Control Strategy, Residence Time Distribution, and Real Time Release Implementation for Continuous Drug Product Manufacturing

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Jennifer is a New York based artist living with Type 1 diabetes.

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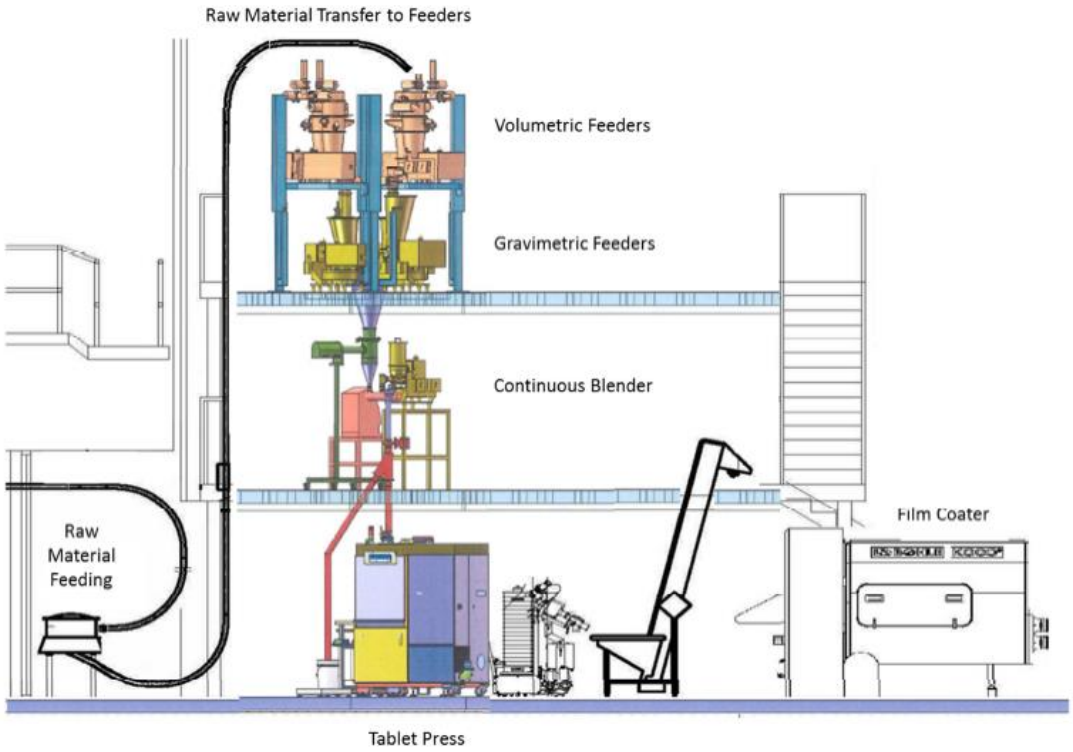
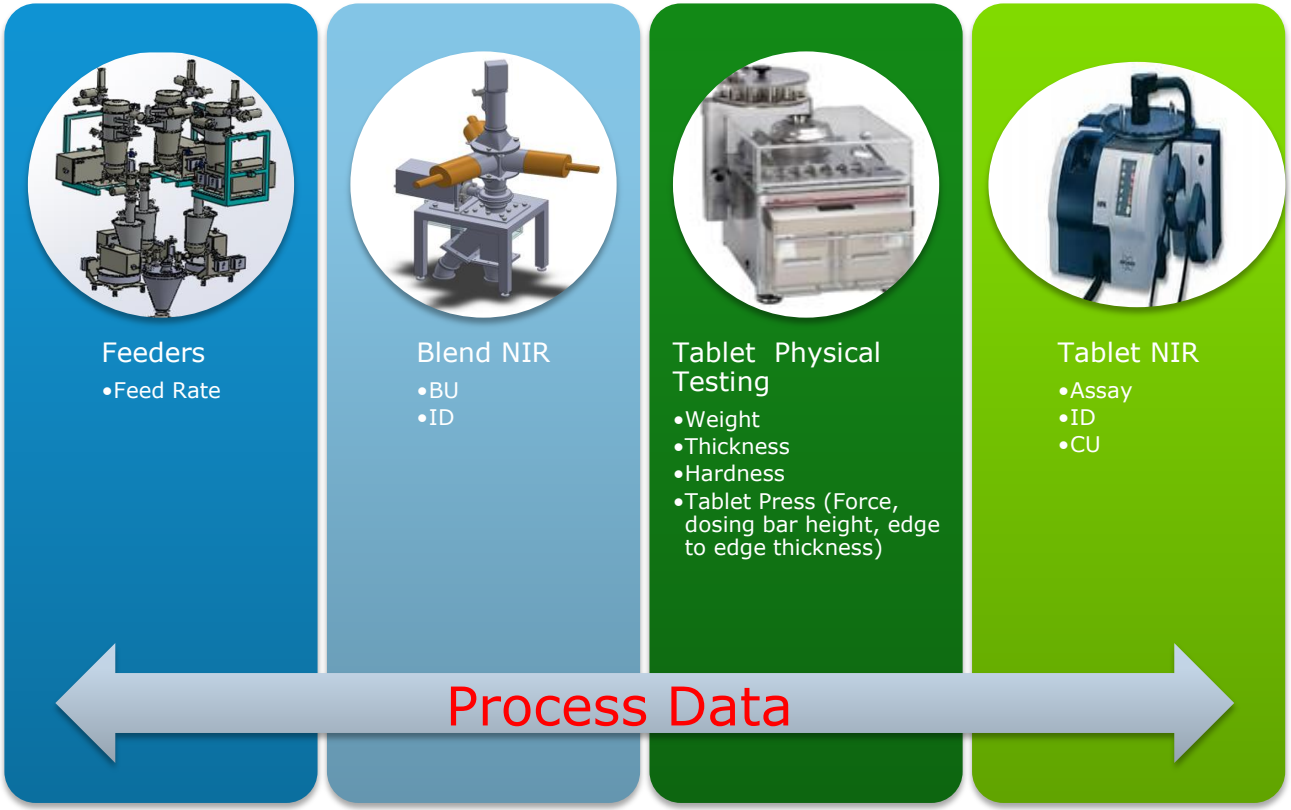
Outline

- Process Data
- Control Strategy
- Residence Time Distribution
- In-Line Blend ID for Process Monitoring
- Tablet ID for Real Time Release Testing



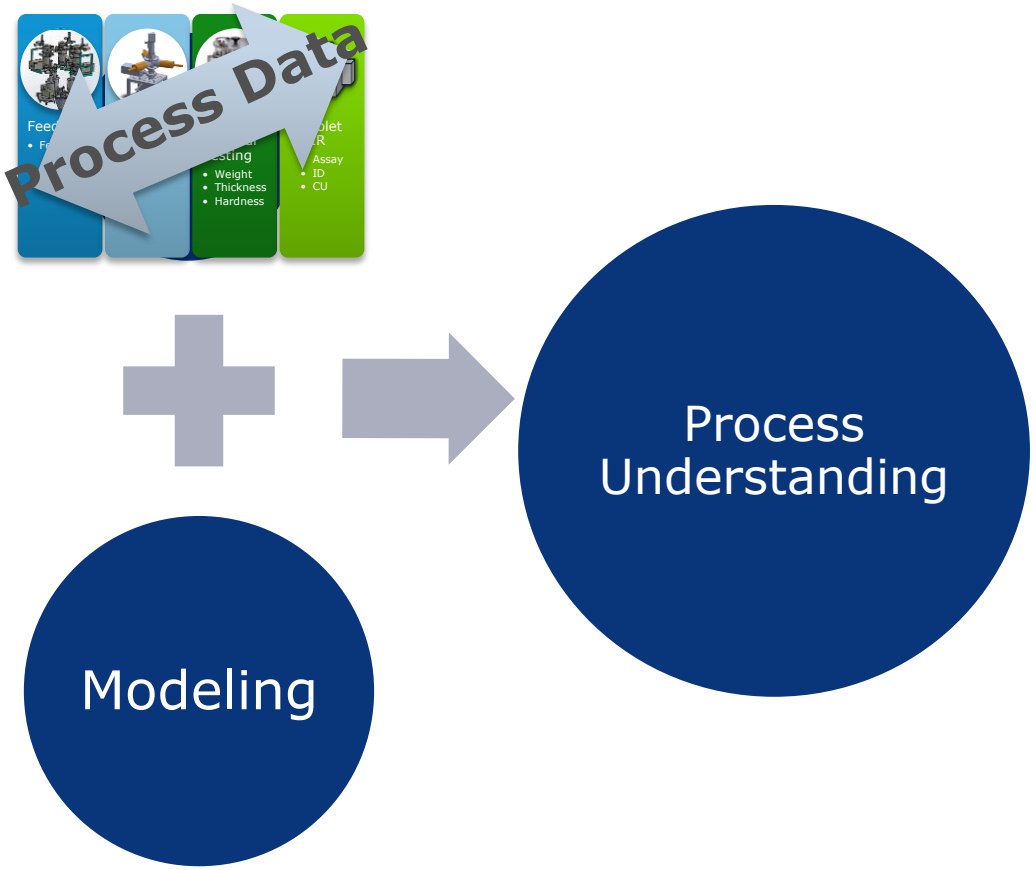
Dry Blend Direct Compression Process

Continuous Manufacturing Process Data Dry Blend Direct Compression Process



Central control system that defines the methods used to integrate process data

Continuous Manufacturing Process Characterization



Three Layered Approach

State of Control

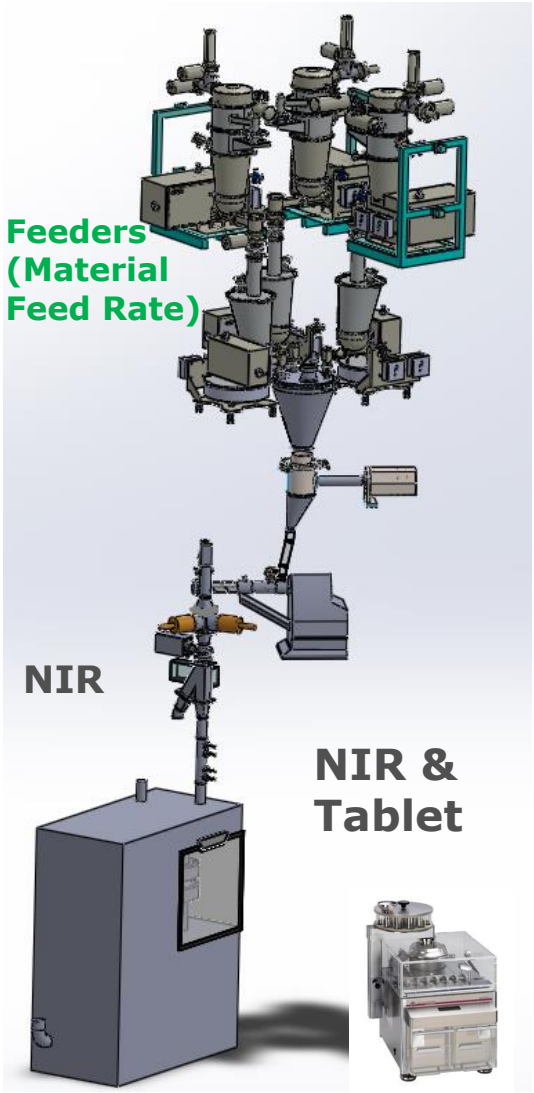
- Includes parameters which are monitored frequently to maintain product quality and stability
- Also includes additional redundant in-process checks

Reject

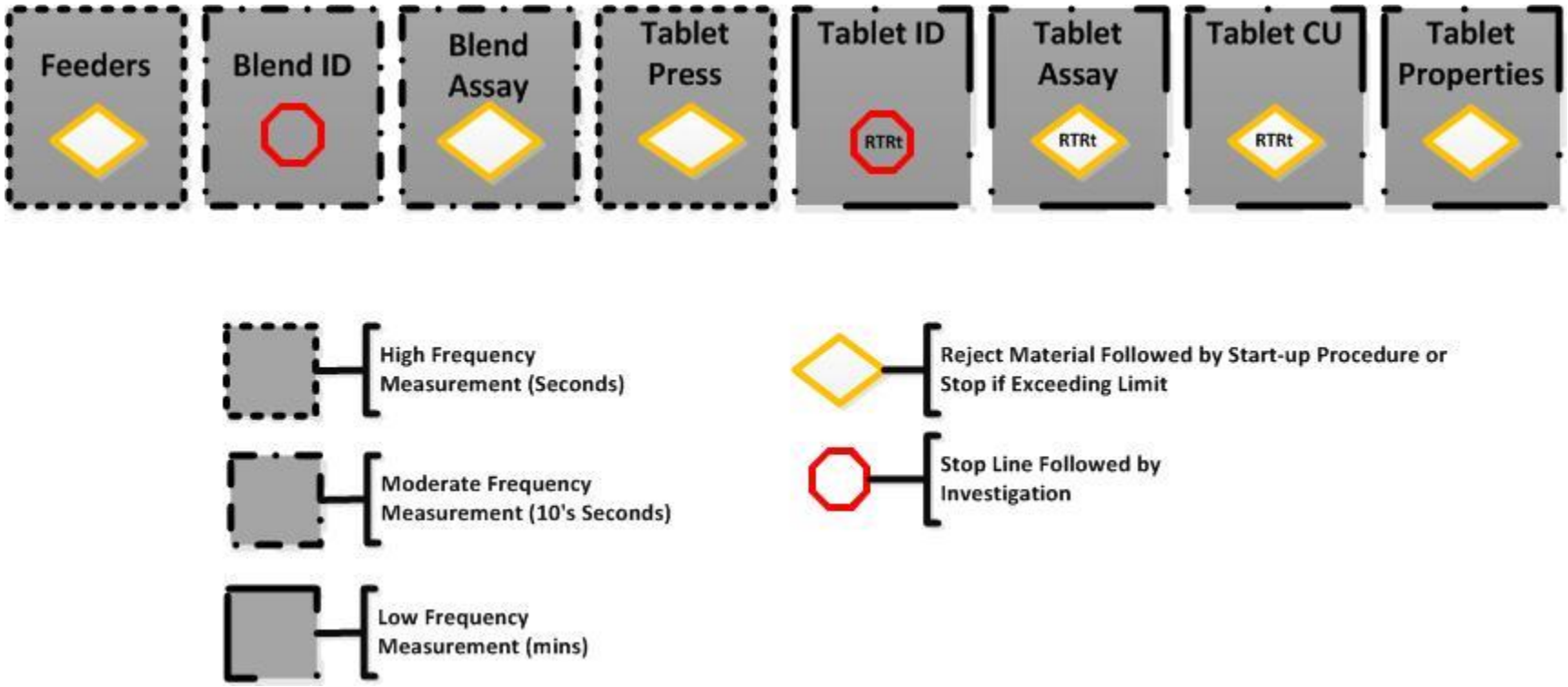
- Disturbance detected with one of the in-process measurements.
- Material is rejected while line comes back to a state of control.

Stop

- Major process problem detected will stop the manufacturing line.

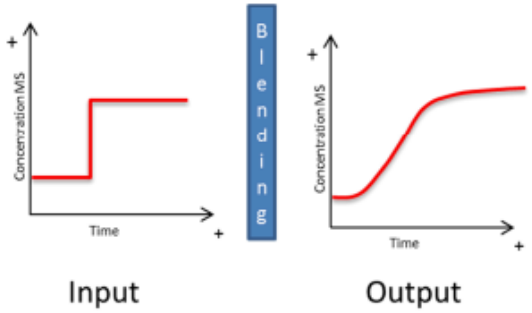


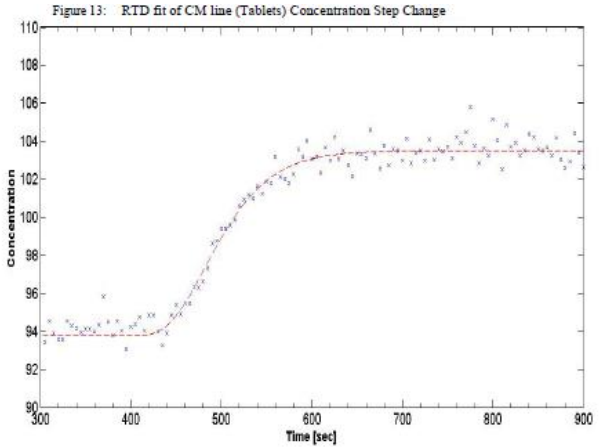
Control Strategy

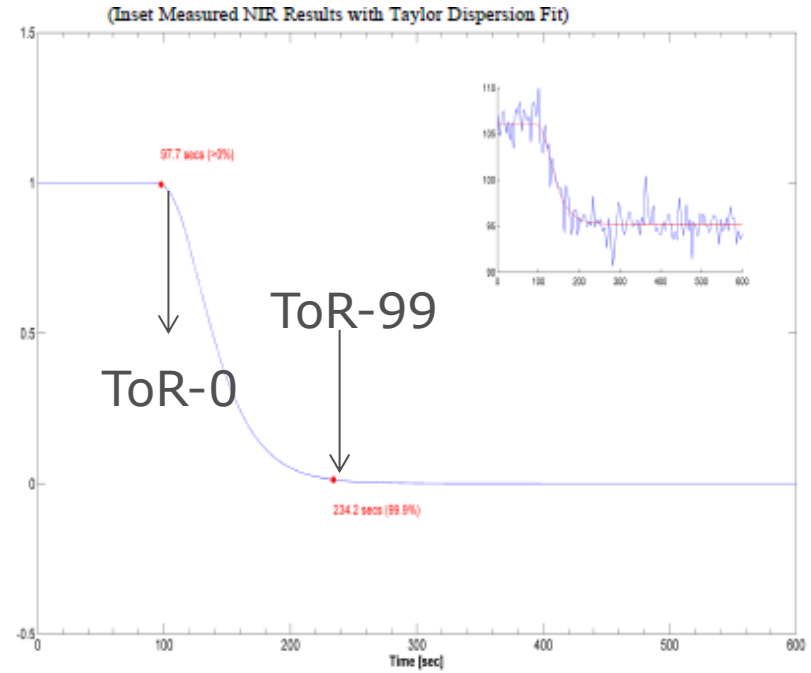


Residence Time Distribution Testing

- RTD is a probability distribution function. Length of time material spends in a system. Mathematically fit to a Taylor dispersion model. Calculate mean residence time (MRT)

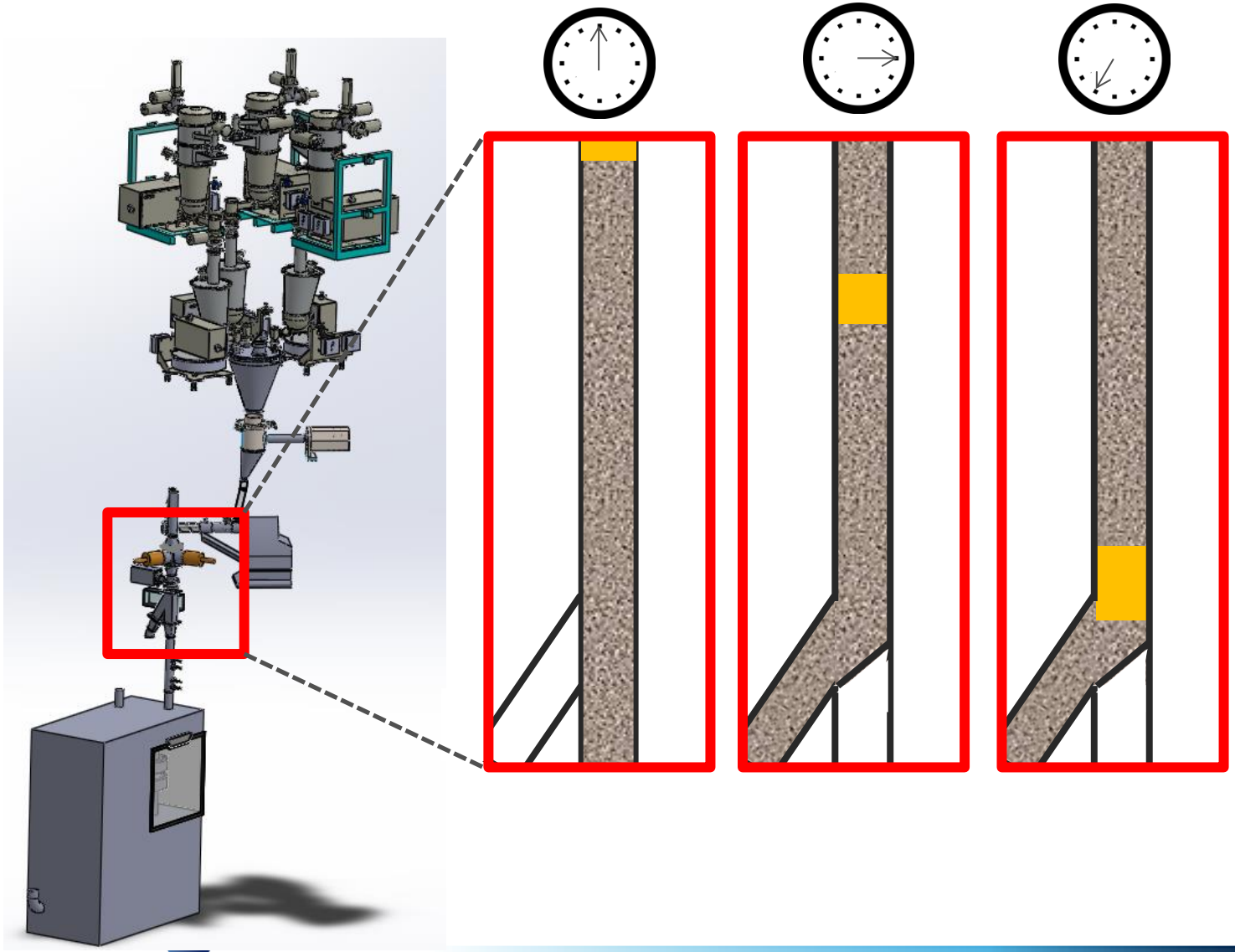






Time from NIR Interface to Diverter Valve 35 Seconds with a 20 second grace period

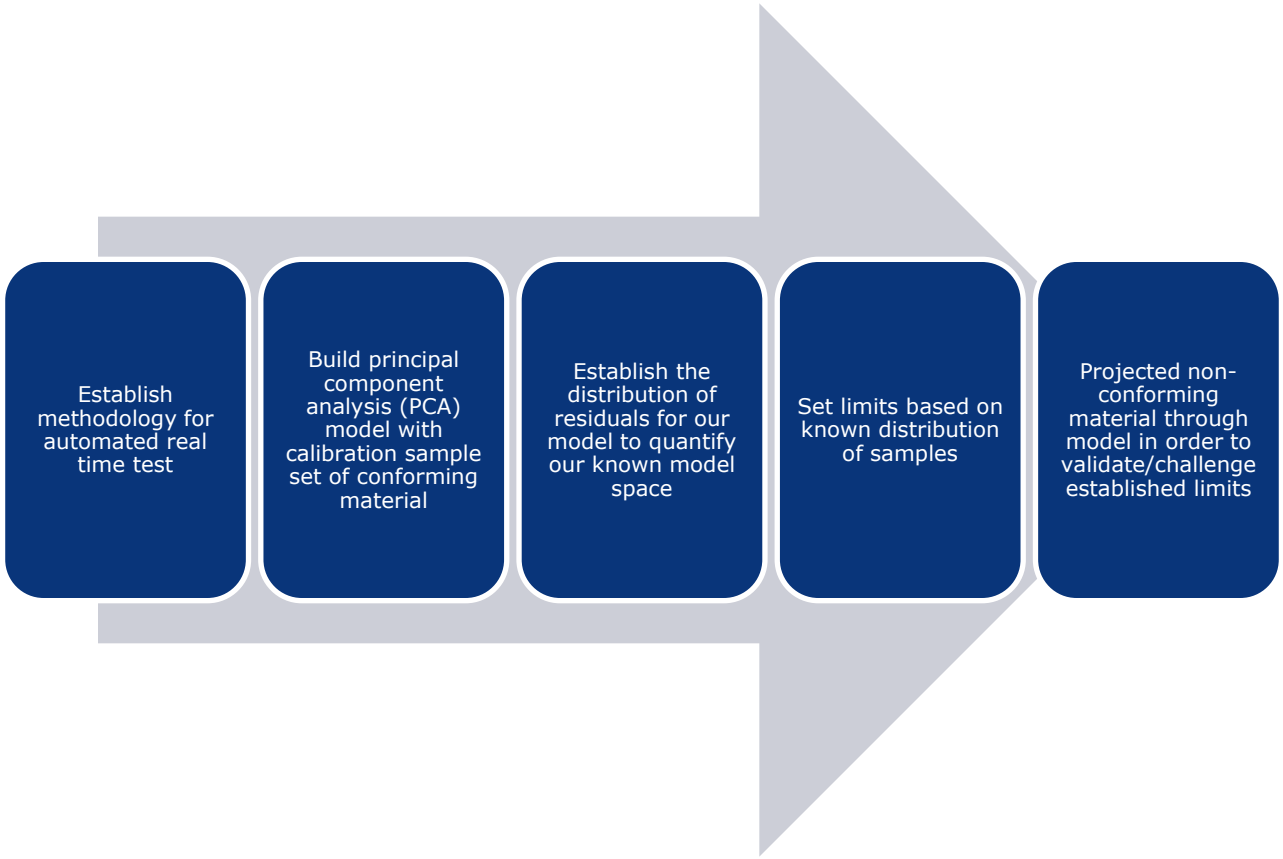
RTD Timeline of Non-Conforming Rejection



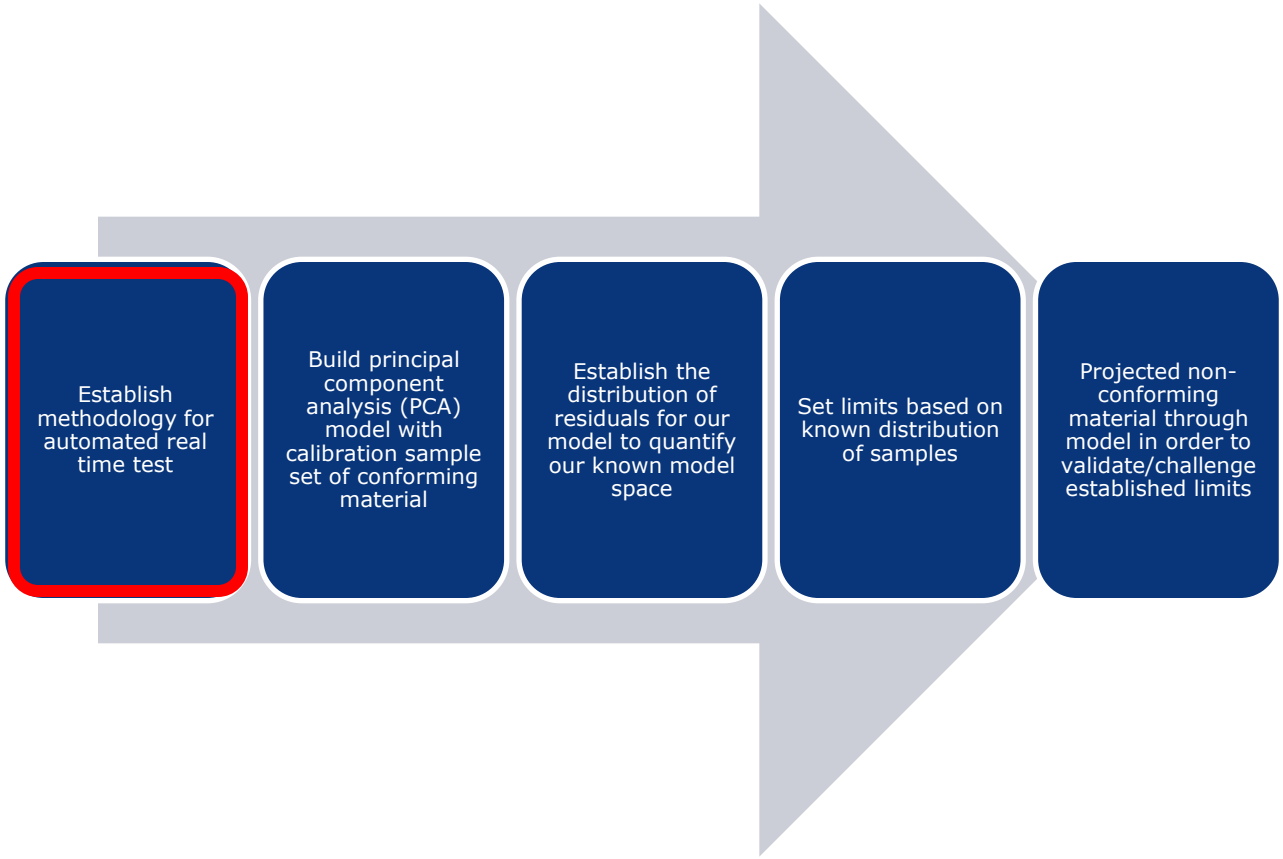
Developing an Automated Blend and Tablet ID Test

- Use NIR spectra and PCA Models X-Space Spectral Residuals to Determine
  - Presence of API
  - Correct API
- X-Space Residual is the lack of model fit statistic

Developing a Real Time Automated ID Model for Blends and Tablets

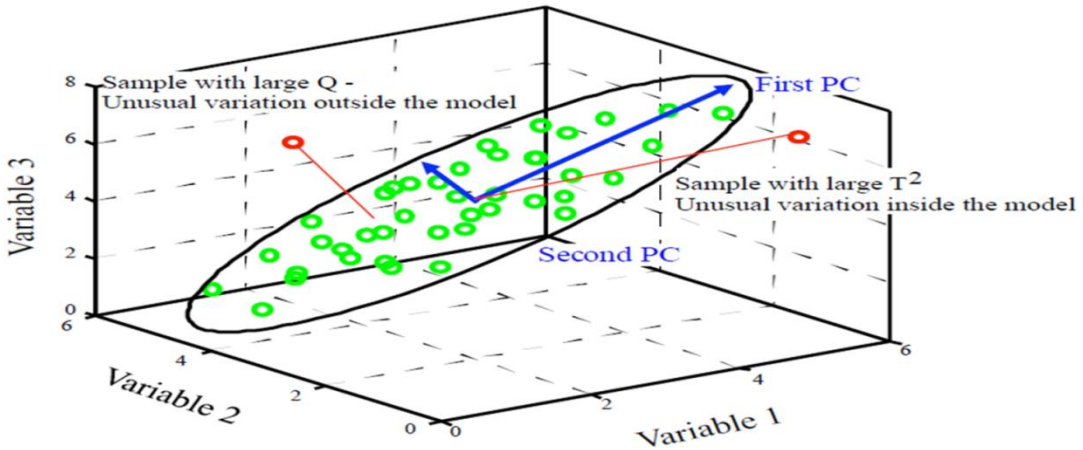


Developing a Real Time Automated ID Model for Blends and Tablets



Using PCA to Identify Tablets Outside Defined Model Space

- PCA captures maximum variance in X
- Use PCA to as outlier detection to ID "unusual" sample
- X-space residual statistics are widely used diagnostic tools for out-of-scope sample detection during multivariate model development
- Contributions to X-Space Residuals show how samples are different from PCA model



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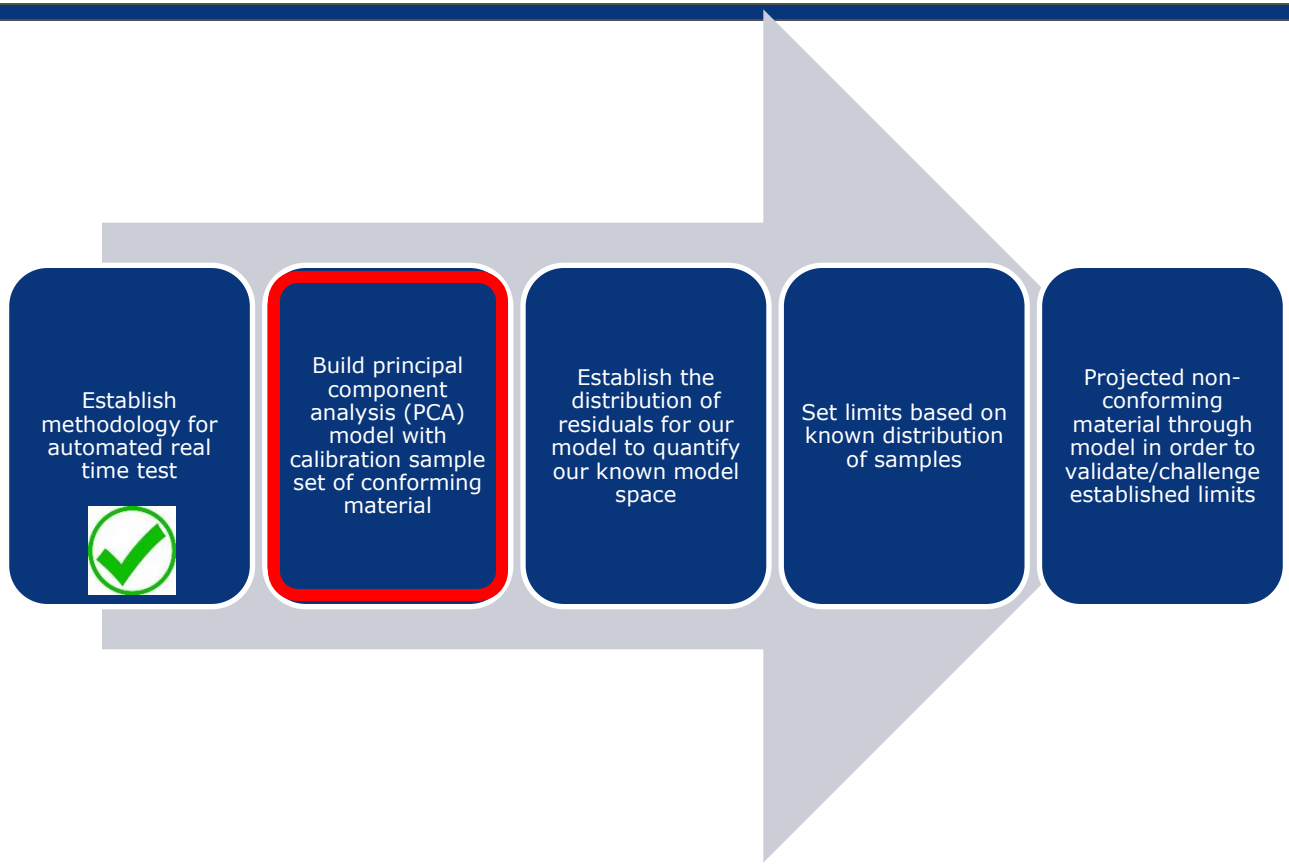
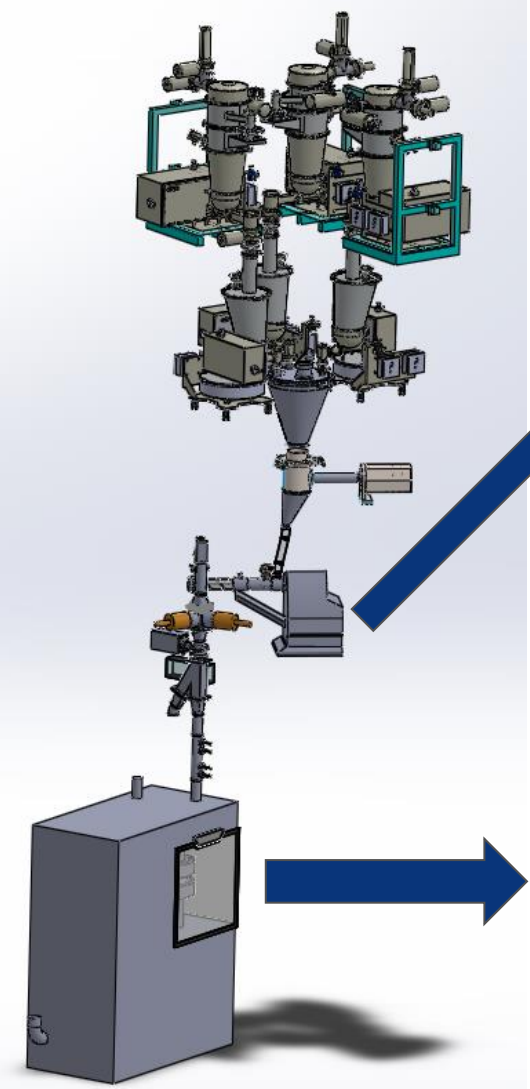


In-Line Chemometric Model Development

Line Run API (%LC)	Line Throughput (kg/hr)
70	40
85	40
100 (API Lot 1)	35,40,45
100 (API Lot 2)	40
115	40
130	40

*Additional samples used to validate model

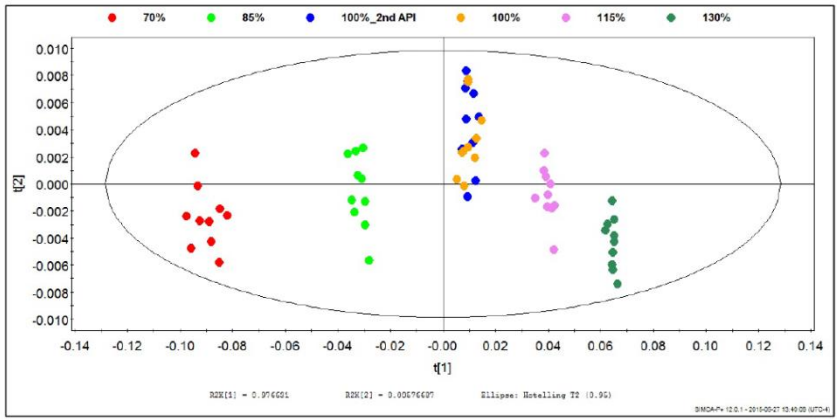


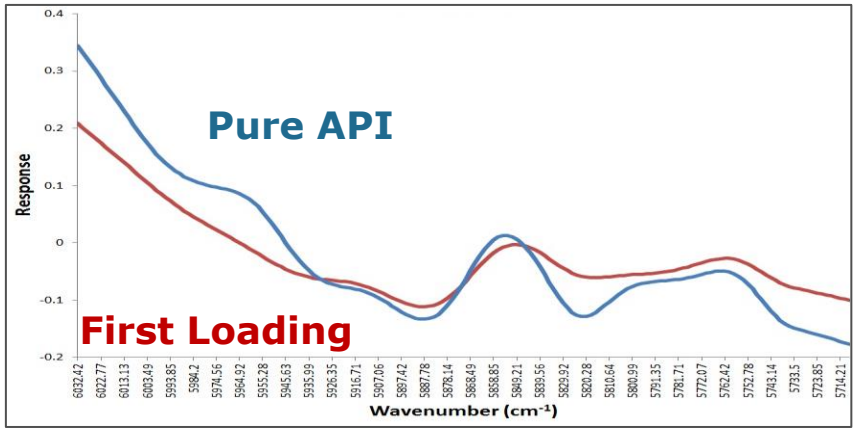
Blend	
Test	Model
ID	PCA
BU	PLS

Tablet		
Test	Model	RTRt
ID	PCA	Yes
CU	PLS	Yes
API Assay	PLS	Yes

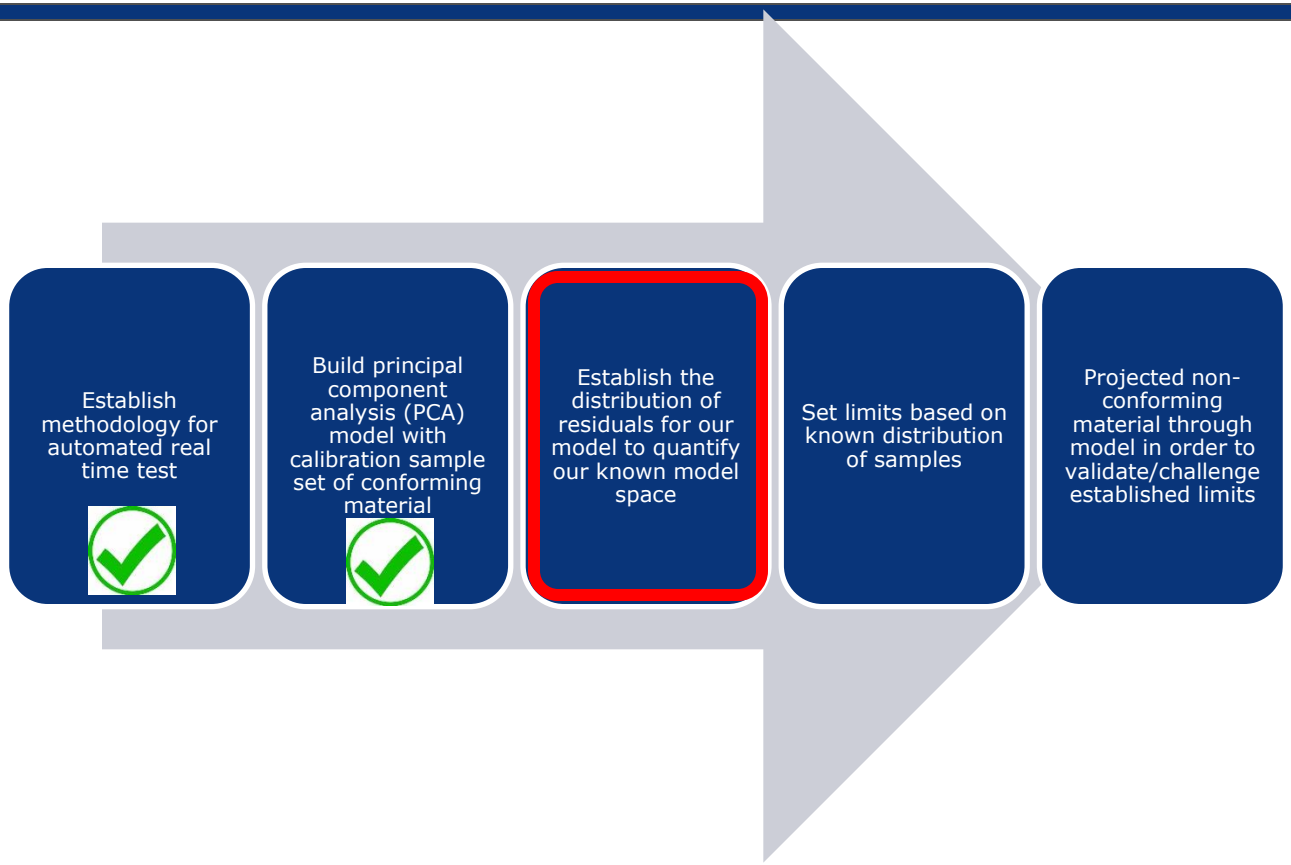
NIR Chemometric PCA Blend Model Development

Parameters	Values
Spectral Region	6032 - 5710 cm^{-1}
Data Pretreatment	SNV + 1st Derivative (25 point window)
Number of scans averaged per spectrum	16
Resolution	16 cm^{-1}
No. of principal components (factors)	2
Concentration Levels in CSS	5
Spectra per Concentration Level (CSS)	10
*Spectra in CSS (API No.1)	50
**Spectra in CSS (API No.2)	10
Total number of spectra in CSS	60

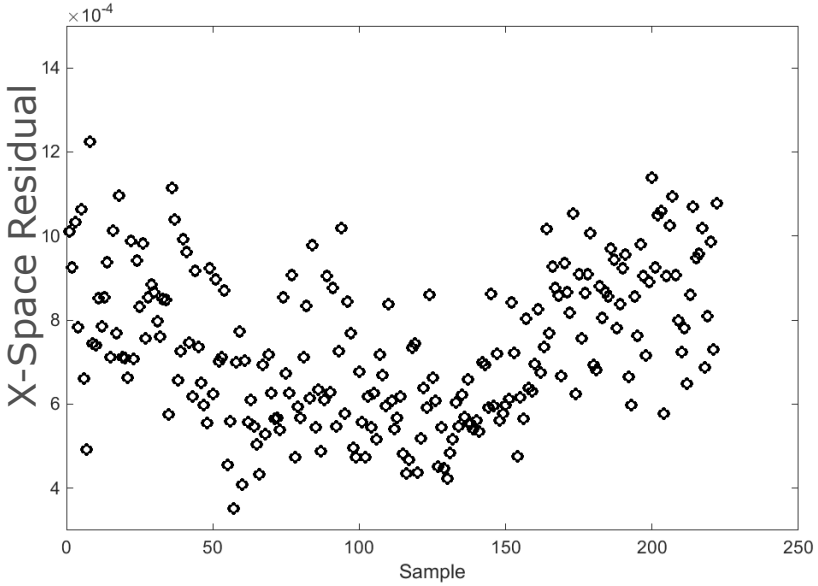




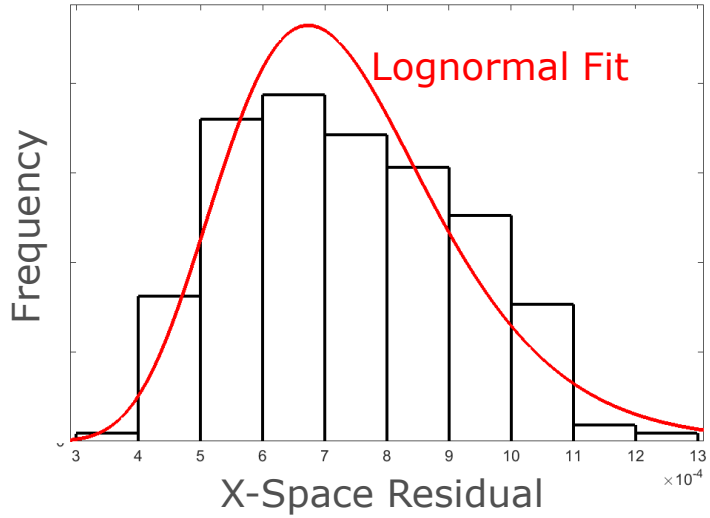
Developing a Real Time Automated ID Model for Blends and Tablets



Creating Blend ID Limits

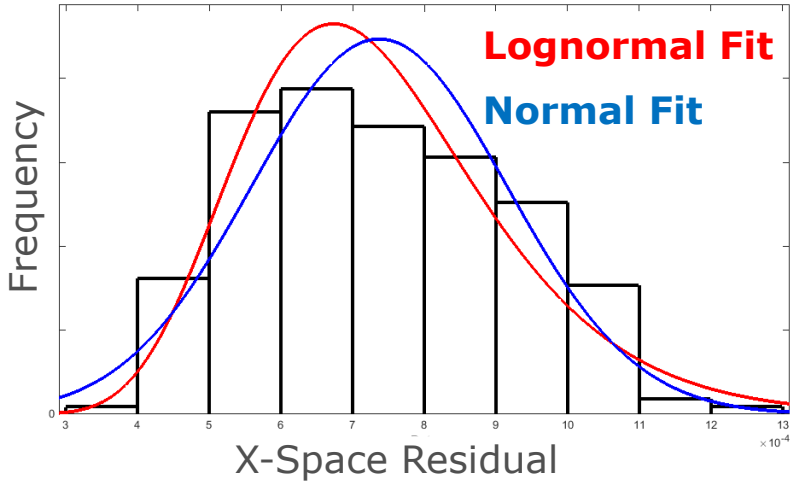


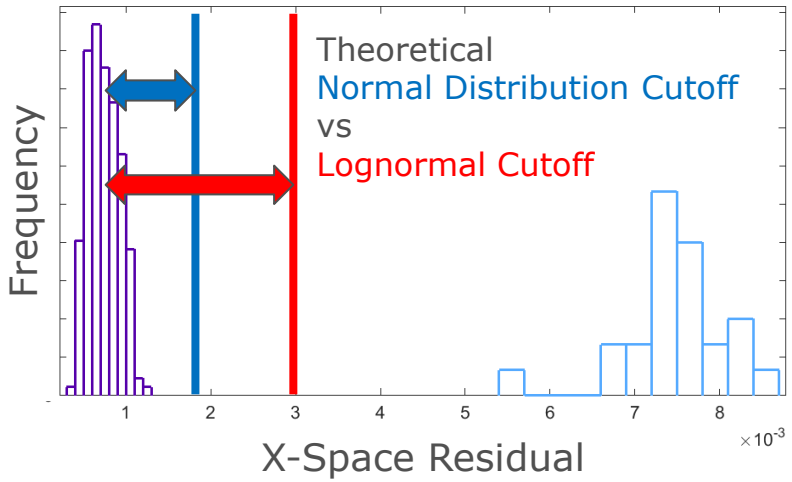
X-Space Residuals of Samples Projected Through Model



Histogram of Residuals

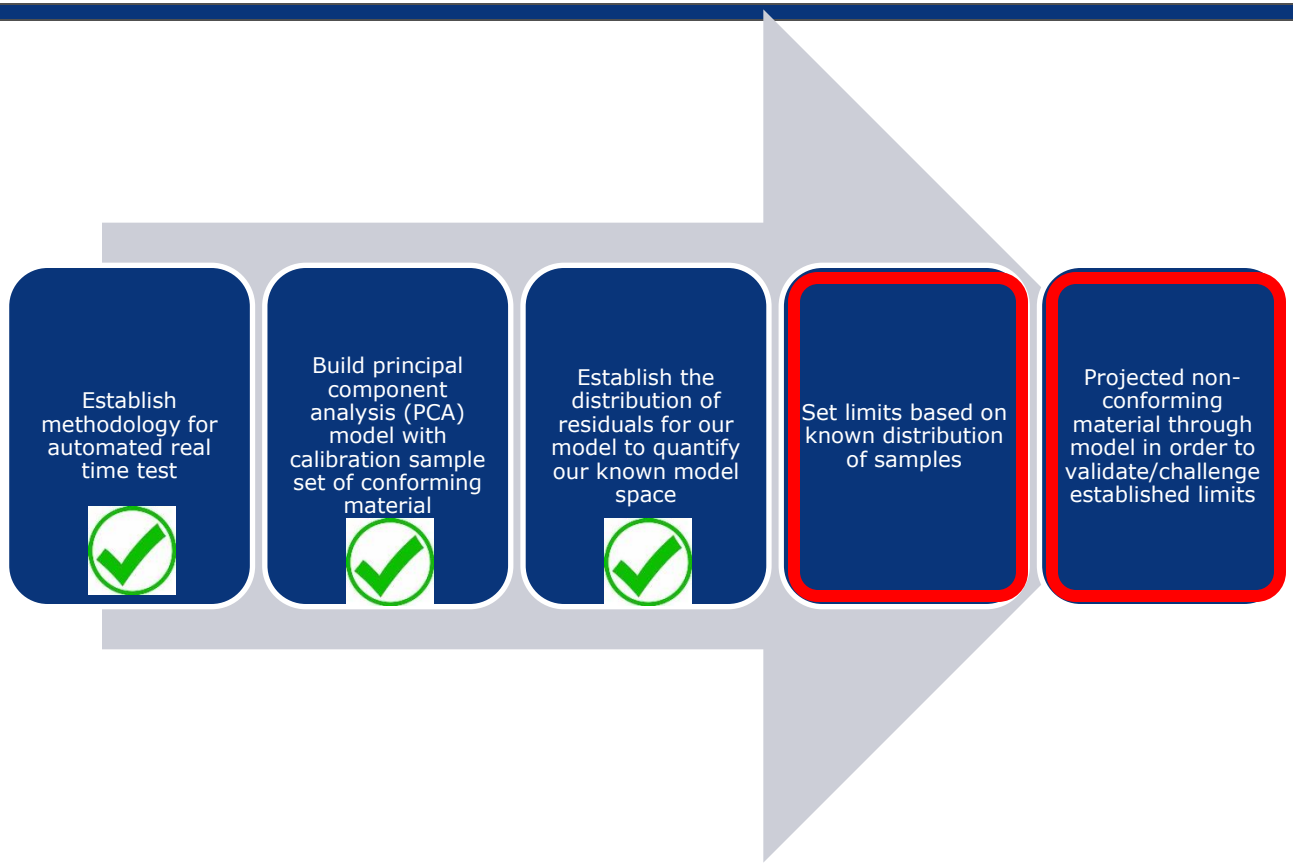
Rejection Limit Statistics





- Appropriate statistics for observed distribution

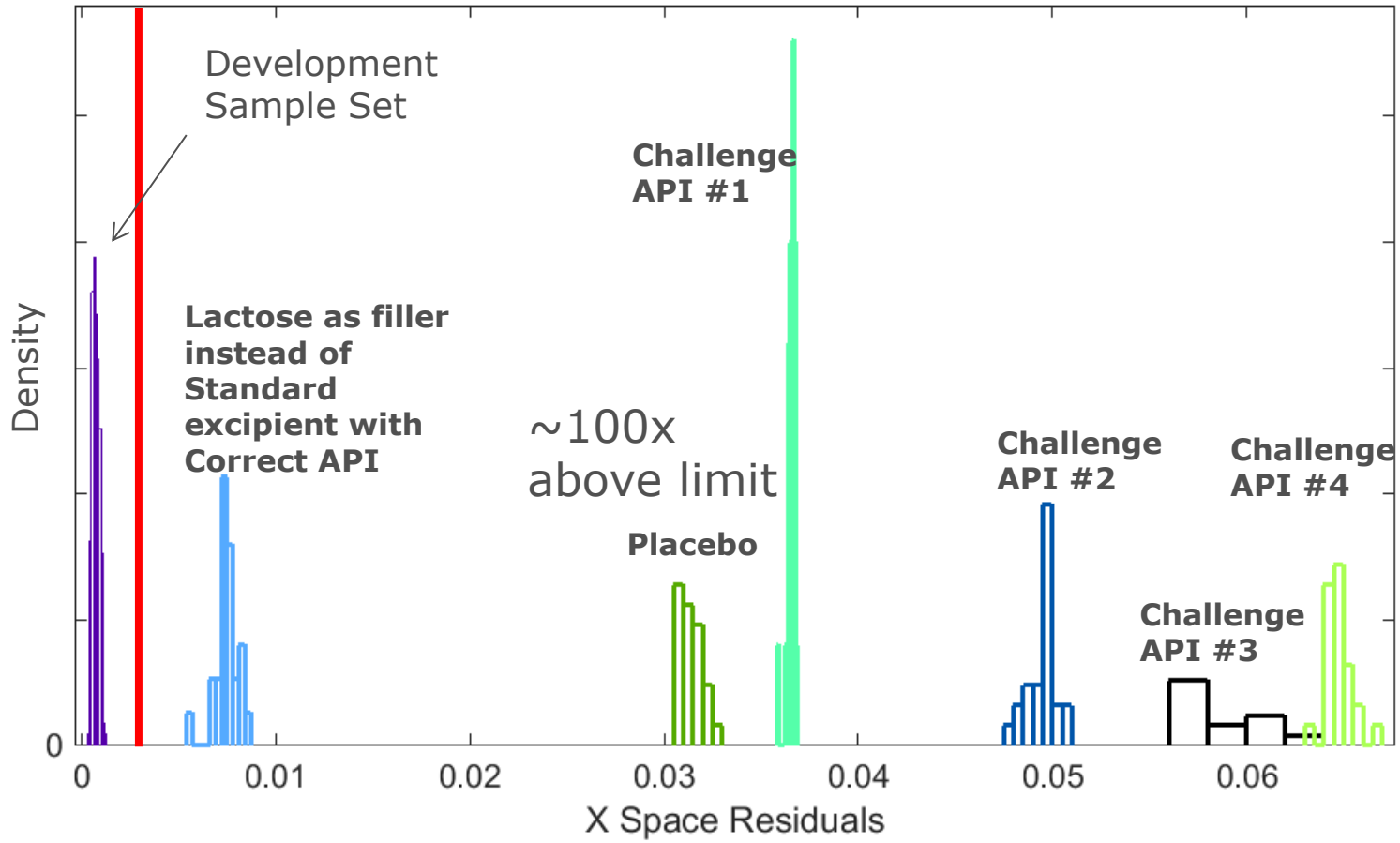
Developing a Real Time Automated ID Model for Blends and Tablets



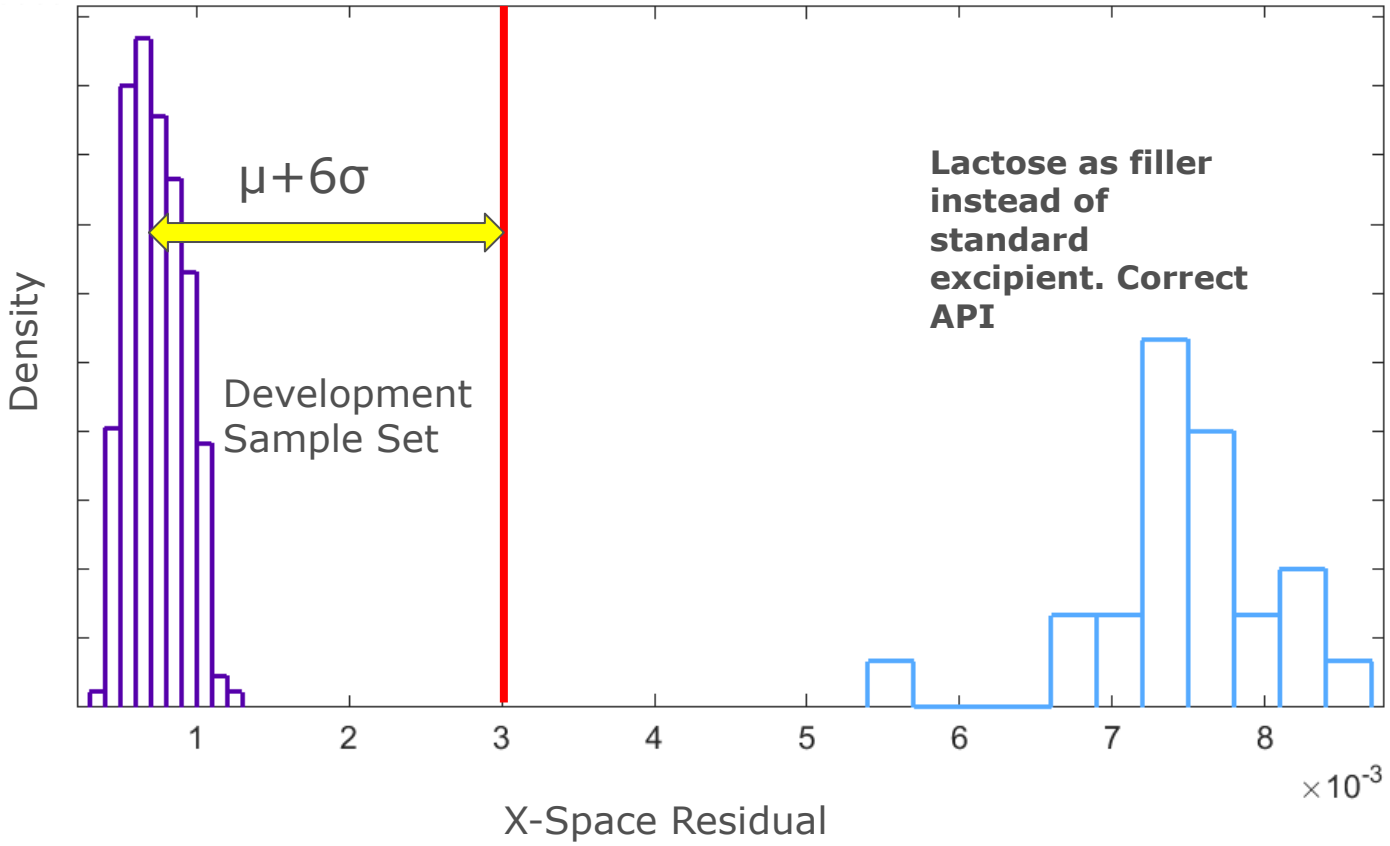
Challenge Samples

- Formulation with correct API lactose swapped for one of the standard excipients
- Placebo Sample
- Correct Formulation with API swapped for a “Foreign API”

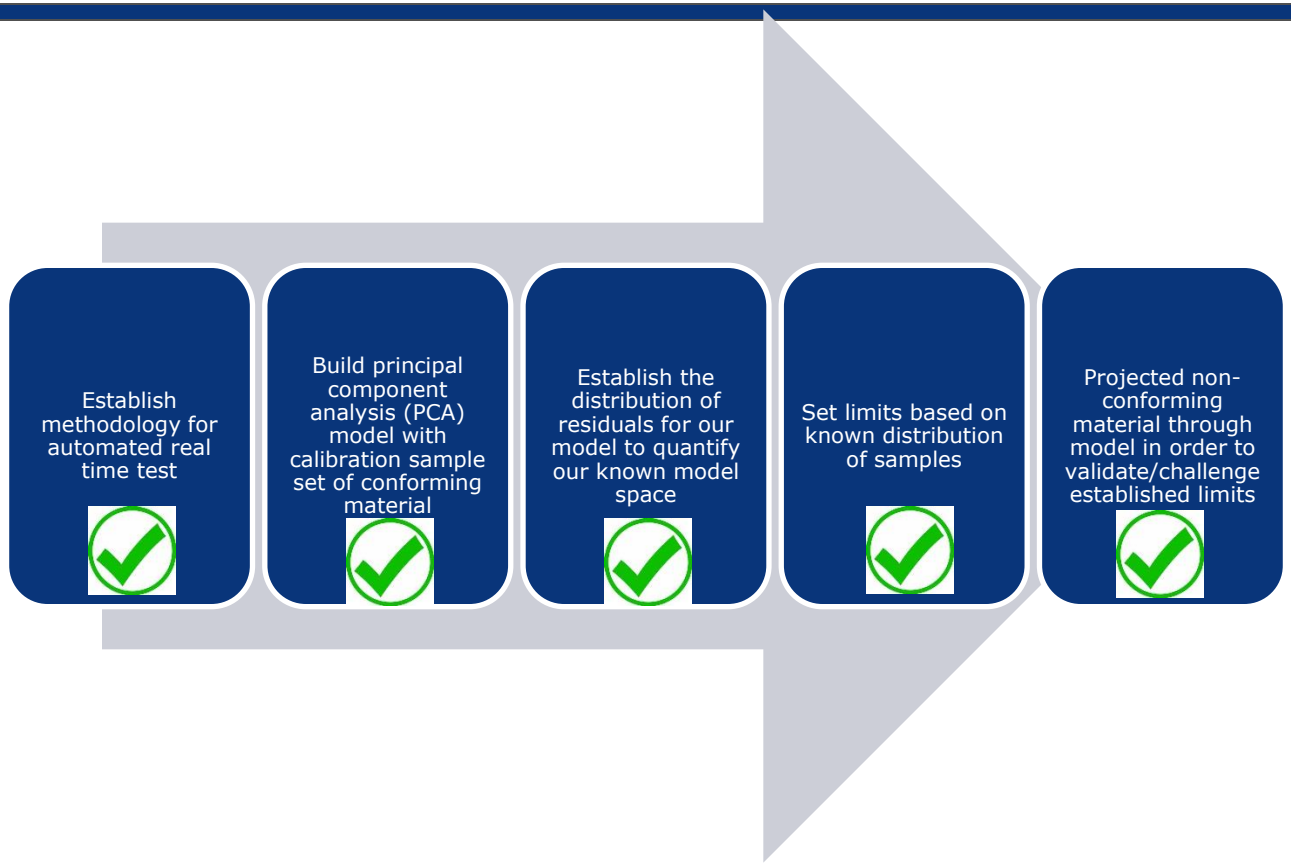
Establishing a Limit – Blend Challenge Samples



Establishing a Limit for Blend ID

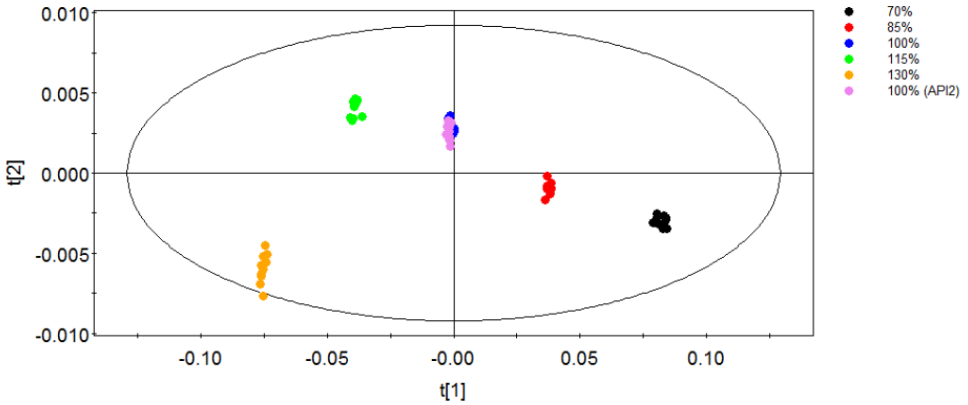


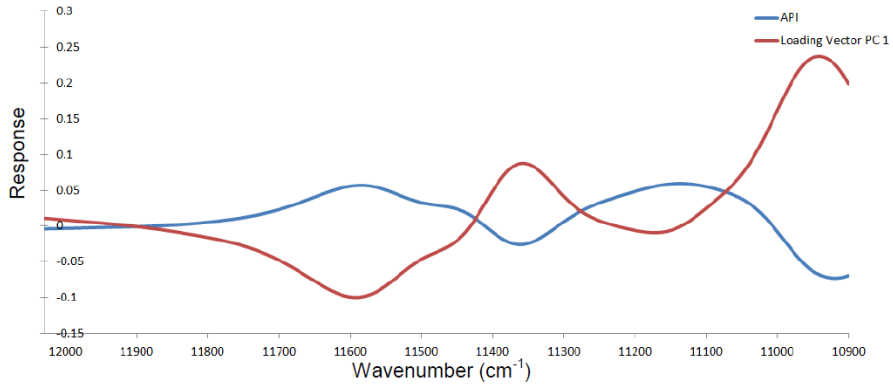
Developing a Real Time Automated ID Model for Blends and Tablets



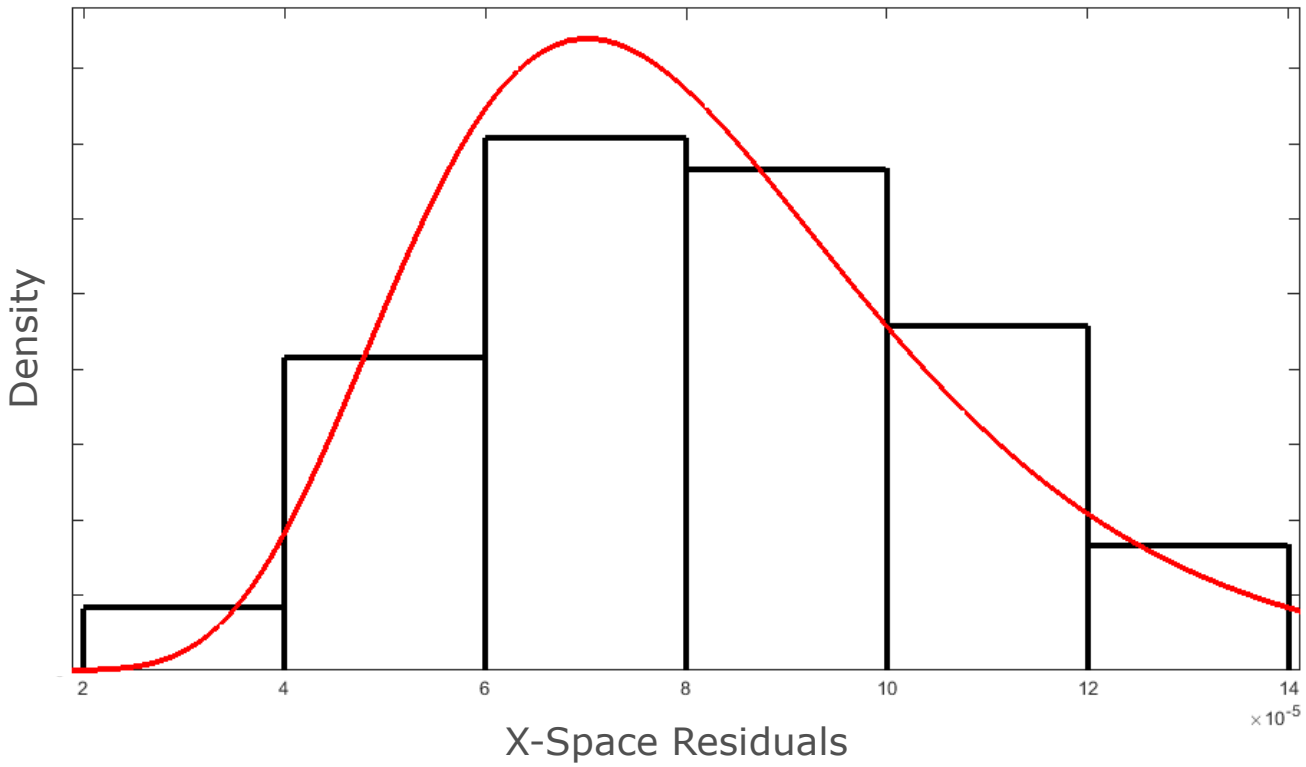
NIR Chemometric PCA Tablet Model Development for RTRt of Tablet ID

Parameters	Values
Spectral Region	12034 – 10900 cm^{-1}
Data Pretreatment	SNV + 1st Derivative (15 point window)
Number of scans averaged per spectrum	32
Resolution	64 cm^{-1}
No. of principal components (factors)	2
Concentration Levels in CSS	5
Tablets per Concentration Level (CSS)	10
Tablets in CSS (API No.1)*	50
Tablets in CSS (API No.2)**	10
Total number of tablets in CSS	60

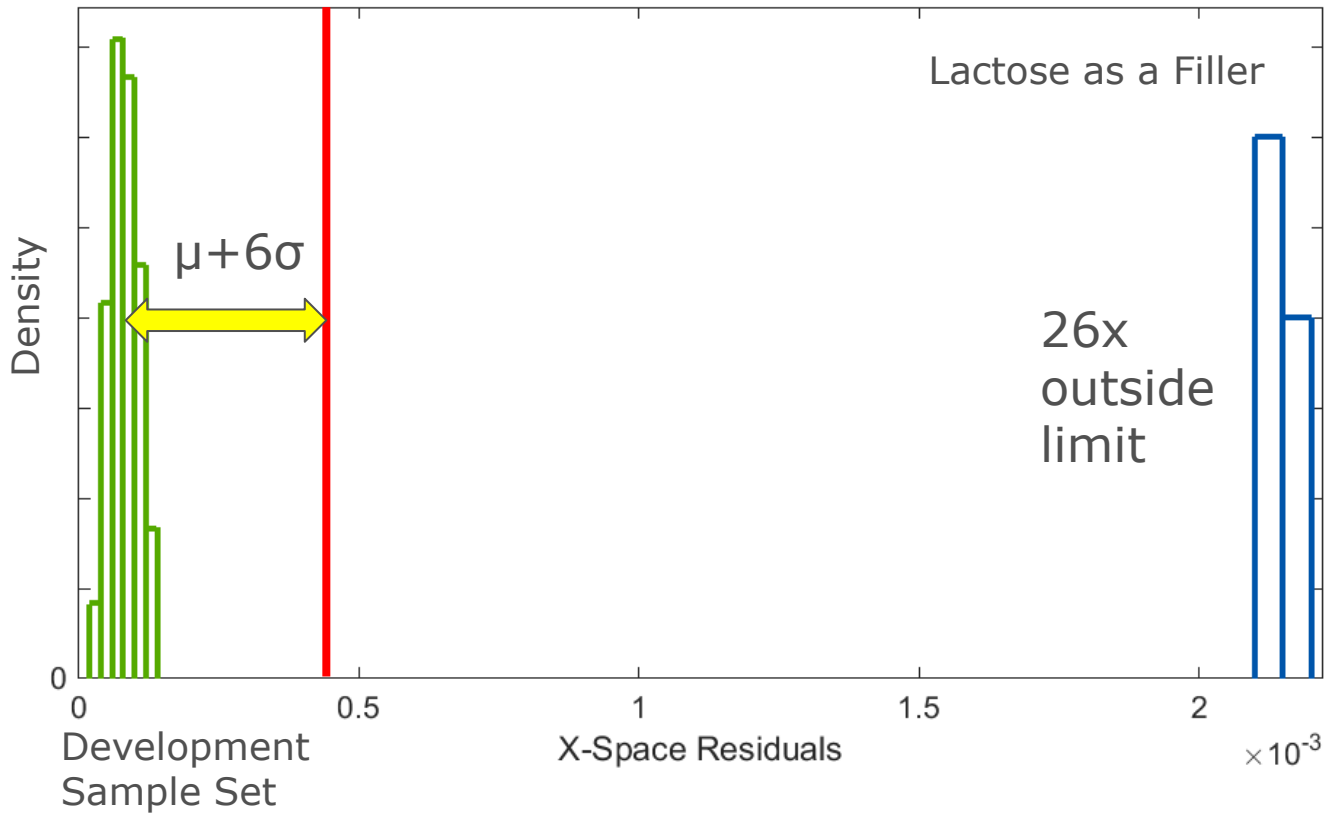




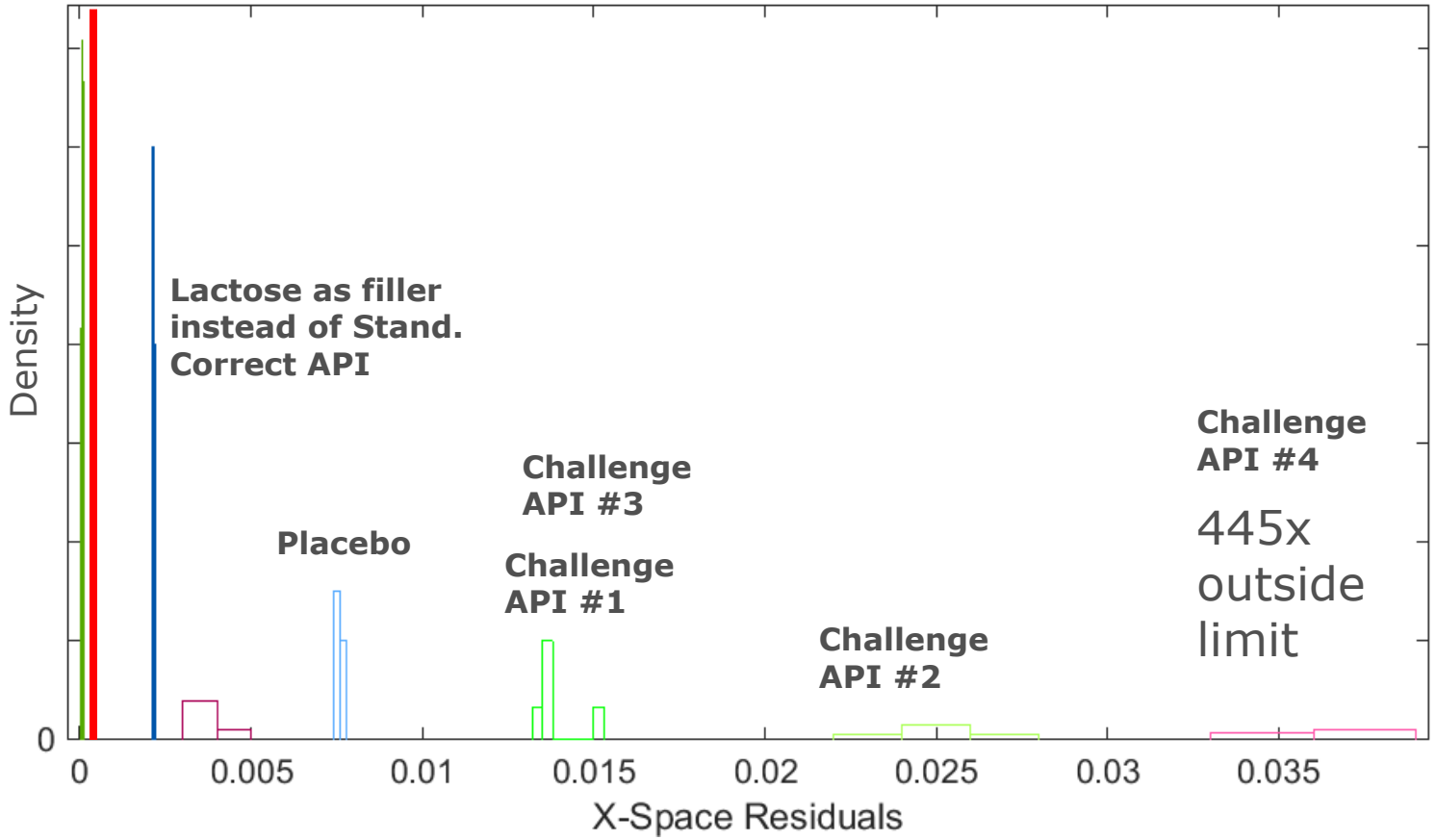
Real Time Release Test for Tablet ID



Setting the Limits RTRT Tablet ID



Tablets ID


Density
0
Lactose as filler
instead of Stand.
Correct API
Placebo
Challenge
API #3
Challenge
API #1
Challenge
API #2
Challenge
API #4
445x
outside
limit
0
0.005
0.01
0.015
0.02
0.025
0.03
0.035
X-Space Residuals

Conclusions

- Established control strategy using PAT as an integral part of monitoring blend and tablet properties
- Accurately determined residence time distribution which enabled real time blend monitoring
- In-Line Blend ID Testing
  - Limits Established using x-space residuals
  - ID Testing confirmed with “challenge blends”
- In-Line Tablet ID Testing
  - Limits Established using x-space residuals
  - ID Testing confirmed with “challenge tablets”
  - Real Time Release Test of Tablet ID