Implementation of PAT for Real Time Release Testing

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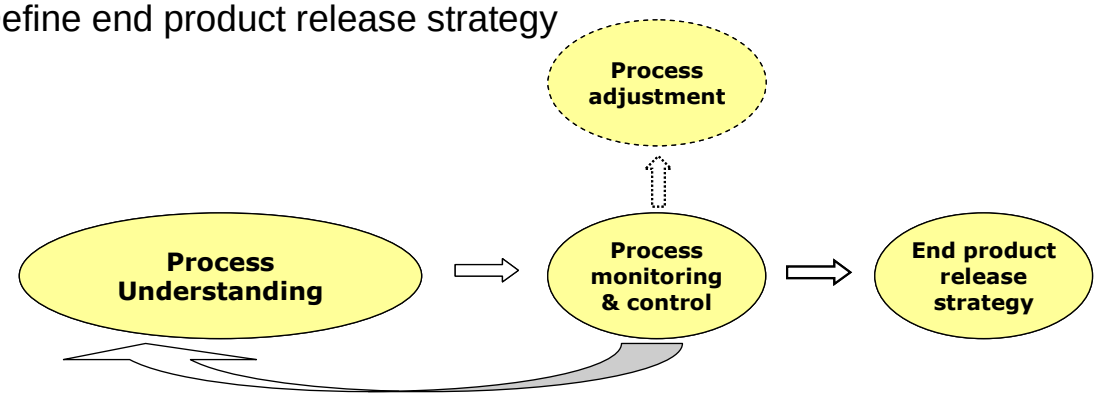
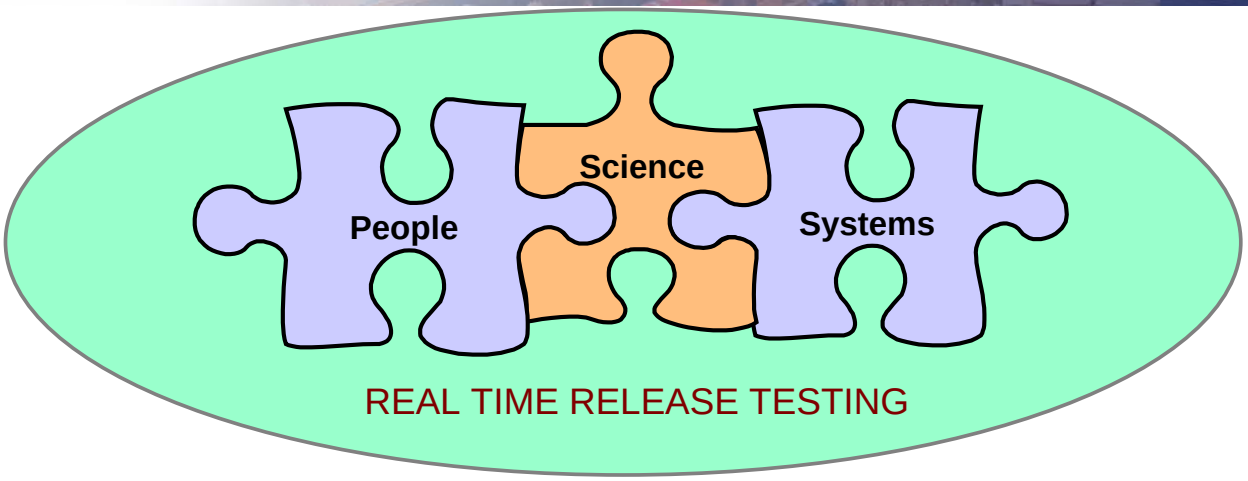
What is RTR Testing

- Real Time Release testing is defined in ICH Q8 (R2) part II as the ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls
- Real time release testing does not necessarily eliminate all end product testing. For example, an applicant may propose RTR testing for some attributes only or not all. If all CQAs (relevant for real time release testing) are assured by in-process monitoring of parameters and/or testing of materials, then end product testing might not be needed for batch release. Some product testing will be expected for certain regulatory processes such as stability studies or regional requirements.
  - Guidance for Industry: Q8, Q9 and Q10 Questions & Answers

RTRt in Pfizer

- Compile process understanding
- Define process monitoring and control requirements
- Define approach for process adjustment
- Define end product release strategy





ICH Q8 Pharmaceutical Development

ICH Q9 Quality Risk Management

ICH Q10 Pharmaceutical Quality System

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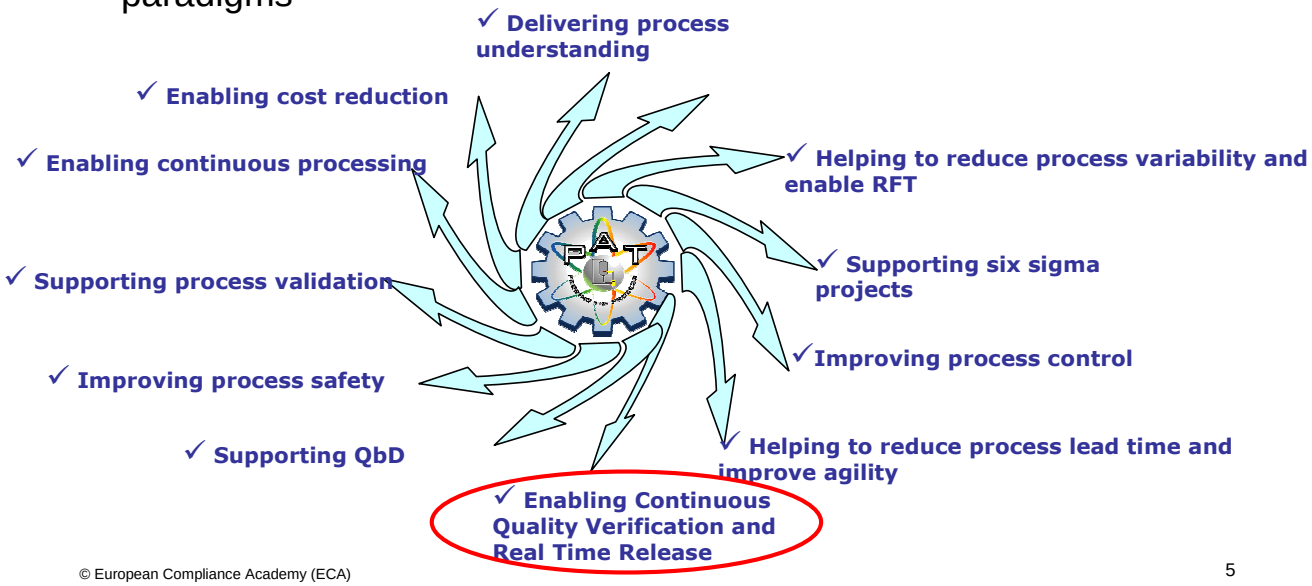
PAT at Pfizer

- A key enabler for transformational strategies and new quality paradigms



PAT at Pfizer

- PAT as a key enabler for QbD and RTRt
  - A means to improve process understanding and minimize variation
  - Monitor & control critical processes to achieve product and process robustness
  - Apply to new or existing products
  - Supports Continuous Quality Verification (Continuous Process Verification)
  - Enabler for continuous processing

Background

- Dosage form
  - BCS Class 1 compound (high water solubility, high permeability)
  - Immediate release tablets
  - Potent, low dose compound, low drug load (1mg in 200mg tablet)
    - ⇨ Launched from small-scale containment manufacturing facility
- Potential for Real Time Release testing
  - One of Pfizer's first QbD product filings
    - ⇨ Sound understanding of KPPs and CQAs
  - Robust control strategy
- Real Time Release testing
  - Redefine control strategy, eliminating or replacing required end product tests by online or at-line testing
    - ⇨ Safety improvements (OEB4 product)
  - Reduce cycle/lead time (lean)
  - Increased process understanding

Original Release Strategy

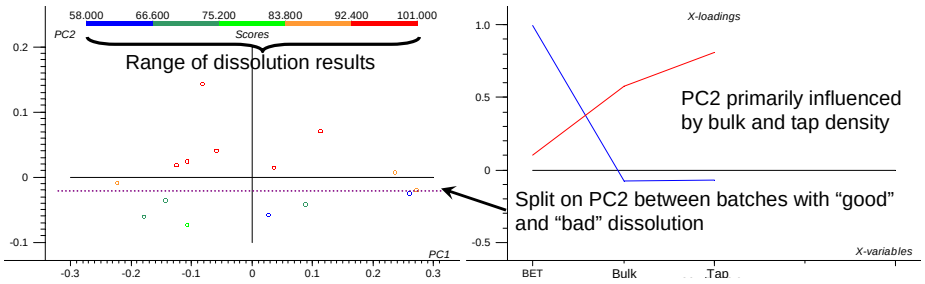
- During registration of the product

Release Test	Location	Technique
Identity	QC	TLC/HPLC
Impurities	QC	HPLC
Assay	QC	HPLC
Content Uniformity	QC	HPLC
Disintegration	Production	Disintegration Tester
Water Determination	QC	Karl Fischer
Appearance	QC	Visual
Microbial Quality	QC	Micro Testing

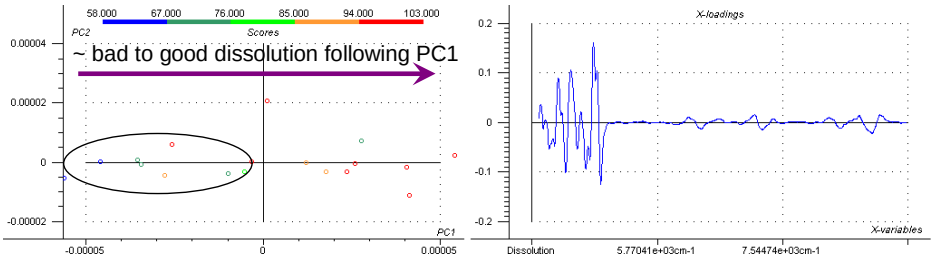
- Dissolution not filed initially

Dissolution – Future Directions

- Surrogate testing and mechanistic modelling
- DP dissolution prediction based on API properties



- DP dissolution prediction based on incoming API NIR spectrum



First Progression

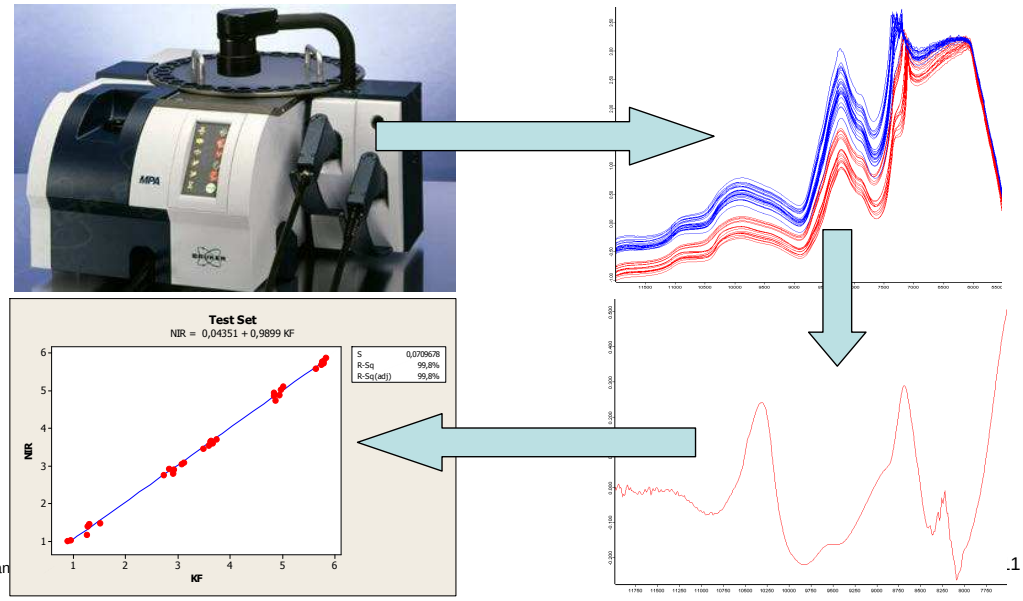
- Replacement of KF water determination method with NIR in QC

Release Test	Location	Technique
Identity	QC	TLC/HPLC
Impurities	QC	HPLC
Assay	QC	HPLC
Content Uniformity	QC	HPLC
Disintegration	Production	Disintegration Tester
Water Determination	QC	NIR
Appearance	QC	Visual
Microbial Quality	QC	Skip Lot Micro Testing

- Rapid with FDA due to flexibility of QbD filing
- Rapid with EMA
- Longer for other markets, with different questions and concerns

NIR for Water Determination

- Conventional lab-based NIR system
  - Validated over range 1 – 6% (historical range and regulatory specification)



NIR for Water Determination

- Positive first experience
  - Flexibility of the QbD filing
  - Openness of regulatory agencies to alternative release methods
    - ⇨ Both KF and NIR maintained on specification in case of breakdown or invalidation of PAT methodology
- Strong driver at site to move towards further projects
  - Quality systems established for NIR
    - ⇨ SOPs etc. put in place
  - Enhanced skill-sets at site to develop and validate NIR methods

Validation of PAT Methods

- Qualification of PAT systems
  - Qualification of the system should be commensurate with the criticality and assessed risk to quality and compliance
- PAT software validation
- PAT Methods/Applications
  - Similar approach to validation of conventional analytical methods, to confirm consistency of method performance and facilitate regulatory approval
    - ICH guideline Q2(R1): 'Validation of Analytical Procedures: Text and Methodology'
  - May involve comparison to a reference analytical method and assessment of their relative performance
  - In all cases, the validation must demonstrate that the PAT method is robust and fit for its intended purpose
- Performance Verification
- Validity Monitoring, Change Control and Model Maintenance / Update

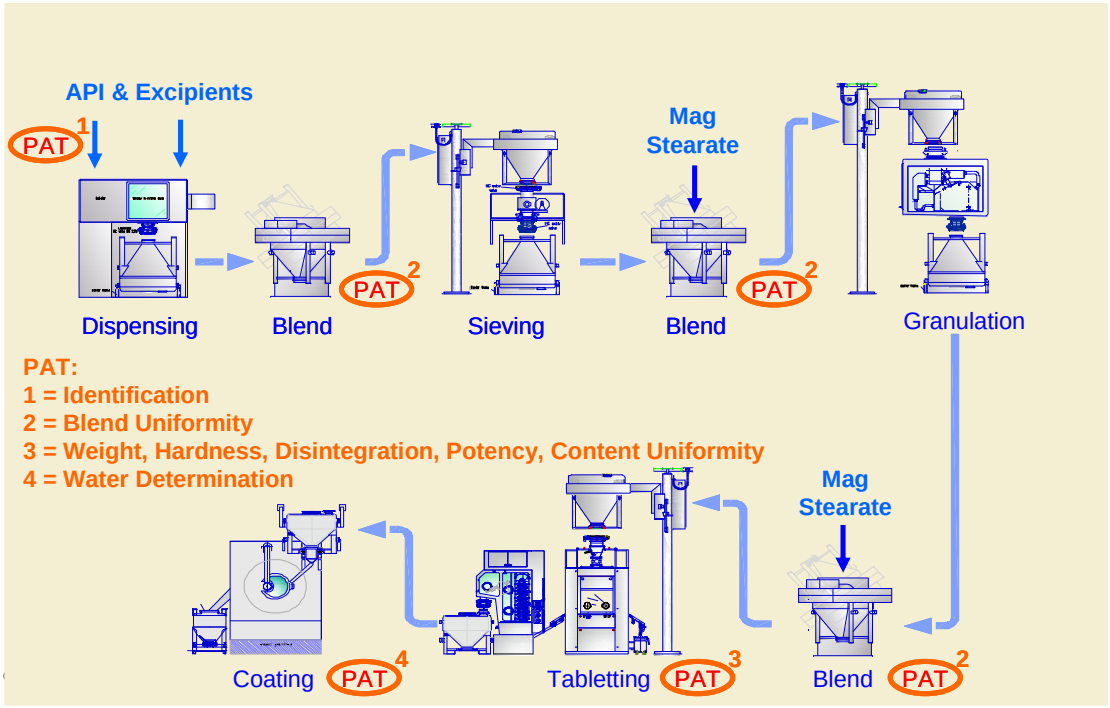
RTRt Strategy

- Cross-functional team established strategy for moving towards RTR testing
  - Strong sponsorship at site and from Quality organisation

Release Test	Location	Technique
Identity	Production (At-line during Dispensing)	NIR
Impurities	Eliminated based on high Process Capability	
Assay	Production (On-line)	NIR
Content Uniformity	Production (On-line)	NIR (Large N)
Disintegration	Production (At-line)	Disintegration Tester
Water Determination	Production (At-line)	NIR
Appearance	Production	Visual
Microbial Quality	QC	Skip Lot Micro Testing

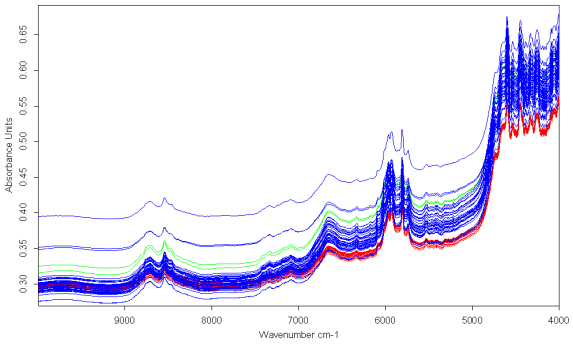
- Filing for all markets (EU, US, ROW)

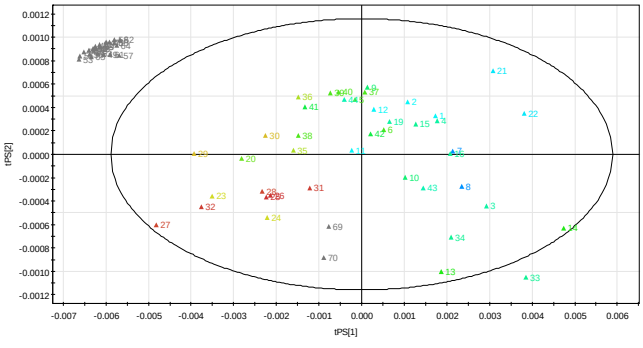
Manufacturing Process



Raw Material Identity Testing

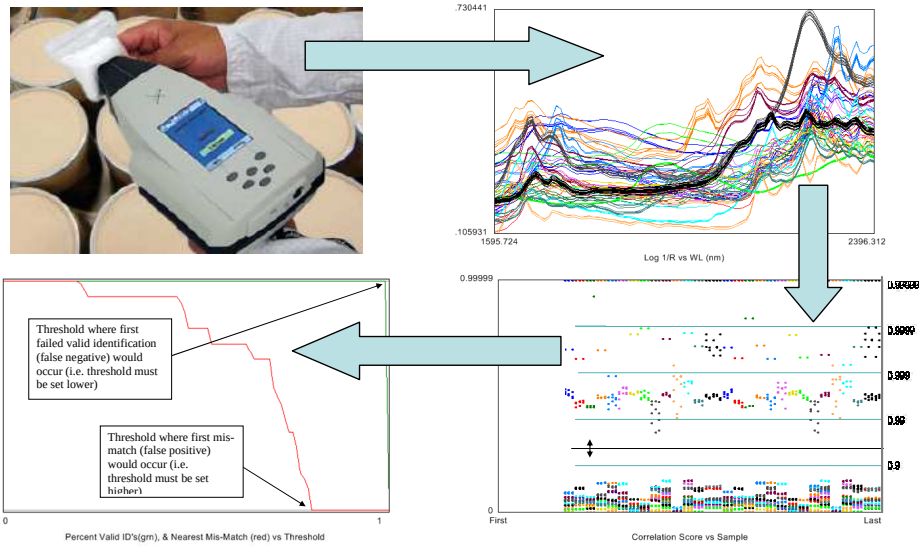
- API identification performed in warehouse on receipt
  - High specification NIR system utilised
- Further application for conformance testing
  - Qualitatively assess and compare incoming API lots
    - ⇨ Potential for process understanding, linking to CQAs
    - ⇨ Potential contribution to NIR method control strategy





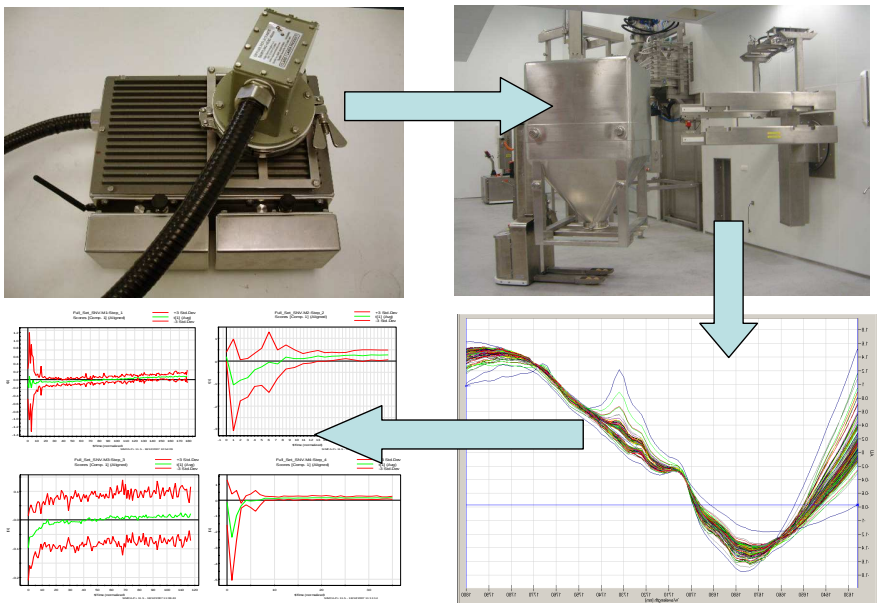
Identity Testing

- Replacement of regulatory release test for API in tablet matrix proposed during dispensing
  - Closed manufacturing facility with single API



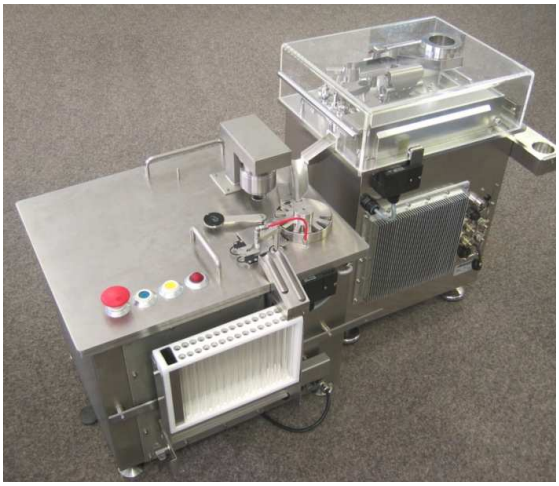
Blend Monitoring

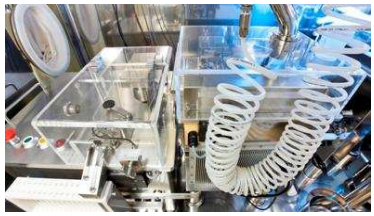
- Blend uniformity is not a regulatory requirement
  - Monitored for process understanding, troubleshooting and process validation



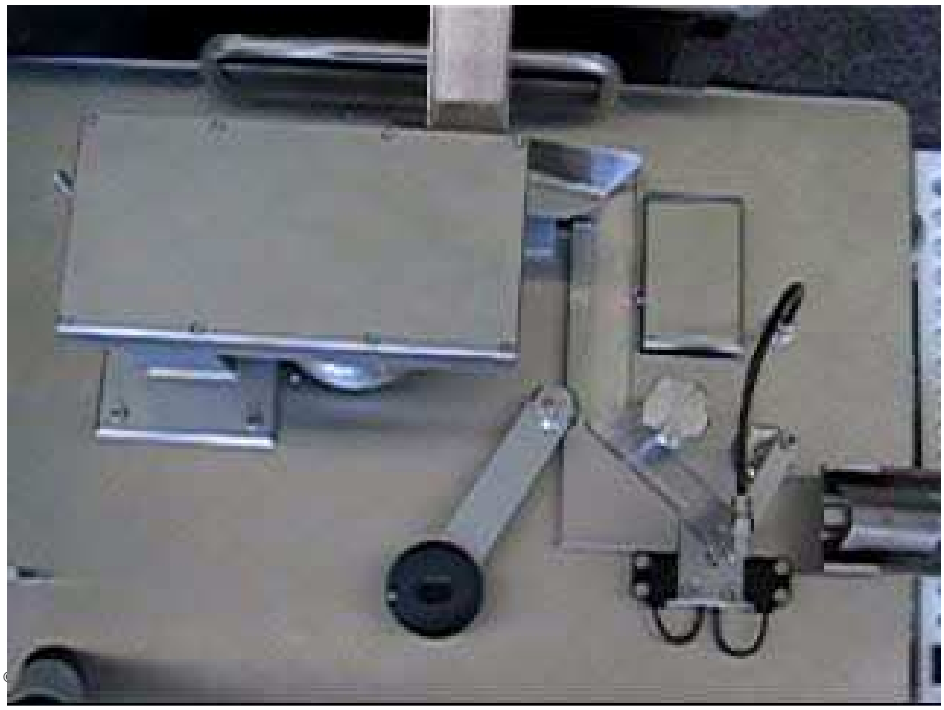
Assay/Content Uniformity

- Performed on-line using the same NIR system and measurement
  - Provides major safety benefit by reducing manual sampling
  - Provides opportunity for increased sampling frequency



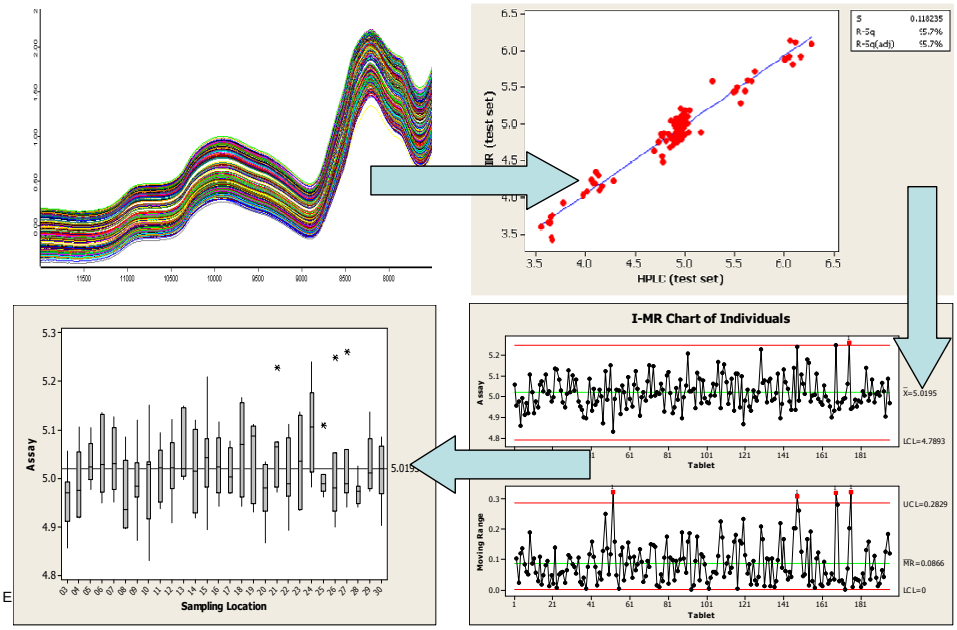


Assay/Content Uniformity



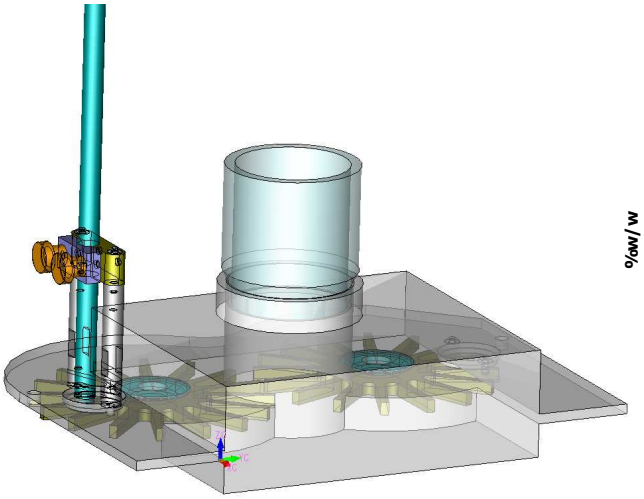
Assay/Content Uniformity

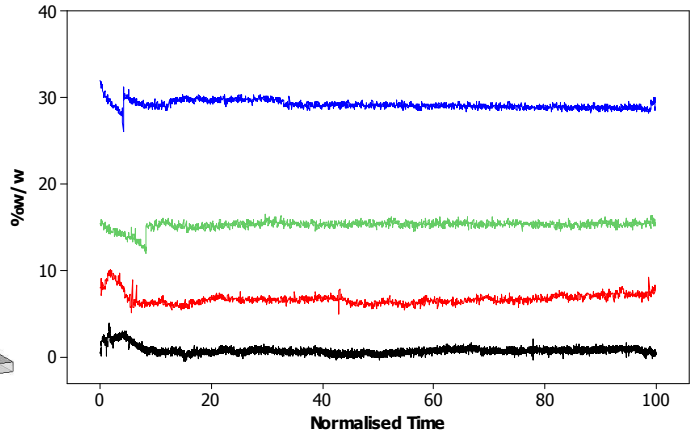
- Extensively developed to encompass product and process variation



Assay/Content Uniformity – Future Directions

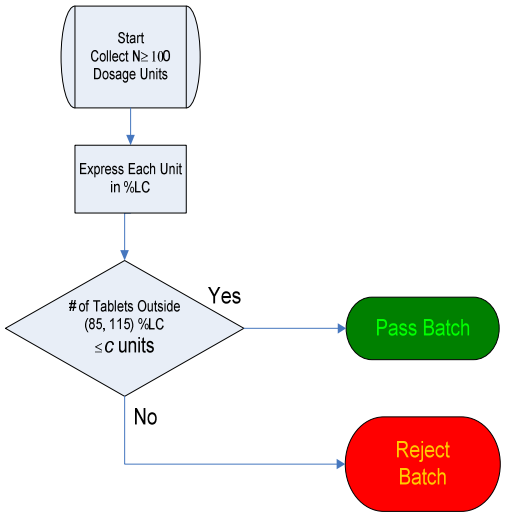
- PAT applied for blend in the feed-frame / encapsultor in combination with tablet weights





Specifications

- With an increased sampling frequency, conventional specifications are no longer applicable
  - ICH UDU applied for 10 (or 30) dosage units
  - If same applied for >30 there is a risk of failing batches based on number of units tested and not quality
- Pfizer, originally through work with PhRMA, proposed to utilise the Large N Counting Test
  - Controls the number of units outside 85 – 115% LC
  - No secondary limit for units outside 75 – 125%



n	100	250	500	750	1000	2000	3000	4000	5000	10000
c	4	11	23	35	47	95	143	191	239	479

Impurity Testing

- Degradation pathways understood for all impurities
  - Impurities generated during API manufacturing are controlled in the finished API and not tested in the drug product
  - No impurities formed during drug product manufacturing process
    - ⇨ Or at low levels compared to ICH limits
- Product with several years manufacturing experience
  - Historical process capability and stability data
    - ⇨ Stability data generated under accelerated and long-term storage conditions demonstrate the product is stable
    - ⇨ Excellent process capability (>10 for both individual and total impurities)
- Proposed to retain impurity testing for stability but to delete as a release requirement

EMA Variation

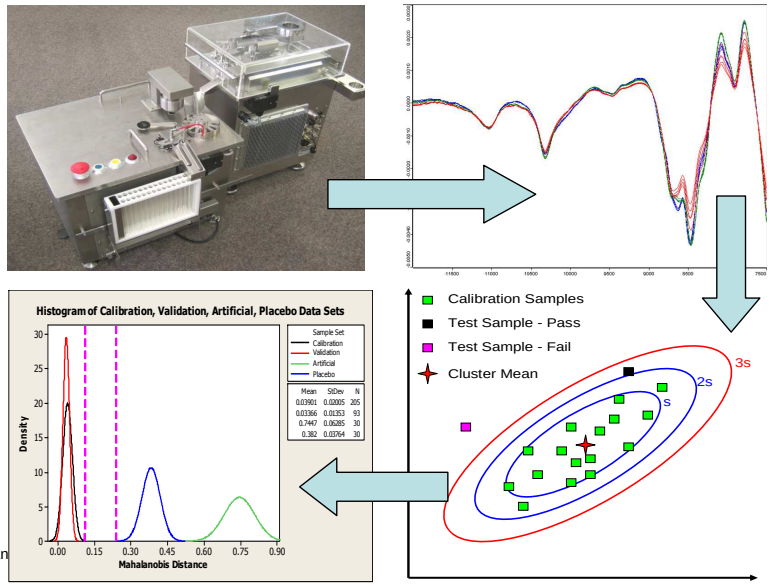
- Engaged with regulatory agency early
  - Prior to submission of RTRt package
  - Face-to-face meeting to discuss overall approach
- Overall very encouraging
  - Excellent level of openness and understanding
- Only point that was highlighted as a potential issue was Large N specifications for Content Uniformity
  - Agency was assessing its position on Large N criteria
  - However, the process capability for CU testing was very high with extensive batch history
    - ⇨ CU remains on specification as “Will comply if tested”
    - ⇨ NIR with Large N utilised as internal control

FDA Submission

- Package with same information submitted to FDA
- Two main issues highlighted
  - Location of identity testing not considered suitable and should be closer to final dosage form
  - Large N criteria not considered suitable as submitted
    - ⇨ Agency have been evaluating different options
- Site audited prior to approval of RTRt
  - Not a dedicated RTRt audit though
- Again, excellent openness and understanding
  - Very valuable discussion throughout the submission process with FDA representatives

New Identity Test

- On-line identity test for API in the tablet cores during compression
  - Discriminates tablet cores prepared using surrogate API



Updated Specifications

- Proposed Large N criteria had residual risk for a specific sample size range
  - Less stringent than current ICH UDU
- Large N redeveloped to be equal or tighter than ICH UDU at all sample sizes
  - Following face-to-face meeting with FDA
    - ⇨ In collaboration with other Pharma experts

Number of tablets sampled	100 - 133	134 - 166	167 - 199	200 - 233	234 - 266
Acceptable number of tablets outside 85.0 – 115.0% LC	3	4	5	6	7

EU vs. US Release Strategy

EU

Release Test	Location	Technique
Identity	Production (At-line during Dispensing)	NIR
Impurities	Eliminated based on high Process Capability	
Assay	Production (On-line)	NIR
Content Uniformity	QC	HPLC Will comply if tested
Disintegration	Production (At-line)	Disintegration Tester
Water Determination	Production (At-line)	NIR
Appearance	Production	Visual
Microbial Quality	QC	Skip Lot Micro Testing

US

Release Test	Location	Technique
Identity	Production (On-line during compression))	NIR
Impurities	Eliminated based on high Process Capability	
Assay	Production (On-line)	NIR
Content Uniformity	Production (On-line)	NIR (Large N)
Disintegration	Production (At-line)	Disintegration Tester
Water Determination	Production (At-line)	NIR
Appearance	Production	Visual
Microbial Quality	QC	Skip Lot Micro Testing

- Major differences are in the location of identity testing and the Content Uniformity

Regulatory Approval Process

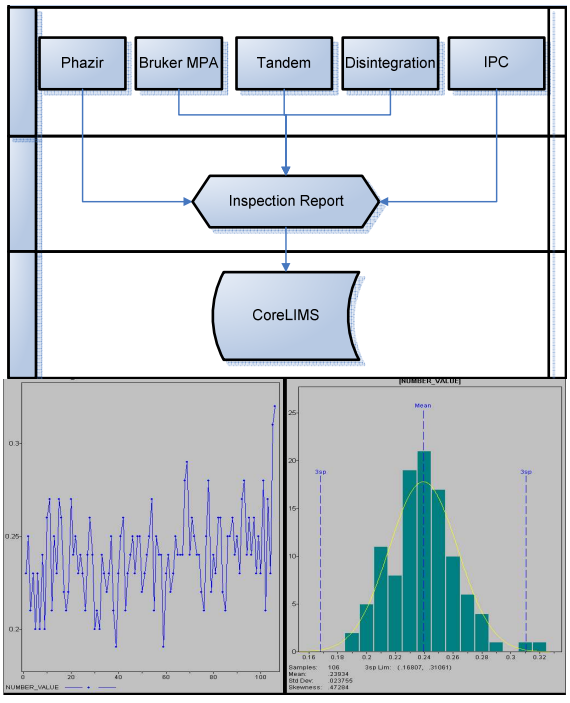
- EMA
  - RTRt variation 10 July 2009
  - Final approval 05 November 2009
    - ⇨ Total 118 days
- FDA
  - RTRt submission 10 September 2009
  - Final Approval 02 August 2010
    - ⇨ Total 326 days
    - ⇨ Impacted by re-development of identity method and Large N specifications
- ROW
  - Now approved in >34 markets
    - ⇨ Following either the US or EU template

Regulatory Queries - Overview

- Development and validation of NIR methods
  - Use of tablet weights in final method
- Control strategy for validity monitoring and change control of NIR methods
  - Scope of revalidation following method updates
- Handling of OOS results
- Criteria for use of PAT systems and back-up strategy
- On-site responsibilities
  - Measurement vs. interpretation of data
- Sampling plan
- Integration of PAT software and LIMS
  - Availability of data
- Calibration/verification of NIR measurement system

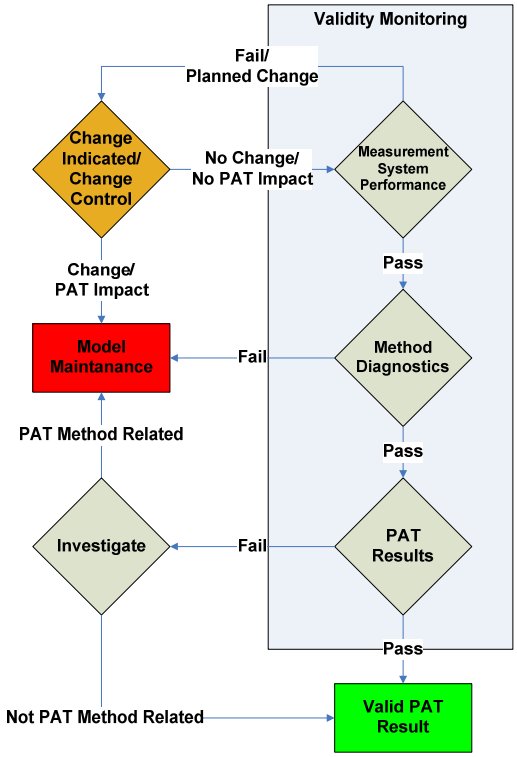
Integration into Site Systems

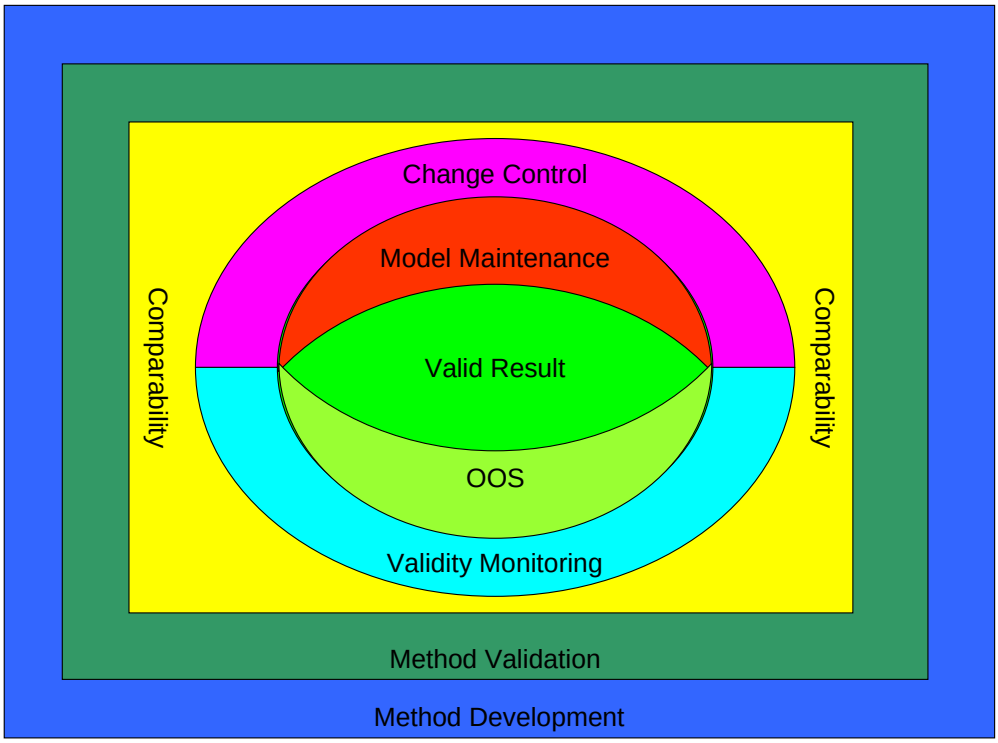
- Data from all PAT systems available in LIMS for evaluation
  - Batch release decisions
  - Troubleshooting or OOS investigations
- Higher sampling frequencies and quantity of data
  - Statistical interface available for simpler interpretation
- Future potential for more in-depth MVA
  - Integrating raw material attributes



NIR Validity Monitoring/Change Control

- Major requirement to monitor the ongoing validity of NIR (all PAT) methods
  - Cannot simply use secondary release method if PAT generates a OOS result
    - ⇨ Adequate control systems must be in place to ensure the integrity of the NIR measurement
- Comprehensive procedure to ensure integrity of product, process and measurement system
  - In relation to subsequent NIR spectrum





Change Control - Example

Parameter	1. Qualification	2. Change Assessment	3. Model Transfer	4. Method Re-validation	By Variation
Software	X				
Hardware Location/Environment	X				
Hardware (Non-Critical Instrument Components)	X				
Regression Algorithm				X	
Wavelength Region				X	
Spectral Pre-treatment				X	
PLS Factor Choice				X	
Hardware (Critical Instrument Components)*	X	X	X	X	
NIR Acquisition Parameters			X	X	
Instrument Type and Model			X	X	
Sampling Device (Tablet Tray)			X	X	
Calibration Set**				X	
Validation Set		X		X	
Regression Coefficients and Loadings				X	
Range of Samples Used**		X		X	

* Can encompass a change of instrument (i.e. to an identical model and type)
** Both can encompass a change to product or process (also how the same samples look after a change to the instrument)

Return on Investment

- PAT is a key enabler for RTR testing
- RTRt can result in different benefits/cost-savings
  - Significant sampling and testing reduction
  - Inventory reduction based on quicker release
  - Asset utilisation/reduction
  - Improvements to process control
    - ⇨ Cost avoidance
  - Cycle time reduction
    - ⇨ Capacity increase
- Critical to evaluate ROI and payback period at project kick-off
  - Some benefits will be strategic
- RTR testing itself will not improve product quality
  - May lead to enhanced process understanding, which may deliver quality improvements

Overall

- Positive experience to date with RTRt and regulatory interactions
  - Similar packages approved by EMA and FDA
- Both RTRt and “conventional” methods detailed on final specification
  - Back-up procedure should PAT systems not be available
  - RTRt does not impact stability specifications
- RTRt does not mean less testing
  - Understanding the product attributes that require testing and performing these tests at relevant points in the process
    - ⇨ Eliminating those tests that don’t add value or predictive modelling from KPPs and CQAs
- RTRt will be different for existing products, based on batch history, compared to new products

Acknowledgements

- Process Analytical Sciences Group
- Pfizer Manufacturing Sites
  - PGS Illertisen
  - PGS Freiburg
- PPD Freiburg
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