Regulatory Perspective on Real Time Release Testing (RTRT)

AAPS Annual Meeting
Washington, DC
27 October 2011

Christine M. V. Moore, Ph.D.
Acting Director
ONDQA/CDER/FDA

Outline

- Overview of Real Time Release Testing (RTRT)
- Clarification of RTRT Terminology
- Guidance Documents Related to RTRT
- Considerations for Sampling, Specifications and Batch Release
- Discussion of Models in RTRT
- Concluding Remarks

Real Time Release Testing

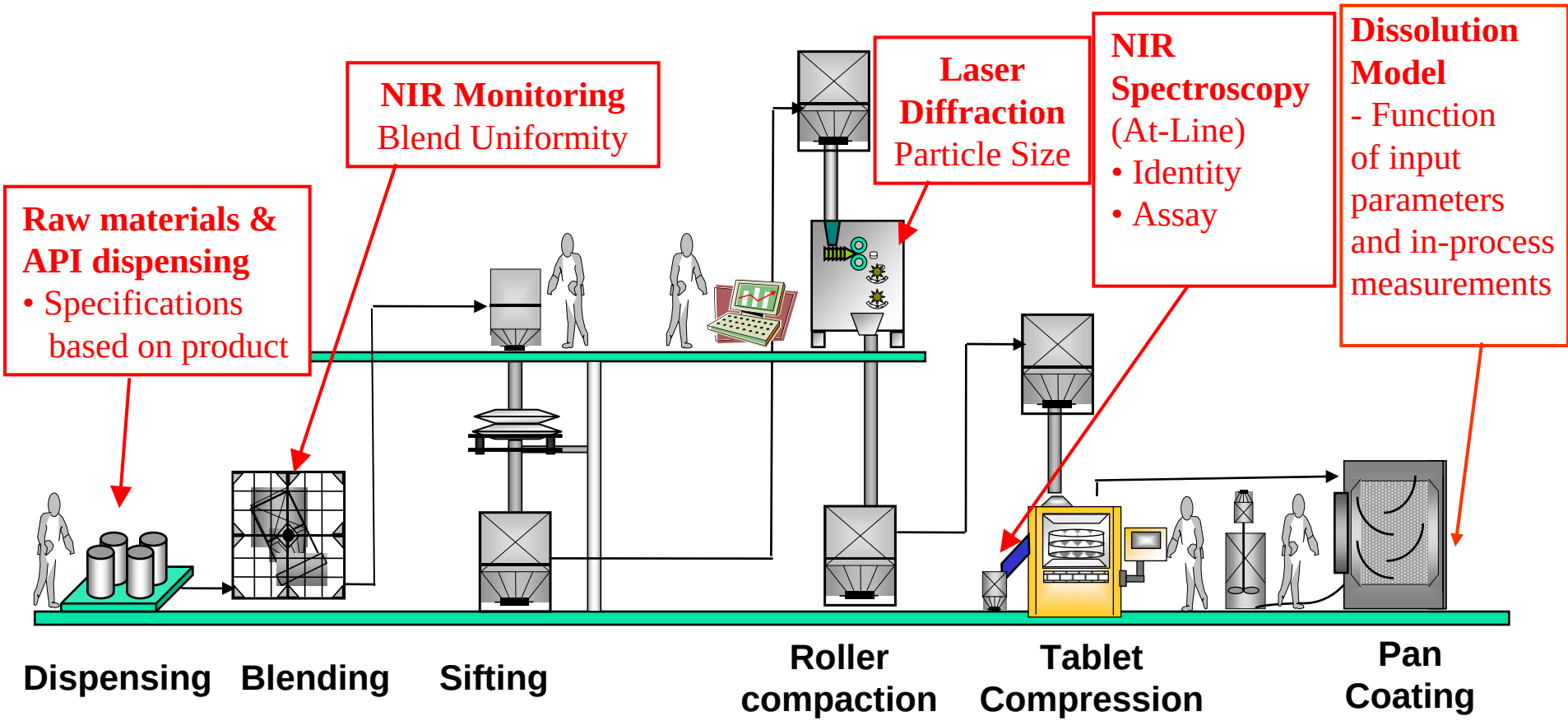
- Real Time Release Testing (RTRT) is the ability to evaluate and ensure the quality of in-process and/or final product based on process data
  - Typically include a valid combination of measured material attributes and process controls

    ICH Q8(R2)

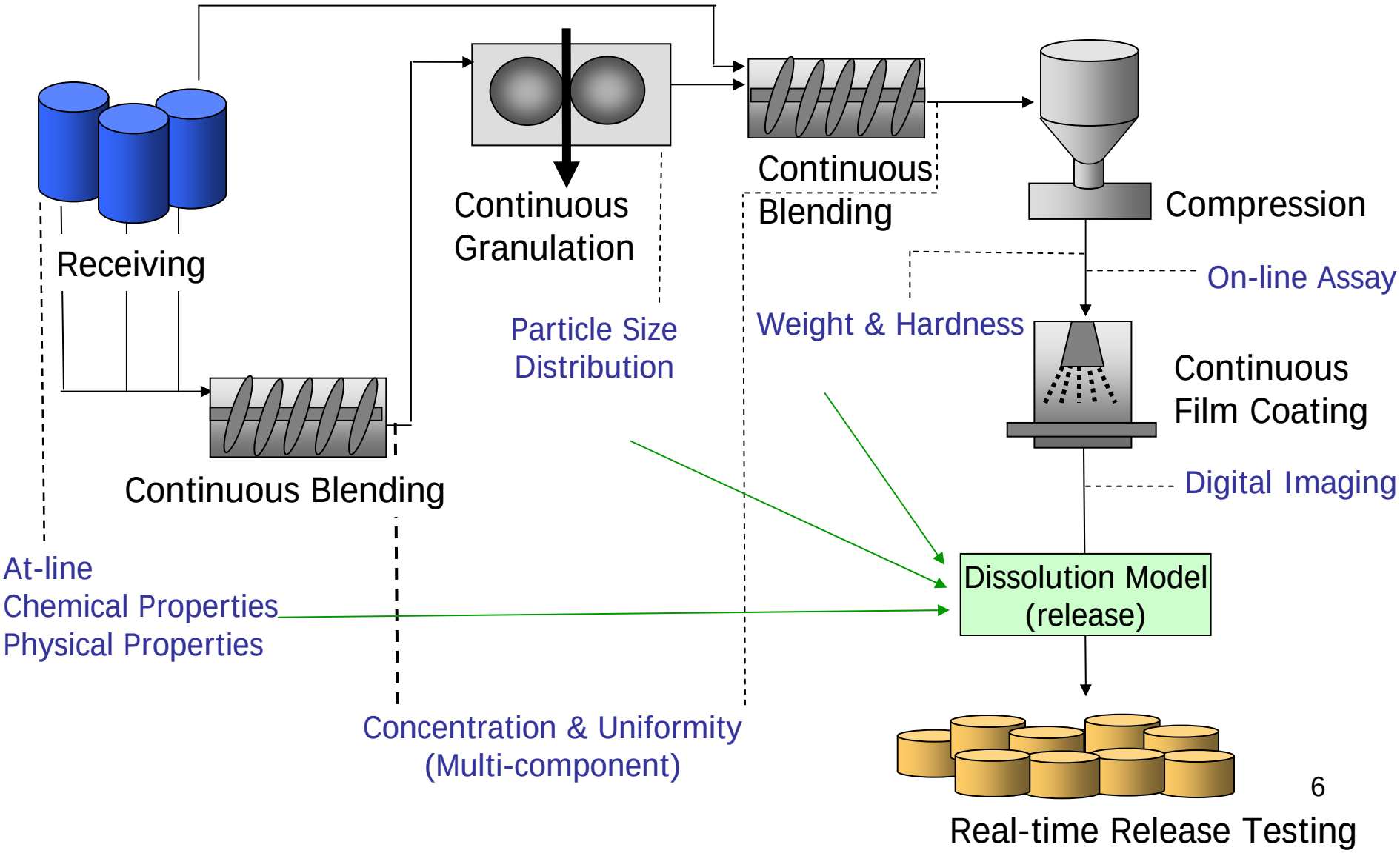
Examples of RTRT Approaches

- On-line or in-line measurements and/or controls, for example
  - Tablet weight after compression
  - Particle size measurement after granulation or milling
  - Moisture measurement during drying
  - Blend uniformity
- Fast at-line measurements, for example
  - NIR for tablet assay
  - Disintegration in lieu of dissolution
- Models as surrogate for traditional release tests, for example
  - Multivariate model as a surrogate for dissolution
- Process signatures
  - *An evolving approach*

Example of An Unified Approach for RTRT



Conceptual Example of Control Strategy for RTRT in Continuous Manufacturing



Benefits of RTRT

- Provides for increased assurance of quality
  - More process data collected
- Provides increased manufacturing flexibility and efficiency
  - Shorter cycle time
  - Reduced inventory
  - Reduction in end product testing
  - Reduction in manufacturing cost
- Allows leveraging of enhanced process understanding
  - Corrective actions may be implemented in real time

Clarification of RTRT Terminology

New Quality Terminology

Real Time Release Testing (RTRT)

Critical Quality Attributes (CQAs)

Design Space

Quality by Design (QbD)

Process Analytical Technologies (PAT)

Control Strategy

Definitions

- **Real Time Release Testing (RTRT)** - the ability to evaluate and ensure the quality of in-process and/or final product based on process data, typically include a valid combination of measured material attributes and process controls *(ICH Q8(R2)*
- **Design Space -** The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval *(ICH Q8(R2))*
- **Quality by Design (QbD) -** A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management *(ICH Q8(R2))*
- **Process Analytical Technology (PAT) –** A system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality *("Guidance for Industry: PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance", 9/04)*
- **Control Strategy -** A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control *(ICH Q10)*
- **Critical Quality Attributes (CQA) -** A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality *(ICH Q8(R2))*

Relationships between RTRT, Control Strategy, PAT and QbD

- RTRT, when used, is part of the Control Strategy
  - Can include some or all of the final product CQAs
- QbD is not directly correlated to RTRT
  - You can have QbD approaches without RTRT
  - However, it would be difficult to justify RTRT without a science and risk based approach
- Not all Process Analytical Technology (PAT) leads to RTRT
  - PAT systems can be designed to control CQAs of raw materials or in-process materials and not contribute to RTRT
- A design space is not required for RTRT
  - Having a design space can increase operational flexibility, without additional regulatory approval

Regulatory Considerations for Real Time Release Testing Approaches

Regulatory Documents Discussing RTRT

- FDA Guidance for Industry: PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance", Sept 2004
  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070305.pdf
- ICH Q8(R2) – Pharmaceutical Development, Aug 2009
  http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf
- ICH Quality Implementation Working Group on Q8, Q9 and Q10, Questions & Answers (R4), Nov 2010
  http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_9_10_QAs/Q-IWG_QAs_Step4/Q8_Q9_Q10_Question_and_Answer_R4_step_4_November_2010.pdf
- ICH Quality Implementation Working Group Points to Consider, June 2011
  http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_9_10_QAs/PtC/Quality_IWG_PtC_16_June_2011.pdf

ICH IWG Q&A's on RTRT

- How is batch release affected by employing RTRT?
- Does RTRT mean elimination of end product testing?
- Is a product specification still necessary in the case of RTRT?
- When using RTRT, is there a need for stability test methods?
- What is the relationship between Control Strategy and RTRT?
- Do traditional sampling approaches apply to RTRT?
- If RTRT results fail or trending toward failure, can end-product testing be used to release the batch?
- What us the relationship between in-process testing and RTRT?
- What is the difference between RTR and RTRT?
- Can surrogate measurement be used for RTRT?

ICH IWG Q&A's on RTRT

- How is batch release affected by employing RTRT?
- Does RTRT mean elimination of end product testing?
- Is a product specification still necessary in the case of RTRT?
- When using RTRT, is there a need for stability test methods?
- What is the relationship between Control Strategy and RTRT?
- Do traditional sampling approaches apply to RTRT?
- If RTRT results fail or trending toward failure, can end-product testing be used to release the batch?
- What us the relationship between in-process testing and RTRT?
- What is the difference between RTR and RTRT?
- Can surrogate measurement be used for RTRT?

Considerations for the Point of Testing

- Is there a potential for the measured CQA to change downstream from the measurement point? For example,
  - Blend desegregation
  - Loss of weight (e.g., chipping) after weighing step
  - Hydrolytic degradation during aqueous film coating
- Is identity determined at a point that is visually unique?
  - Mitigation of potential human and/or system error
  - Unique identifiers on the intermediate when measured (e.g., embossing, size, shape)
- Risk assessment is valuable to exploring potential failure modes

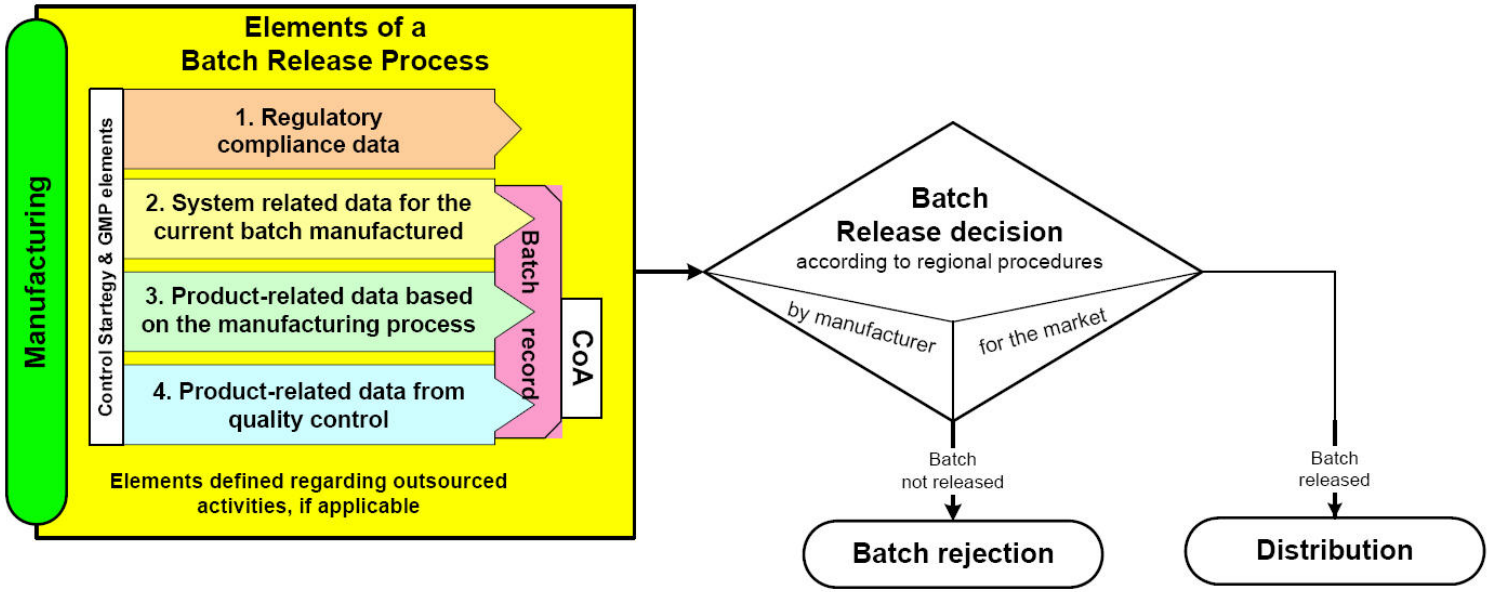
Sampling Considerations

- Probe/sample location representative of entire vessel
- Sample frequency representative of entire batch
- Sample acquisition time
  - Suitable for system dynamics/mixing
- Sample volume/mass
  - Determine amount of sample measured
  - Representative of unit dose
- Sample interface
  - Remains constant over the process (e.g., no fouling)
  - Environmental factors (e.g., temperature, humidity)

Considerations for RTRT Specification

- Specification still required in an RTRT approach (CFR §314.50(d) and CFR § 211.165(a))
- Should be representative of actual measurement
  - Can include in-process measurements (e.g., NIR measurements for assay of uncoated tablets)
  - Can include surrogate measurements (e.g., models for dissolution)
  - Methods should be appropriately validated (including models used as surrogate measurements)
- Alternatives can be included for stability monitoring
- Appropriate statistical criteria for large sample sizes

Batch Release Decision for RTRT



- In principle, end product testing should not be substituted for failure of an RTRT release method. The failure should be investigated and followed up appropriately.

Models in RTRT

Types of Models in RTRT

- Calibration models for spectroscopic analysis (e.g., NIR, Raman, FTIR)
  - Typically use chemometric analysis
- Surrogate models for time-consuming measurements
  - Dissolution models relating process parameters and/or material attributes to dissolution
- Design space models
  - Surface response plots
  - Mechanistic models
- Process control models
  - Tunable controllers for individual unit operations
  - Statistical process control and multivariate statistical process control
- Other models

Chemometric Model Development Considerations

- Calibration data
  - Include potential sources of variance (e.g., operating conditions, raw materials, scale)
  - Cover intended areas of operation/design space
  - Appropriate distribution of spectra over the analysis range
- Model development
  - Appropriate data pre-treatment
  - Appropriate spectral ranges

  } preferred to have physical basis
  - Number of model factors justified (avoid overfitting)
- Model validation
  - Internal validation using subsets of calibration data
  - External validation using an independent data set
- Robust and representative reference method

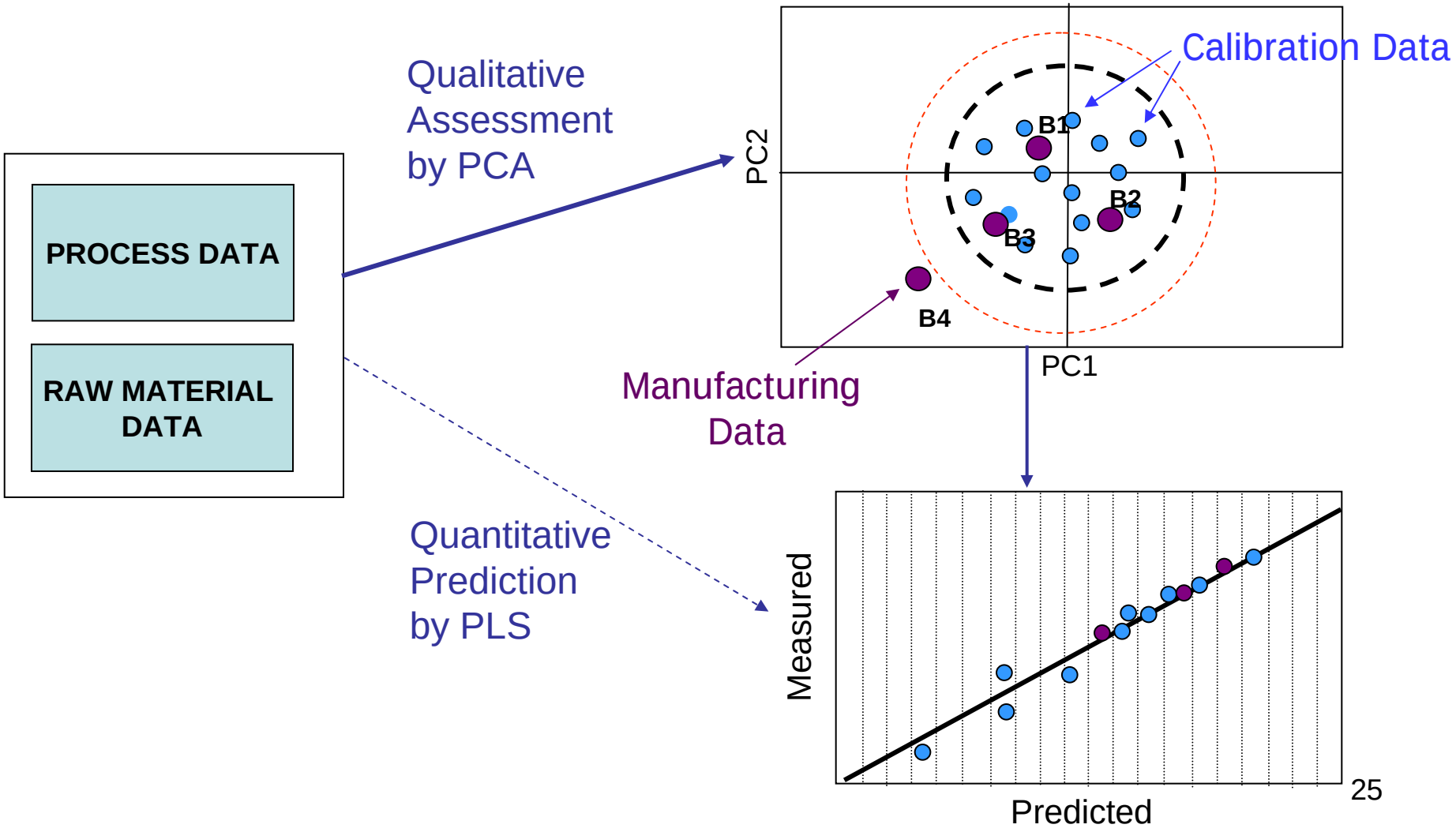
Chemometric Model Maintenance and Update Considerations

- NIR model results may change with time as new sources of variability are introduced
  - Changes in raw material suppliers, process or analyzer changes
- Evaluation of outliers as part of maintenance
  - Can detect bad spectra or interface problems
  - Usually implemented through examination of residuals
- Procedures in place to monitor and update the model
  - Done under the manufacturer's quality system
  - Include frequency and methods of periodical model evaluation
- Depth of validation done on updated model, depending on level of change

Considerations for Models Serving As Surrogates for Release Tests

- Robust calibration model
  - Use an appropriate reference method
  - Include variations in raw materials
  - Cover the entire design space
- Include an independent dataset for validation
- Demonstrate model performance at commercial scale
  - Understand and work within the model limitations and model assumptions
  - Compare model results to a reference method for a statistically acceptable number of batches

Multivariate Model for Predicting Dissolution



Considerations for Maintenance of Models

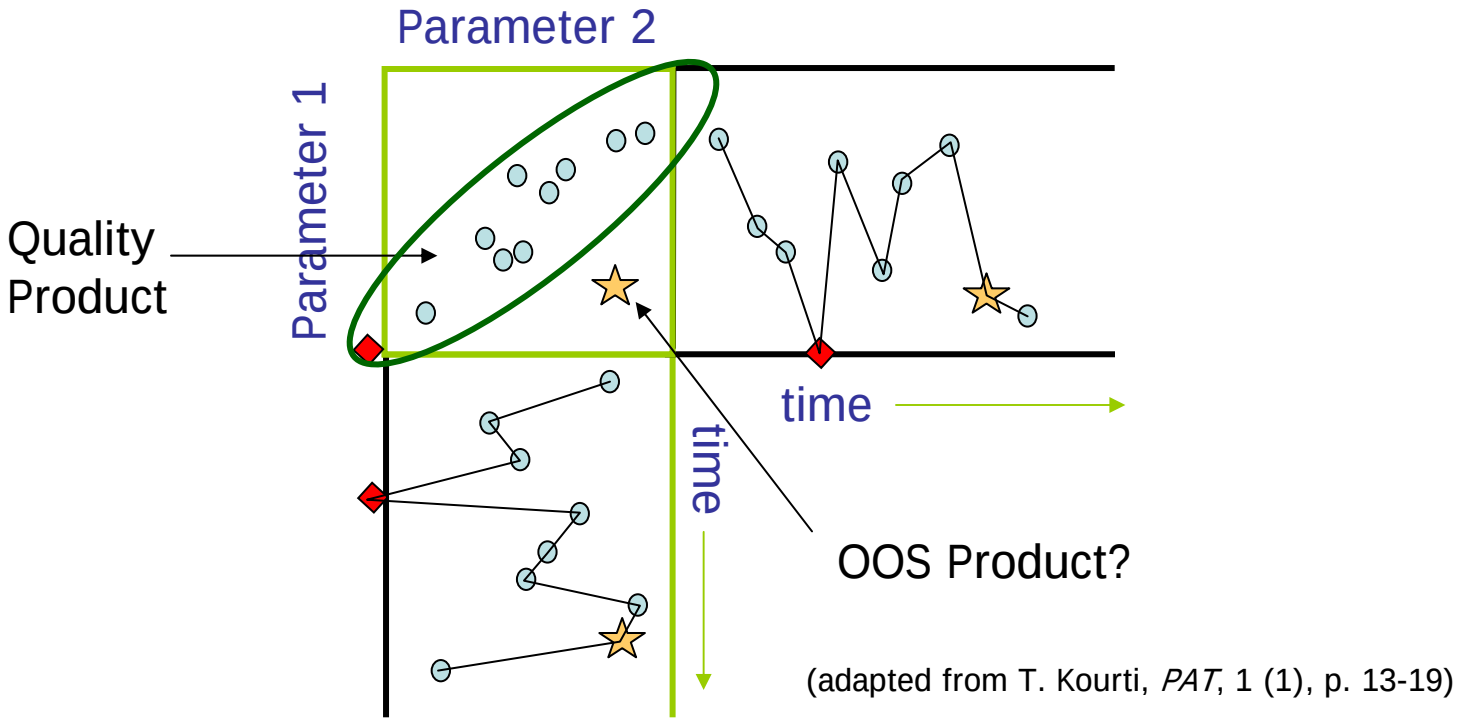
- Develop and document procedures on how to evaluate and update the calibration model
  - How to deal with OOS results
  - Develop criteria for model re-calibration
- Verify or recalibrate the model for process changes:
  - Revising the operating ranges
  - Change in raw materials
  - Change in manufacturing equipment or measuring instrument
- Include plans for model maintenance/update in the firm's Quality System
  - Tracking/trending (for process monitoring) included within the Quality System

Considerations for Submission of Models

- **Level of detail in submission should depend on the importance of the model to the overall control strategy**

- **Low Impact Model** (e.g., Models for development)
  - General discussion of how model was used to make decisions during process development
- **Medium Impact Model** (e.g., Design space models)
  - More detailed information about model building, summary of results and statistical analysis
  - Discussion of how the model fits into the control strategy
- **High Impact Model** (e.g., RTRT models)
  - Full description of data collection, pretreatment and analysis
  - Justification of model building approach
  - Statistical summary of results
  - Verification using data external to calibration set
  - Discussion of approaches for model maintenance and update

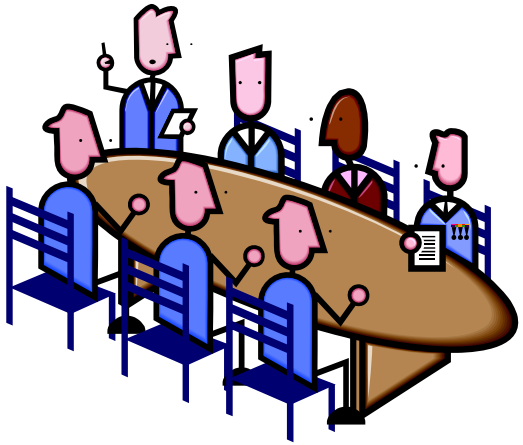
Multivariate Statistical Process Control



(adapted from T. Kourti, *PAT*, 1 (1), p. 13-19)

- Process variables often track together
- Reducing the dimensionality of the process into principle components (combined variables) can simply fault diagnosis
- Multivariate approach can identify some quality issues that univariate analysis might not detect in RTRT approach

Communicate Early and Often!



Interactions with FDA

- Request meeting according to guidance "*Formal Meetings Between the FDA and Sponsors or Applicants*"
  - Clearly state as CMC meeting for RTRT
  - Both CMC and GMP questions can be included
- End of Phase II or Pre-supplement submission is a good time to start dialogue
  - Initially, not all details or data are expected to be available
  - Discuss desired or expected approach
  - Ask specific questions
- Additionally, a Pre-Operational Review (or Pre-Operational Visit, POV) can be requested
  - See PAT Guidance (2004) or "ORA Field Management Directive 136"

Concluding Remarks

- RTRT can provide a higher assurance of product quality
  - Real-time analysis and control of process
  - Enhanced process understanding
  - Operational flexibility
  - Framework for continuous manufacturing
  - Support of continual improvement
- ICH has published several documents providing guidance on implementation of RTRT
- FDA supports the implementation of RTRT approaches using a science and risk-based approach
  - Recommend early and frequent discussion with Agency before implementation

Thank you!

Questions, comments, concerns:

NewDrugCMC@fda.hhs.gov