Manufacturing Benefits of Real Time Release Testing

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So what is RTRt in Practice?

- Fundamentally, RTRt enables the ability to release a batch with no post-manufacturing sampling or QC testing
- QbD can be an enabler to achieve RTRt but it is not necessary – product/process understanding **is** required
- RTRt can be applied to existing products as well as new products
- Which products are suitable for RTRt?
  - Volumes are important
  - Extent to which the "novel" analytical tools can be used to replace traditional analytical tools
  - Partial RTRt may still be valuable (i.e. for testing some, but not all, product attributes)

Business Benefits of RTRt

- **Lower manufacturing costs**
  - Problems can be identified and corrected in real time
  - Improved yields through less waste
  - Fewer deviations and/or rejects
  - Increased data available for any investigations (→ root cause)
  - Reduced QC resources (no post-manufacturing testing)
- **Faster cycle times**
  - Eliminates or reduces end product testing time
  - Allows for a more speedy release process
  - Reduces inventory and accompanying carrying costs
- **Increased assurance of quality for our patients**
- **Business Case still very challenging for Pfizer!!**
  - Withdrawn some filings due to regulatory inflexibility, technical challenges with the model and cost of model maintenance

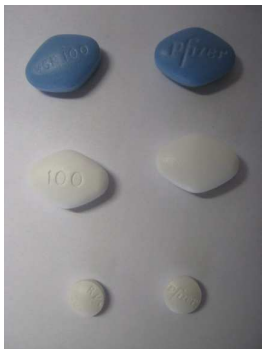
Case Study 1: Viagra & Revatio RTRt

Objectives :

- Development and implementation of a RTRt process based on in process controls and analysis of process parameters

Scope

- Viagra (25, 50 and 100mg tab)
- Viagra generic formula (25, 50 and 100mg tab)
- Revatio (20 mg tab)
- All markets



RTRt strategy

Traditional QC testing

Appearance (Visual – At line)
Assay (HPLC)
Mass/content uniformity
Water content (KF)
Sildenafil identity (IRFT)
Citrate identity (HPTLC)
Dissolution

Once per year :
Degradation products (HPLC)
identification (TLC/colorimetry)
Microorganism count

RTRt testing *Same NIR scan

Appearance (Visual – At line)
Assay (NIR at line) *
Content uniformity (NIR at line)*
Water content (NIR at line)*
Silldenafil identity (NIR at line)*
Citrate identity deleted
Automated Dissolution

Once per year :
Degradation products (HPLC)
identification (TLC/colorimetry)
Microorganism count

⇨ **All routine tests « at line »**

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

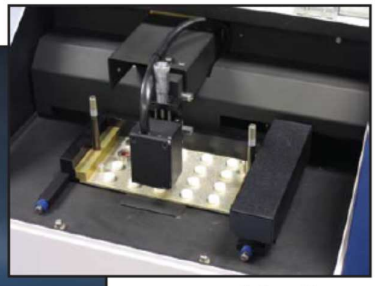
Product with several years manufacturing experience

- Historical process capability and stability data
  - Stability data generated under accelerated and long-term storage conditions demonstrate the product is stable
  - Excellent process capability

Impurity testing for stability but to delete as a release requirement

RTRt PAT Instrumentation

FOSS XDS MasterLab™



Transmission Mode for Tablets

Reflectance Mode for Vials and Tablets

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Project timing

Project start **Nov 2010**

- Background information gathering with input from other PGS sites

RTR :

- Briefing document (regulatory strategy) 1Q2011
- NIR equipment purchase and method development & validation 1Q2011 to 1Q2012
- **Market submission** **3Q2012**
- Approval granted in EU Centralized, Albania, Angola, Australia, New Zealand, Ghana, Nigeria, Philippines, Sri Lanka, Switzerland, Ukraine
- Formulating responses to FDA queries

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Expected business results

Process understanding and control improvement

- Alignment with QbD principles and Agency expectations

Reactivity improvement in case of production out of trend

Production cycle time reduction

Cost reduction

- CIP ~ 90 k€ /year

Better preparation for generics competition after Viagra LOE

Case Study 2: Champix RTRt filing

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

Recently withdrew this RTRt filing

- Proposed to divest the Pfizer Illertissen plant
- RTRt requires significant technical expertise and maintenance of equipment which will not be available to the site going forward

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

First Progression

Replacement of KF water determination method with NIR in QC

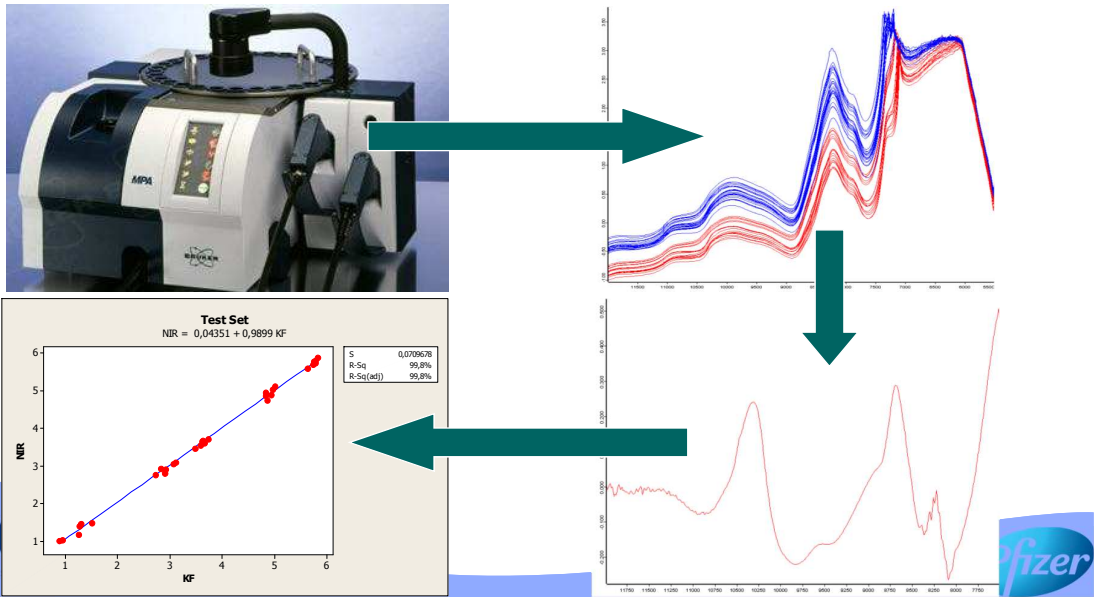
Release Test	Location	Technique
Identity	QC	TLC/HPLC
Impurities	QC	HPLC
Assay	QC	HPLC
Content Uniformity	QC	HPLC
Disintegration	Production	Disintegration Tester
Water Determination	QC	NIR
Appearance	QC	Visual
Microbial Quality	QC	Skip Lot Micro Testing

- 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%
  - Tablets dried and “spiked” to encompass 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

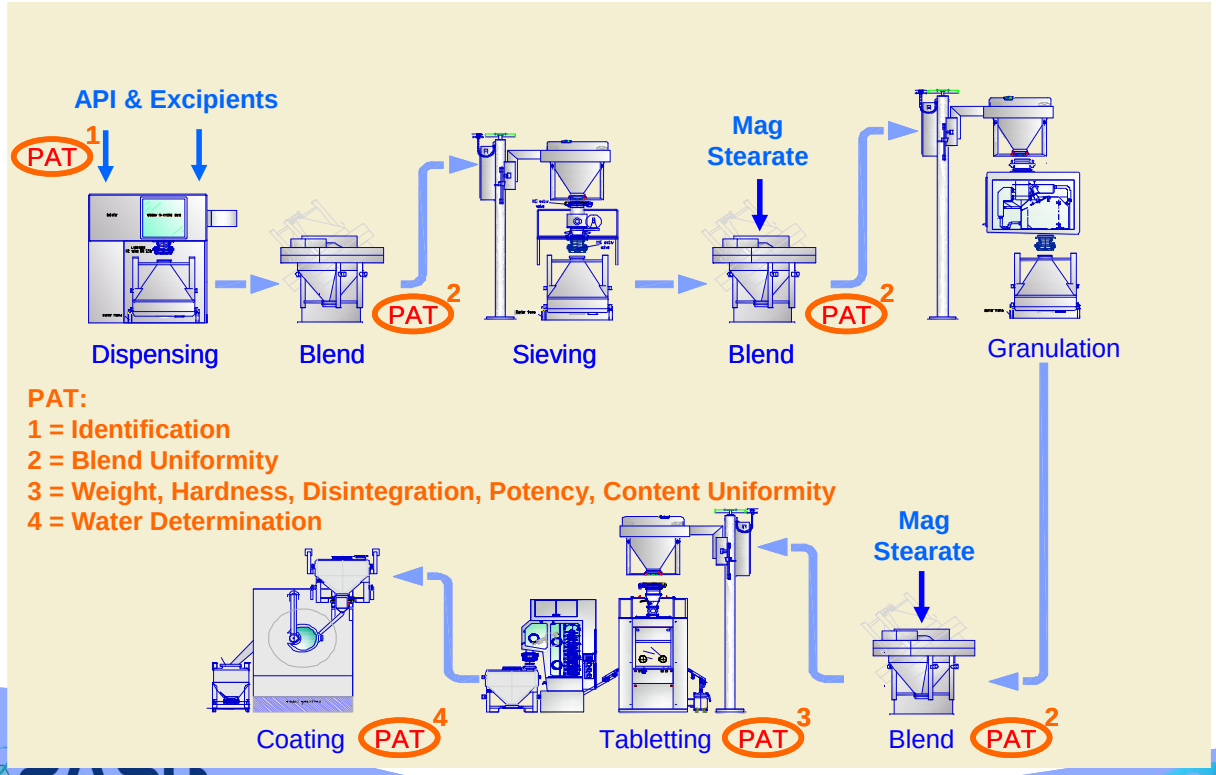
RTR Strategy

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

Manufacturing Process



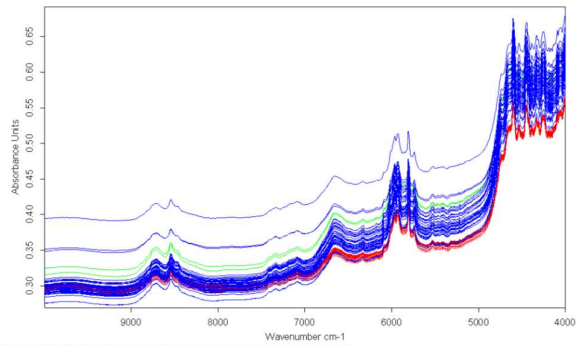
Raw Material Identity Testing

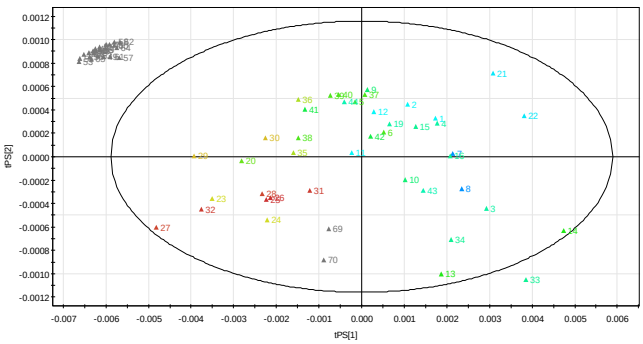
API identification performed in warehouse on receipt

- 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

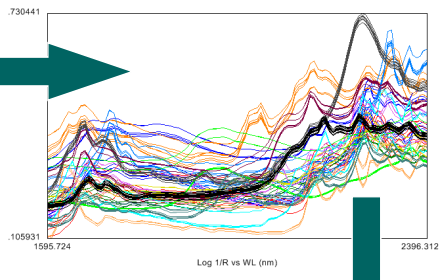


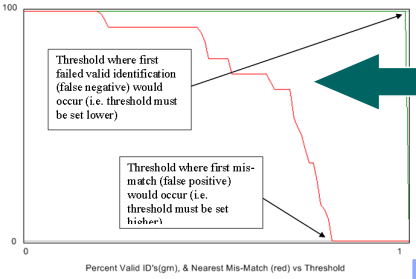


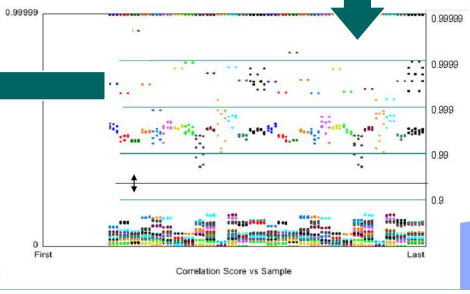
Identity Testing

Replacement of regulatory release test for API in tablet matrix proposed during dispensing

- Closed manufacturing facility with single API
  - Library discriminates all APIs received on-site



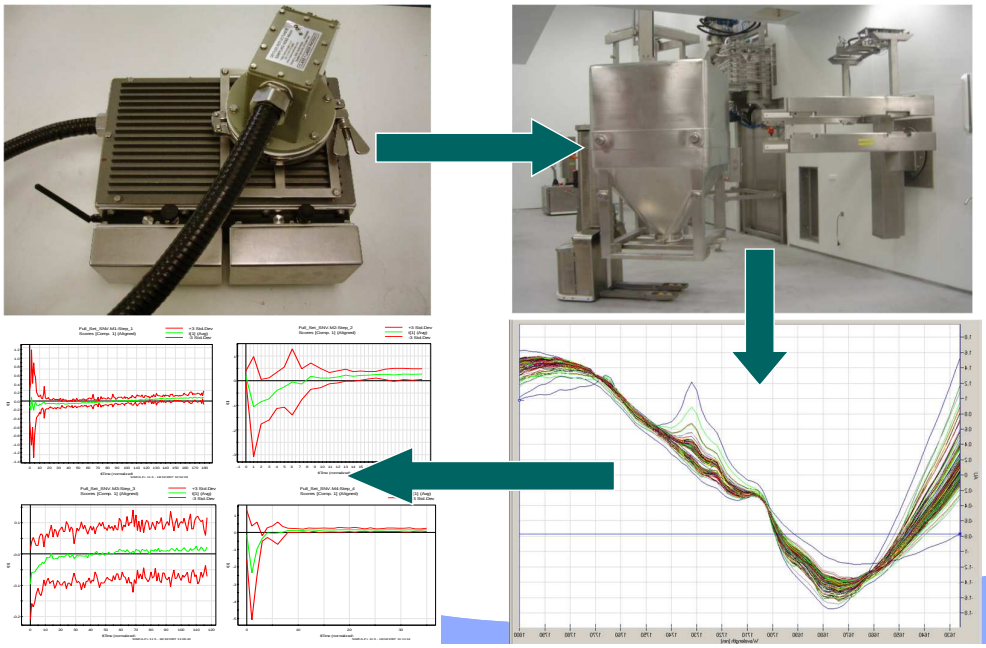




Blend Monitoring

Blend uniformity is not a regulatory requirement

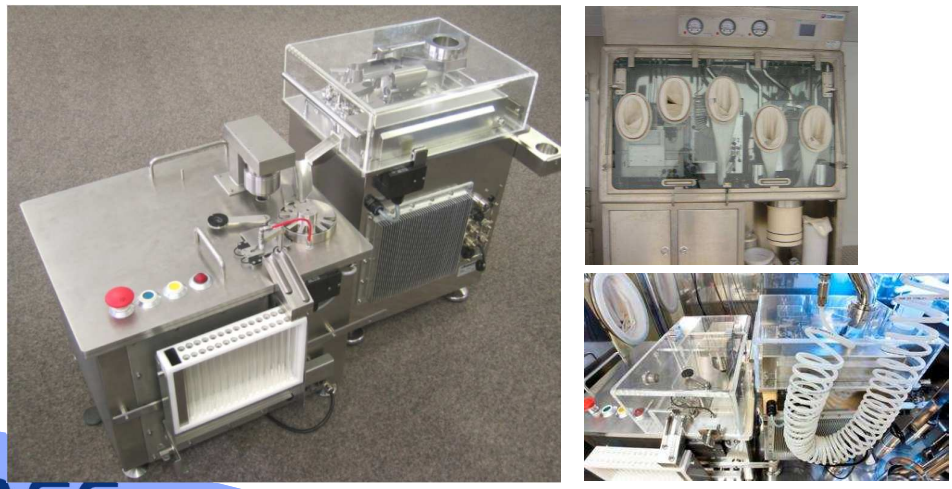
- Monitored on-line by NIR for process understanding and for troubleshooting or process validation activities



Assay/Content Uniformity

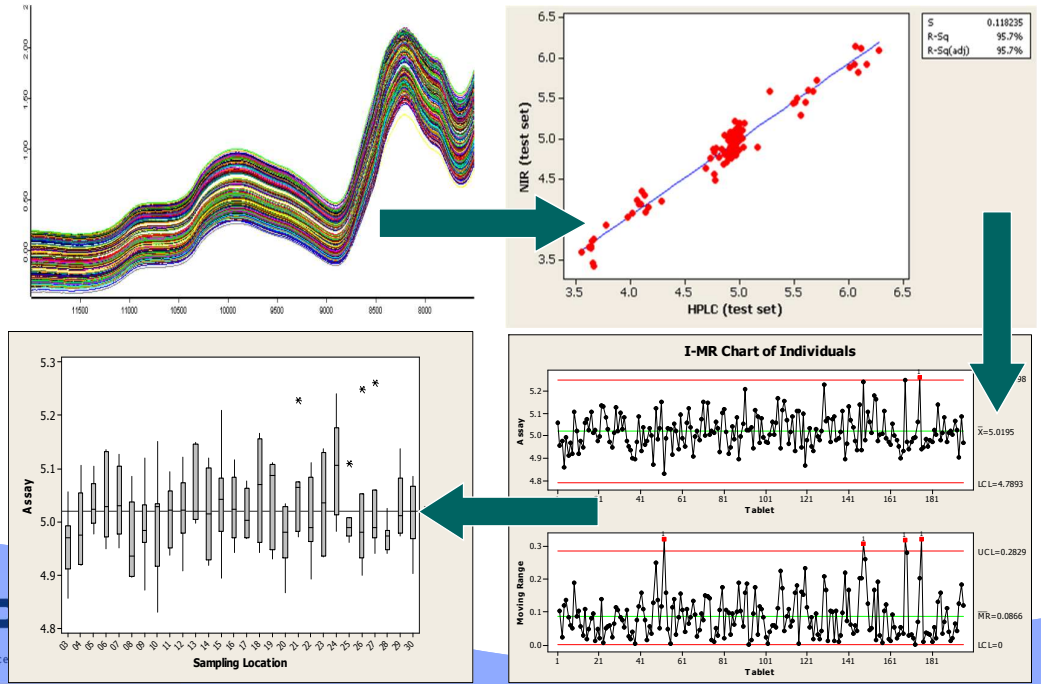
Performed on-line using the same NIR system and measurement

- Provides major safety benefit by reducing manual sampling
- Provides opportunity for increased sampling frequency



Assay/Content Uniformity

Method extensively developed to encompass product and process variation



EMA Variation

Engaged with regulatory agency early

- Prior to submission of RTR 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 EMA
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 RTR

- Not a dedicated RTR audit though

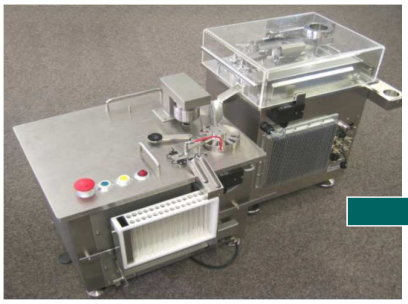
Again, excellent openness and understanding during the submission process

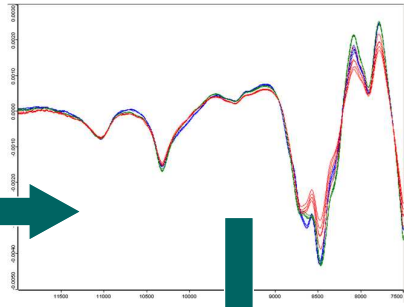
- Very valuable discussion throughout the submission process with FDA representatives

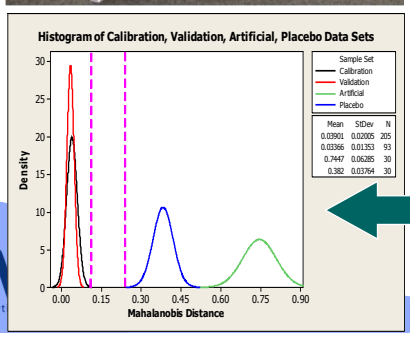
New Identity Test

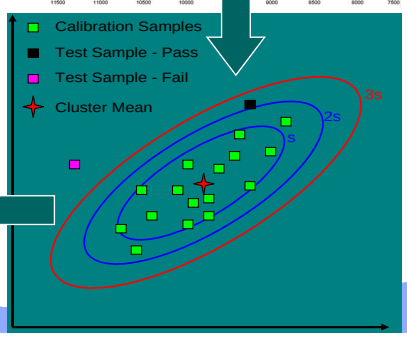
Identity test developed for API in the tablet cores

- Measured on-line during compression
- Discriminates tablet cores prepared using surrogate API









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 Queries - Overview

Variation in Comments/expectations from different Regulatory Bodies

- This has made approval in a number of markets very challenging and time consuming for Pfizer and making the benefit questionable

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

Considerations for Implementing Real Time Release Testing

Science and Technology
- Control strategy
- Process analyzers and data management
- Analytical methods and specifications?
  - Sampling and Statistics
  - Acceptance criteria

People
- Organization and Training?

Pharmaceutical Quality System
- Quality risk management?
- Disaster recovery?
- Model maintenance?
- Handling of outliers?
- Batch disposition?

Regulatory Interactions

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Overall

Both RTR and "conventional" methods detailed on final specification
- Back-up procedure should PAT systems not be available
- RTR does not impact stability specifications

RTR 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

RTR will be different for existing products, based on batch history, compared to new products

Questions