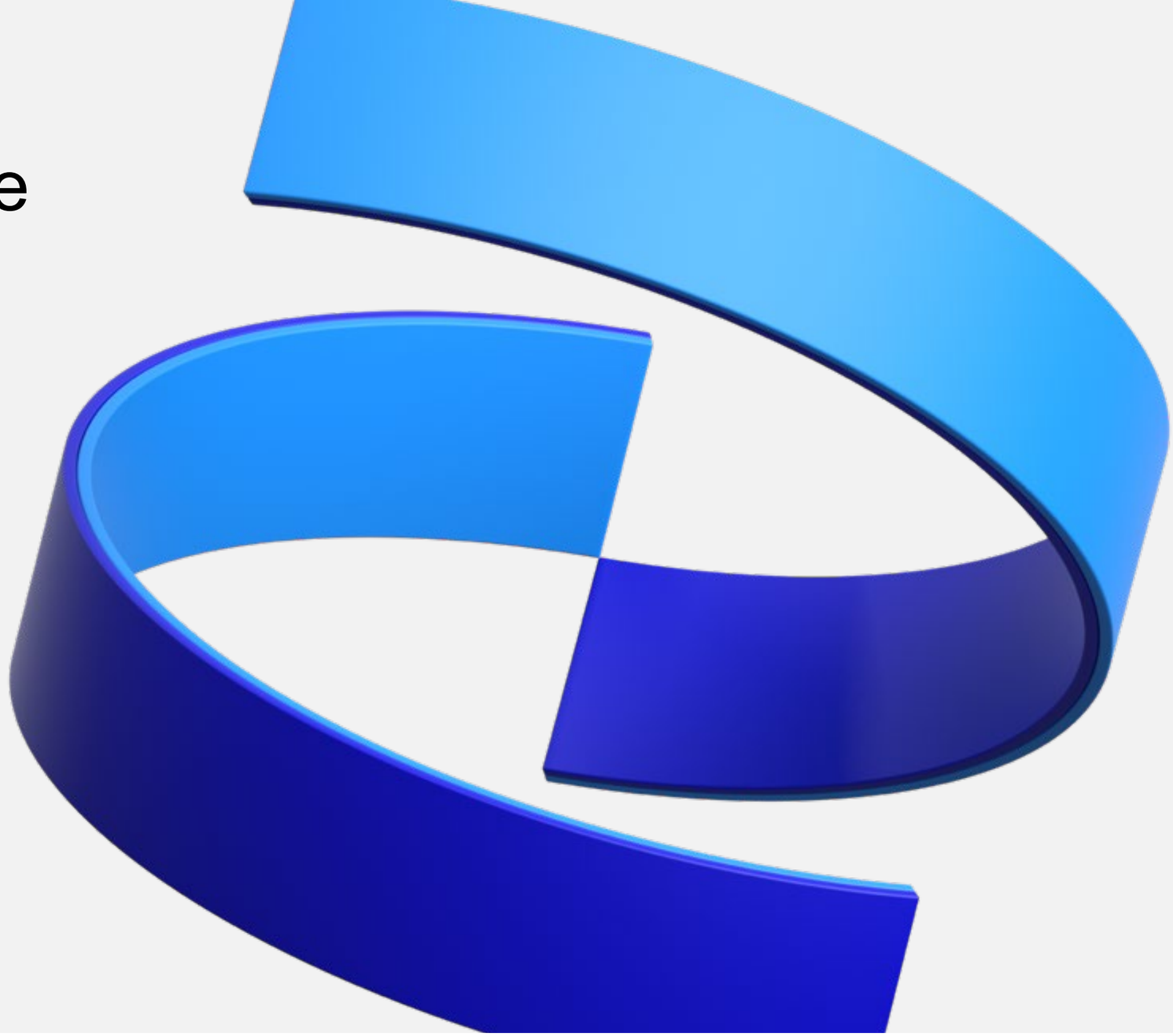
NIR – Soft Sensor Case Study for Q12 and Q14 Implementation



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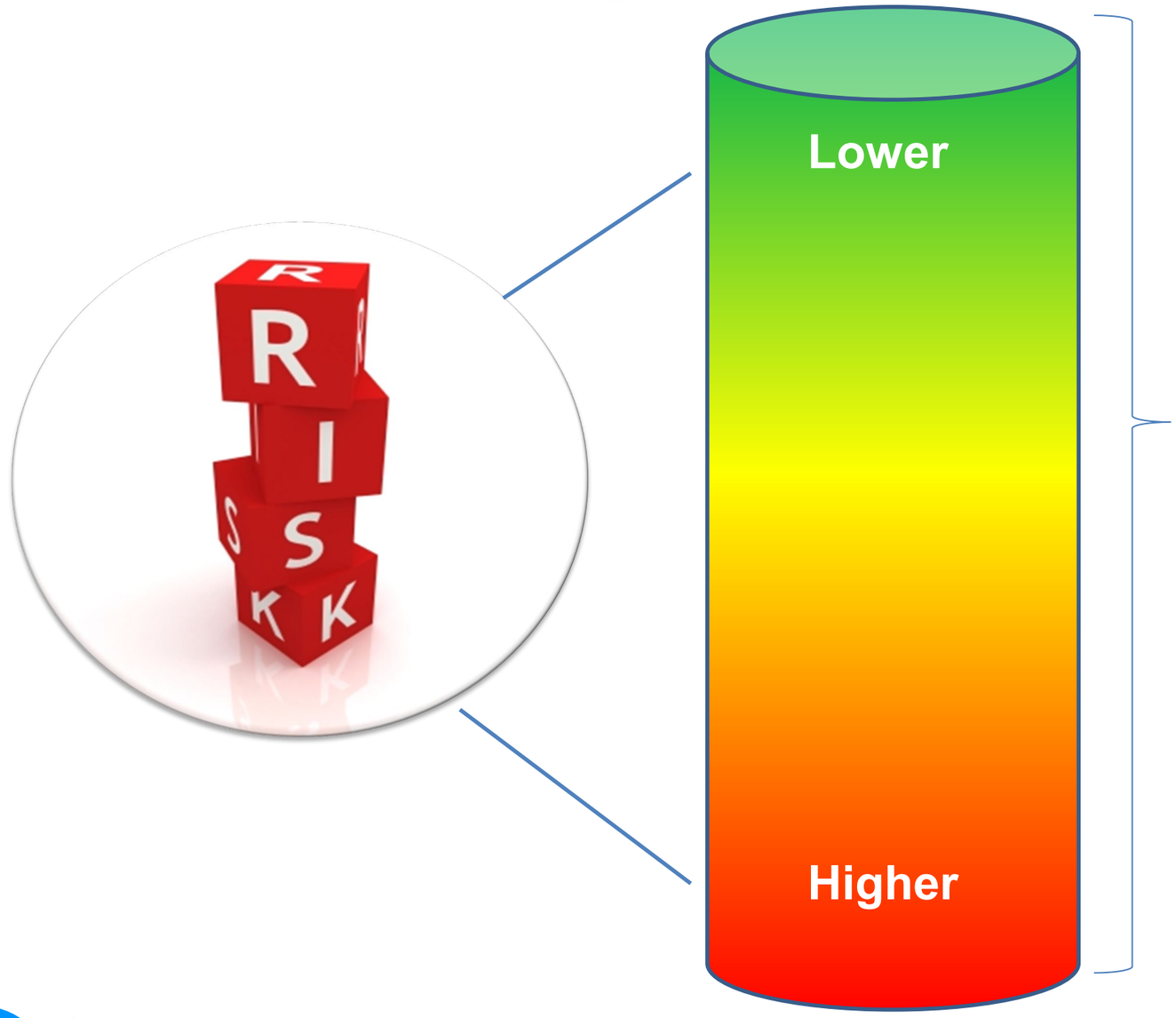
25 January 2023

Performance-Based Approach to Analytical Procedure Lifecycle

- A performance characteristic is a technology independent description to ensure the quality of the measured result. Typically, accuracy, precision, specificity/selectivity and range may be considered.
- A performance criterion is an acceptance criterion describing a numerical range, limit or desired state to ensure the quality of the measured result
- With an enhanced approach to development, there should be an increased understanding of the relationship between analytical procedure parameters and performance to facilitate identification of which factors require control and thus enable a more appropriate set of Established Conditions. These can focus on performance characteristics
- Purpose of development is to ascertain conditions (parameters) such that the performance characteristics can be met
- Demonstration of adherence to the performance characteristics through validation and robustness studies (where appropriate) must be achieved before the procedure can be implemented

ECs and Defining Risk

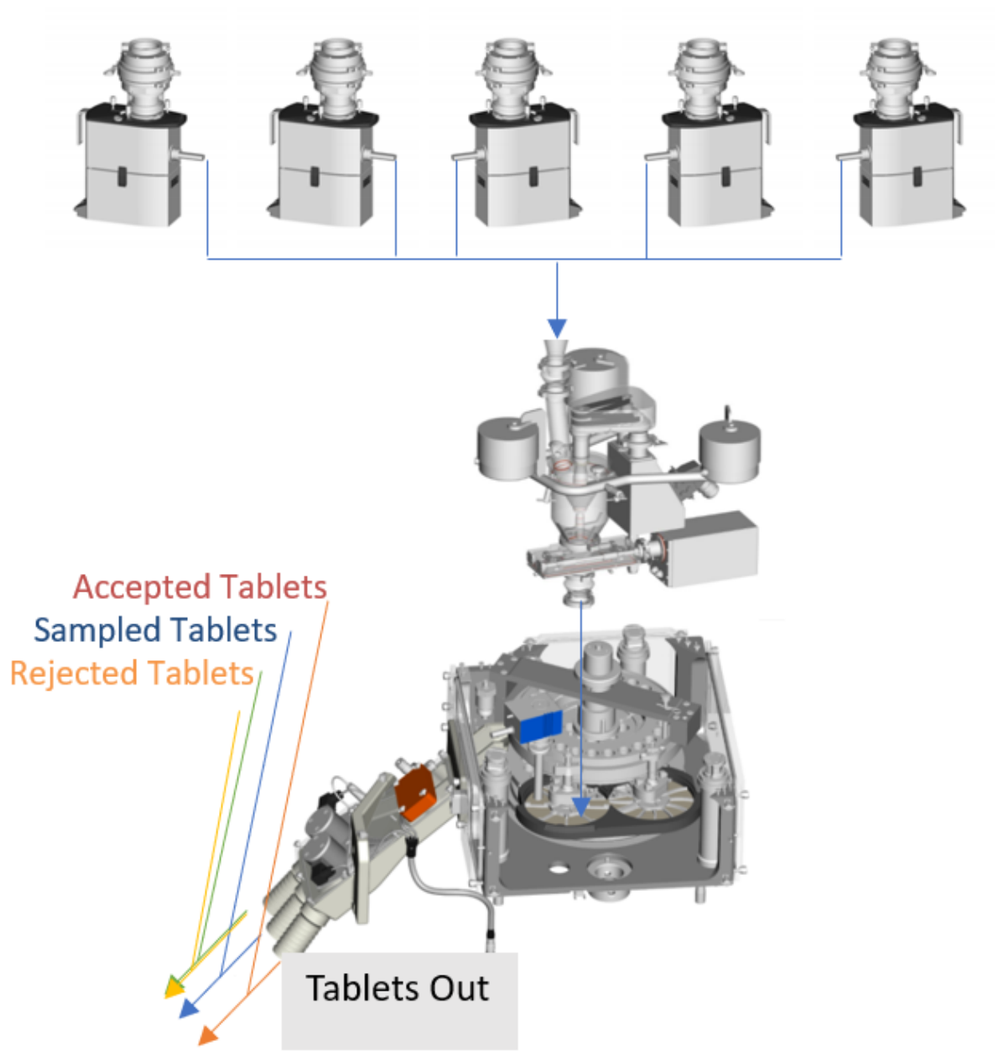


Enhanced Approach: Parameters controlled through performance characteristics and criteria may not need to be defined as an EC or may be assigned a lower reporting category

Continuum of Risk: Considering product and procedure knowledge, what is the risk associated with a potential change

Minimal Approach: Number of ECs may be extensive with fixed procedure parameters and set points

Procedure to be Discussed: Hybrid NIR-Soft Sensor Feed Frame Blend Potency Assay



Control Element #1
Material Attributes

Control Element #2
Feeder Process Parameters

Control Element #3
Mixer Process Parameters

Control Element #4
Residence Time Distribution Model

Control Element #5
NIR Control

Control Element #6
Tablet Core Physical Attributes IPC

Control Element #7
Off-line release testing of film-coated tablets

Established Conditions – Analytical Target Profile and Performance Characteristics

Established Condition		Reporting Category
Analytical Target Profile Intended Purpose: The in line method will be used as an in process test to assess blend potency in real time during continuous manufacture and to trigger tablet core diversion if blend potency exceeds the control limits.	Specificity Spectral range and PLS loadings and model regression vector demonstrate API unique spectral features. Linearity • The correlation coefficient of the NIR predicted value vs. reference value is statistically close to 1 and a y-intercept not statistically different from zero • Residuals are randomly distributed (show no trend) Accuracy: RMSEC ≤3.0% and RMSEP ≤ 3.0% Precision: RSD ≤2.0% Working Range: Minimum 92.0 -108.0%	**Prior Approval** Note: If widening the performance characteristics is necessary, it will be reported as PA.

Established Conditions – Procedure Principle and Parameters

Established Condition		Reporting Category	Justification and Comment
Analytical Procedure Principle: • NIR with PLS (partial least squares) model. • A dispersive NIR spectrometer with a diode array detector • Minimal Spectral Collection Range: 1300-2000 nm • Sensing location: Tablet press feed frame		NM	Adherence to ATP ensured by control strategy and defined bridging strategy (see below) to assess impact of changes. Changes to the method principle will be reported as NM. There is a strong understanding between product knowledge, intended purpose, and the analytical procedure performance established.
NIR instrument	Change of instrument (with no change of the measurement principle, i.e., NIR reflectance spectroscopy, a dispersive spectrometer with a DAD)	NR	All changes to any parameters are re-evaluated, confirmed, and verified to assure performance (regardless of reporting category) Model Validation will be conducted where needed.
Sampling frequency	Change to more than 4 seconds	NM	The revised method must meet the validation criteria defined above and appropriate for the process dynamic.
	Change to less than 4 seconds	NR	All changes to any parameters are re-evaluated, confirmed, and verified to assure quality. Method validation will be conducted where needed.
Software: PharmaX Real Time Manager and Real Time Stations – change of vendor with the same capability.		NL	Still able to manage the PAT systems to perform Hybrid NIR-SS measurement and trigger diversion in real-time (same functionality as the existing system)
Acquisition time (Sample volume): approximately 1.2 sec		NL	Must satisfy approximate unit dose level sampling volume requirement
Detailed Model parameters: • Preprocessing: SNV followed by 9 points Savitzky-Golay 2nd derivative and 2nd degree polynomial • PLS model range: 1300-1800nm • Number of latent variables: 3 • Model Suitability Criteria and Threshold: Hoteling T^2 of the PLS model ≤ (mean+5 x stdev)		NL	The detailed model parameters and model suitability test thresholds are optimized/changed as the consequence of model updates. Validation results reported against the performance criteria should demonstrate that the revised method is aligned with the requirements of the method.

Drivers for Changes to Analytical Procedures (NIR)

- Changes in API or excipient attributes leads to a need for model update
- An additional instrument is introduced at the manufacturing site
- Change in software used for model build and processing
- Technology innovation leading to continuous improvement

Change Example: New Instrument

Change: An additional NIR instrument is introduced as an alternate instrument for manufacturing method use. The new instrument is the same type manufactured by the same vendor as the existing instrument

Performance Assessment: A risk assessment of the change was conducted, and it was determined that the PLS model will be updated with additional data from the new instrument to enhance robustness. Performance criteria are re-evaluated through model validation to support implementation of the new NIR instrument

Regulatory Assessment: Implementation of the new NIR instrument of the same type manufactured by the same vendor was agreed to be managed in the PQS (NR), but the change resulted in a change to the detailed PLS model parameters, which has a reporting category of Notification Low, regulatory action is required

Acknowledgments

- Connie Langer
- David Wilsdon
- Brent Harrington
- Michael Cohen
- Angela Liu
- Sonja Sekulic
- Timothy Watson
- Lisa Skeens