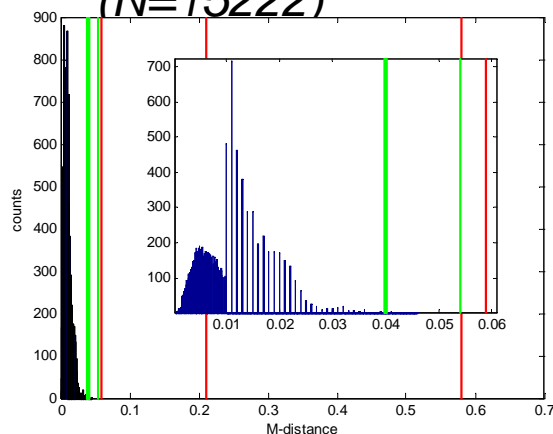


# Historical Metrics for B model case

Calibration data (N=149)



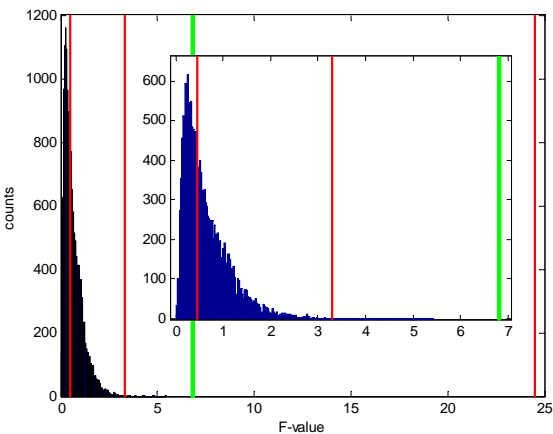
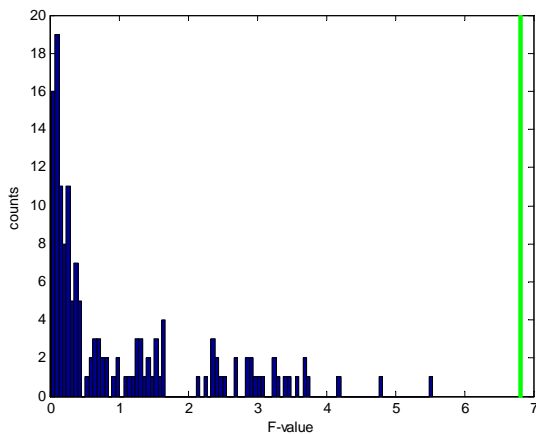
Process data (N=15222)



- well-distributed outlier metrics in calibration data
- MD metric “catches” all 3 known positives, F-value catches one of them
- assumption of F-distributed metrics a good one, especially for the F-value “out-of-space” metric!

M-distance

F-value



- Metric limit used at the time
- - - MD limit based on 95% CL
- Metric value for a known positive case



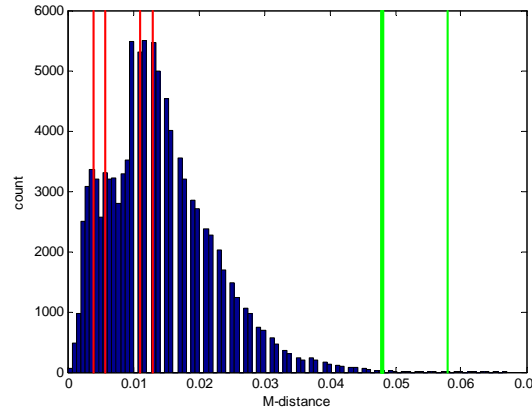
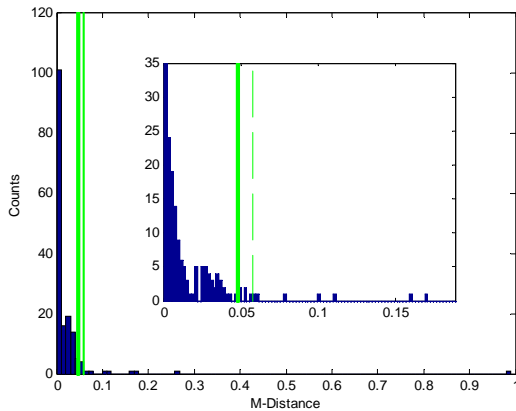
# Historical Metrics for C model case

Calibration data (N=167)

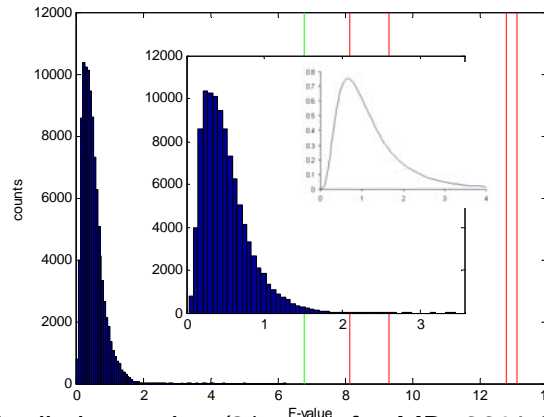
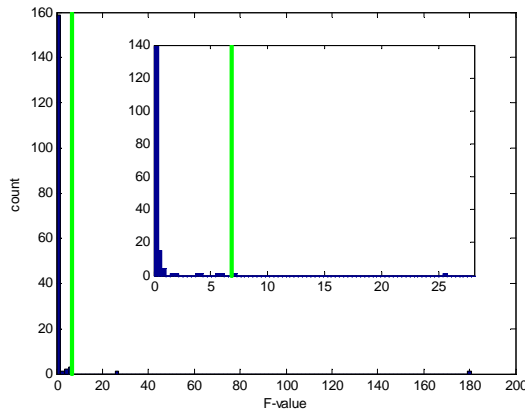
Process data (N=101310!!)

- some MD and F-value outliers in the calibration data, causes higher limits when using theoretical method
- nonetheless, all 4 known positives were correctly detected!
- assumption of F-distributed metrics a good one, especially for the F-value “out-of-space” metric!
- the “OR” alarm logic is needed: **none** of the 4 known positives exceeded the MD limit (all correct alarms depended on the F-value metric)

M-distance



F-value



- Metric limit originally in service ( $2 \times \text{mean}$  for MD, 99% CL for F)
- - - MD limit based on 95% CL
- Metric value for a known positive case



# Conclusions for Spectral Outlier Historic Review

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- Initial assumptions for distributions are holding up very well when real data are filled in
- Outlier limits are set appropriately to detect true quality issues
- With large process history, opportunity to adjust limits in future to mitigate nuisance investigations



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# Tablet weight results for content uniformity



# Tablet Weight Data: Non-Parametric Counting Test for Sample Sizes (n) > 100

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- Collect the results for n dosage units
- Express each individual result as percent of label claim
- Count the number of results outside 85-115% LC
- The batch complies if no more than **c** units are outside 85-115% LC. (No zero tolerance criterion)



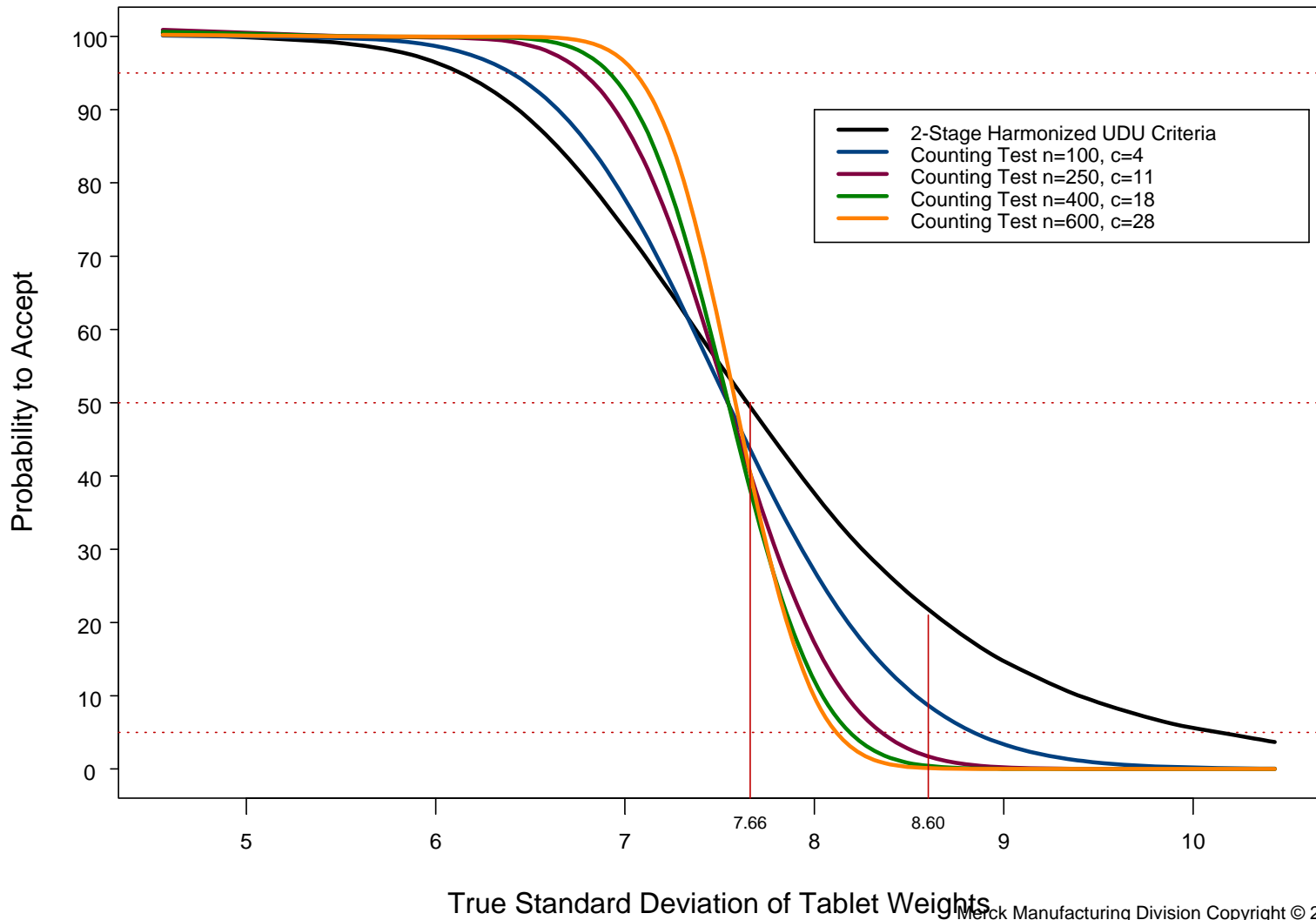
# Two Versions of the Acceptance Limit For JANUVIA

**Acceptance limit,  $c$ , for several sample sizes.**

$n$	100	250	500	750	1000
$c$	4	11	23	35	47
$c^*$	3	7	13	19	25

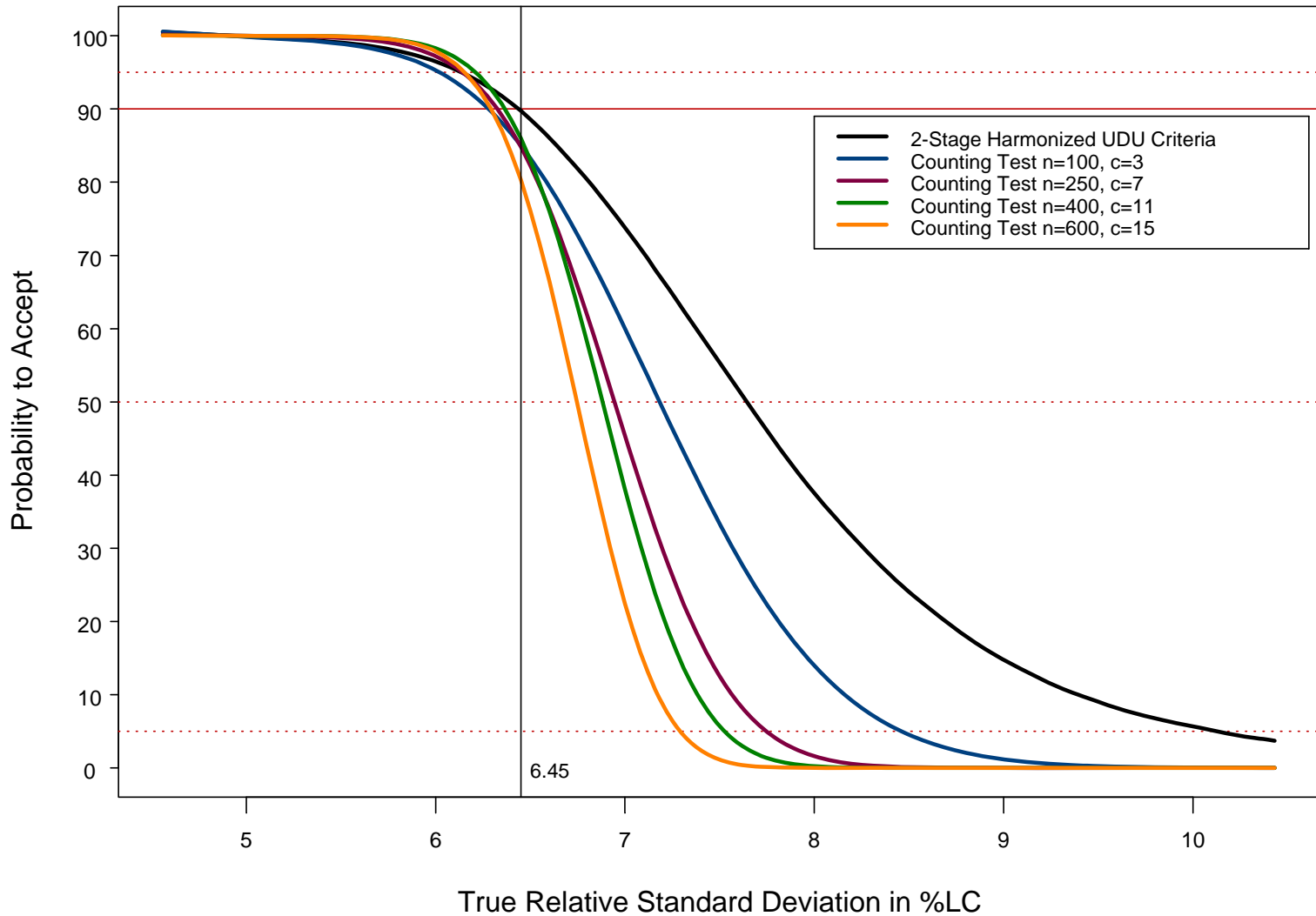


# Operating Characteristic (OC) Curves for c



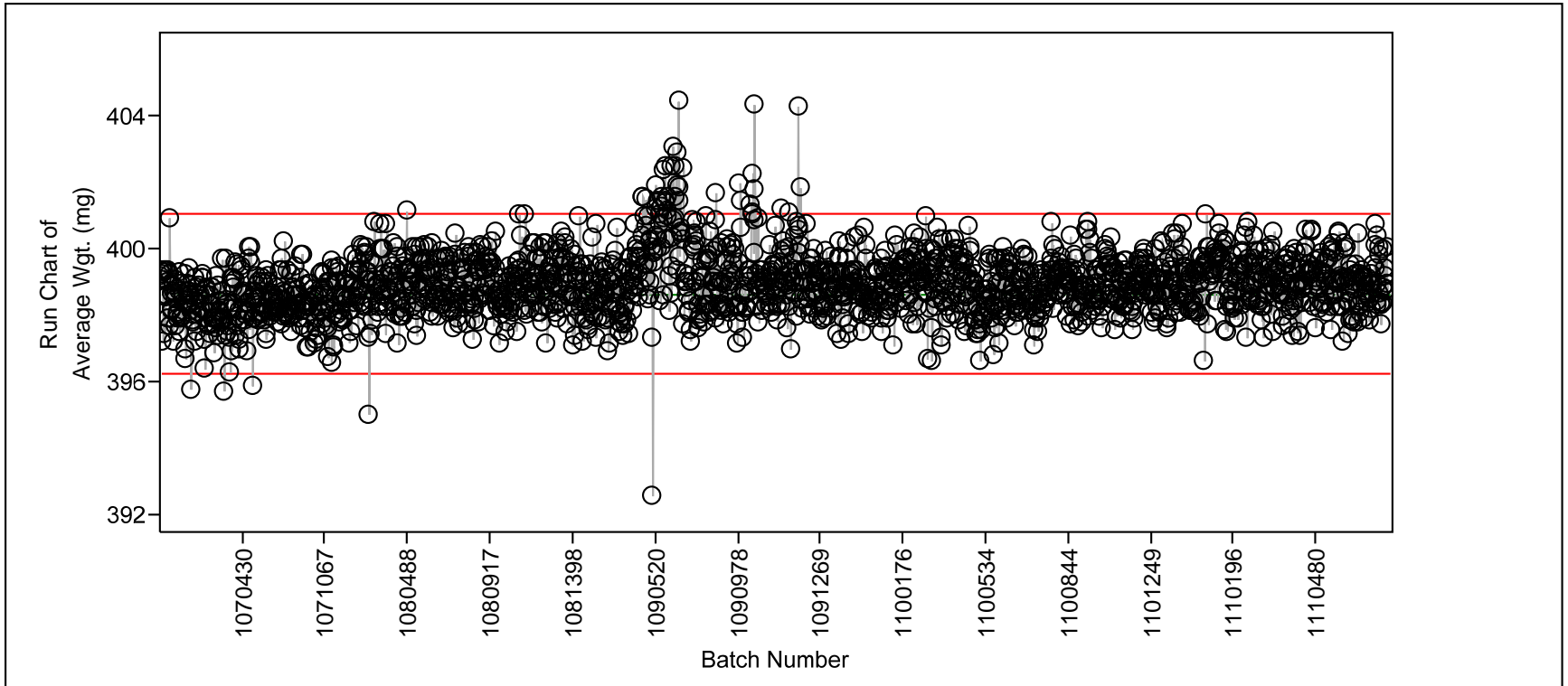


# OC Curves For $c^*$





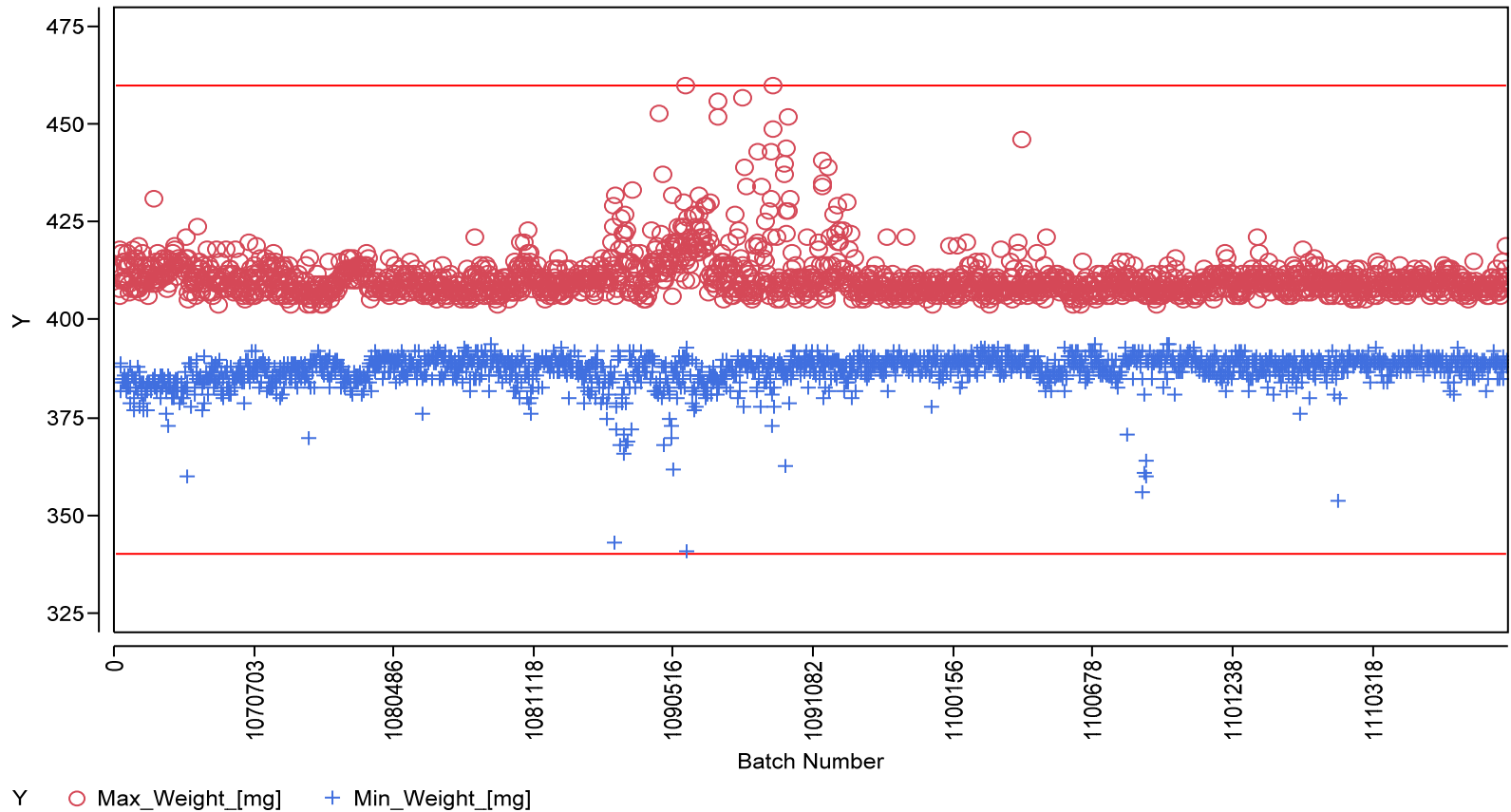
# Tablet Weights (1,992 Batches)



- Original control limits shown based on first 30 batches.
- Weight relatively stable throughout.



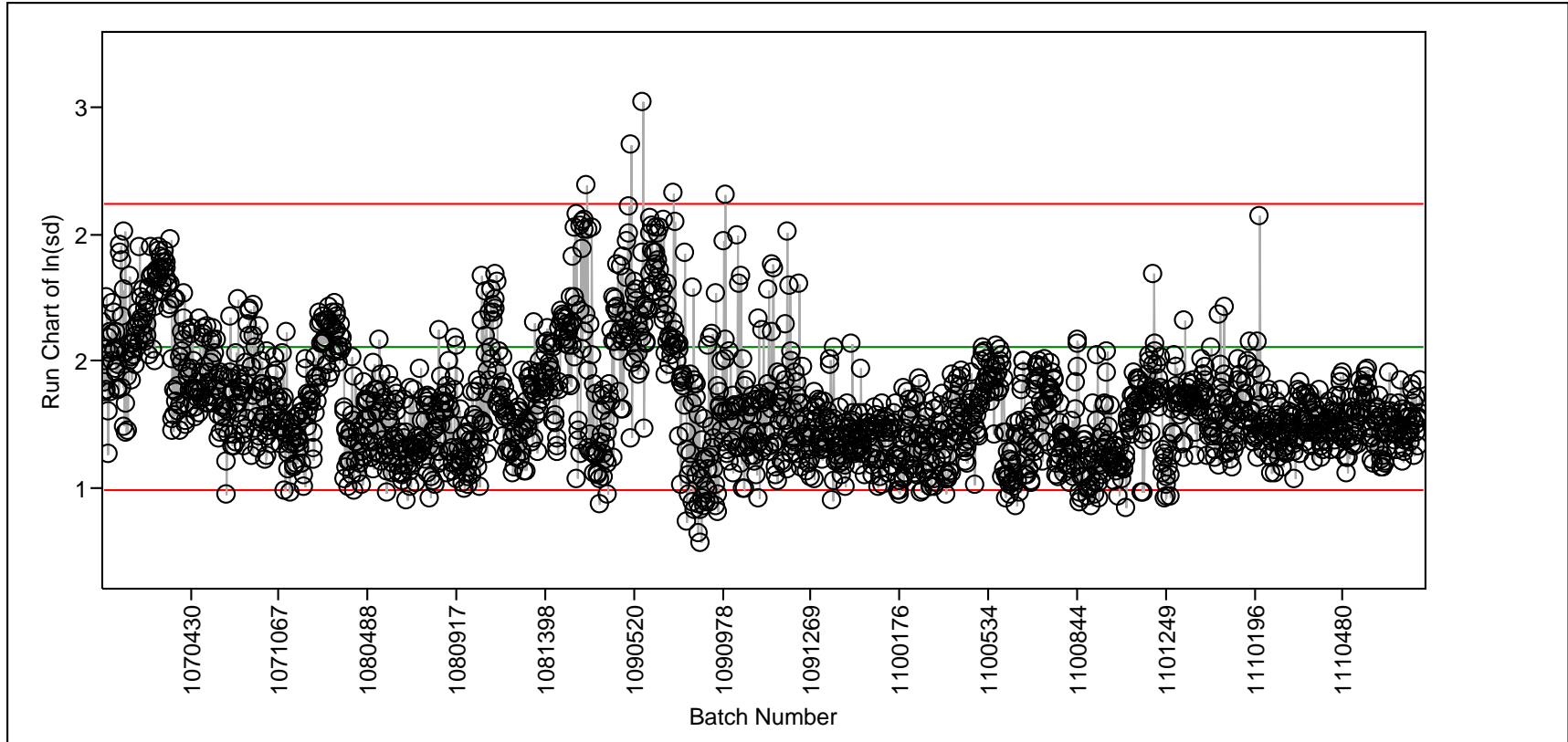
# Max and Min Tablet Weights



- Individual Max and Min tablet weights.
- Red Lines indicate 85% and 115% of target weight.



# Within Batch Tablet Weight Variation





# Conclusions for Tablet Weight/Uniformity Data

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- Valuable information through routine sampling with large sample size
  - Allows for good statistical analysis of intra- and inter-batch trends
- For this product good history of uniformity



# How to routinely look at data: Process Monitoring Plan

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- A comprehensive process monitoring plan in place that monitors (for each batch and across batches)
  - Tablet Weights:
    - Batch Average
    - Batch Standard Deviation
    - Number of Tablets Outside of 390 to 410 mg
  - Label Claim, Batch Average
  - Concentration:
    - Batch Average
    - Batch Standard Deviation
    - Within Batch: concentration and standard deviation by location and side of press
  - Disintegration Time
    - Batch Average
    - Batch Standard Deviation
- Implemented in 2006 based on risk assessment and control strategy for product
- Valuable trending information



# Conclusions

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- Over 5 years of high-volume process data on a high-volume RTRT product available
  - Product shows good robustness in all quality and process monitoring attributes
- Available volume of data used for release decisions and continued process understanding
  - Significant Enabler for this QbD approach to data usage was sampling plans and specifications for large sample sizes



# Acknowledgements

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- Eric Ahuja, Manoharan Ramasamy, John Higgins, Nathan Pixley, Charles Miller
- Beppe Mazzochi, Gianmaria Ghisoni, Paola Carrera, Jennifer Blatteau



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# Backup slides



# Challenges for use of spectral outlier limits

- Commercial software:
  - **Insufficient capabilities**
  - **Lack of harmonization:** nomenclature and math!
- Must identify EXACT math of each metric
- Then, **where** to set the limit?.....

- “Leverage”
- “Mahalanobis Distance”
- “*M-distance*”
- “Hotelling T<sup>2</sup>”
- “T<sup>2</sup>”
- .....

This application uses Bruker’s OPUS software:  
- “**M-distance**” in-space metric: can change the limit:  
- “**F-value**” out-of-space metric: **Fixed** by OPUS software at 99% confidence level

- “Residual”
- “Spectral Residual”
- “Q-residual”
- “DmodX”
- “*F-value*”
- “Residual X-variance”
- .....