Regulatory Perspective on Implementation of Multivariate Statistical Process Control for Pharmaceutical Manufacturing

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Bogdan Kurtyka, PhD.
Review Chemist
FDA/CDER/ONDQA

Outline

- Guidance and Points to Consider documents related to Multivariate Statistical Process Control (MSPC) and Real Time Release Testing (RTRT)
- Examples of MSPC implementation
- Considerations for MSPC development
  - Training data selection
  - Model development
  - Validation
- Consideration for MSPC implementation
- Conclusions

ICH Guidances on RTRT

- ICH Q8(R2)
  - RTRT is “the ability to evaluate and ensure the acceptable quality of in-process and/or final product based on process data, which typically includes a valid combination of measured material attributes and process controls”
- ICH Quality Implementation Working Group (QIWG) Q&A
  - RTRT is an element of the control strategy in which tests and/or monitoring can be performed as in process testing rather than tested on the end product.
  - RTRT can be based on measurement of a surrogate (e.g., process parameter, material attribute) that has been demonstrated to correlate with an in process or end product specification

ICH QIWG Points to Consider Document

- Section 5. Role of Models in Quality by Design
- MSPC development:
  - These models are used to detect special cause variability; the model is usually derived and the limits are determined using batches manufactured within the target conditions
- Role of MSPC in control strategy
  - If an MSPC model is used for continuous process verification along with a traditional method for release testing, then the MSPC model would likely be classified as a medium-impact model.
  - However, if an MSPC model is used to support a surrogate for a traditional release testing method in an RTRT approach, then the model would likely be classified as a high-impact model

FDA's PAT Guidance

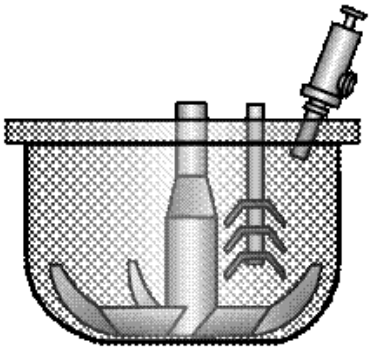
- RTRT is “the ability to evaluate and ensure the acceptable quality of in-process and/or final product based on process data”
- Typically PAT component of RTRT includes a valid combination of assessed material attributes and process controls. The combined process measurements and other test data gathered during the manufacturing process can serve as the basis for RTRT of the final product
- The guidance states that RTRT meets the requirements of testing and release for distribution described in 21 CFR 211.165

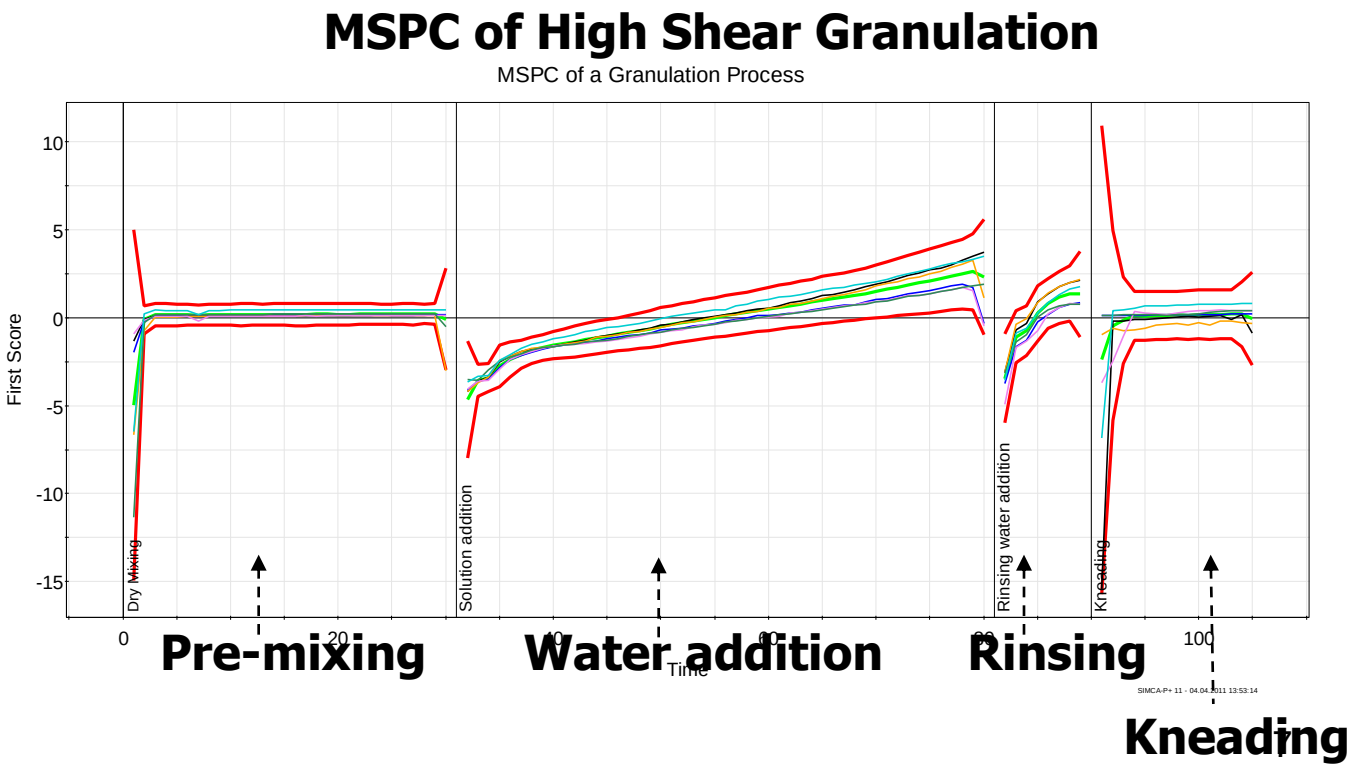
Role of MSPC in Control Strategy

- Dual modes of implementation possible
- Routine monitoring
  - consistency checking
  - medium impact on control strategy
- Surrogate for traditional release test
  - supports RTRT approaches
  - high impact on control strategy
- Level of detail in filing depending on impact on control strategy

Example: Routine Monitoring of High Shear Granulation

Aim of MSPC model is to understand current state of the process and 'flag' deviations



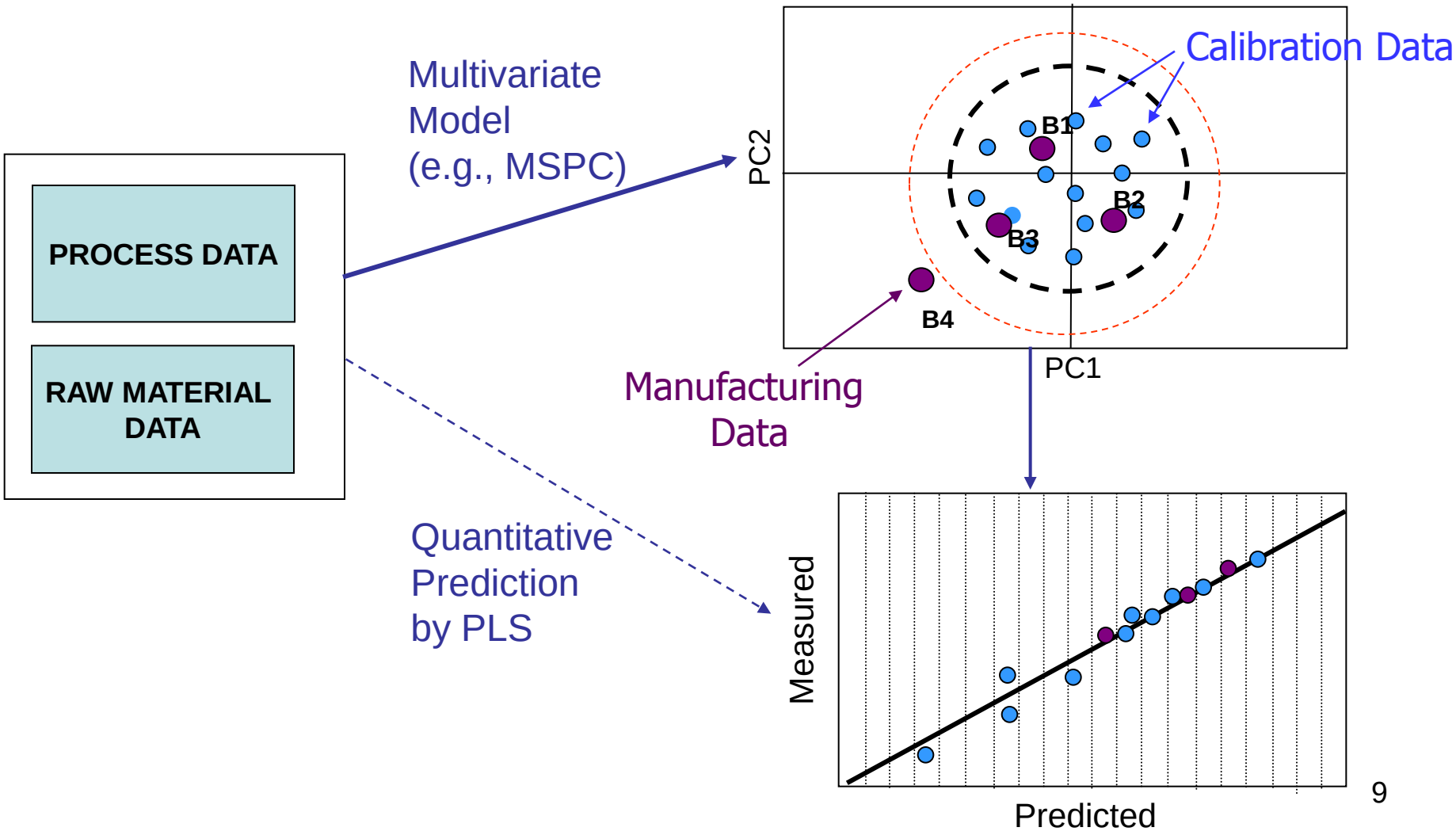


Source: Sharmista Chatterjee

Example: Routine Monitoring of Drug Substance Manufacturing

Source: Novartis

Example: Surrogate Dissolution Model in RTRT



Considerations for MSPC Development and Implementation

- Training data selection
- Model development
- Validation
- Implementation

Consideration for Training Data (1)

- Data from batches yielding quality product
  - Implement for routine manufacturing
  - Typically manufactured at target operating conditions/Normal Operating Ranges (NOR)
- Choice of training set impacts robustness of MSPC model

Consideration for Training Data (2)

- Range of training data includes expected variability during routine production
- Suitable training data may include
  - Sufficient variability in raw materials
  - Variability in process parameters (within NOR)

Consideration for Development of MSPC models (1)

- Multiple papers/resources describe approaches to MSPC
- Many variables used, usually data reduction involved (latent variables)
- Variables are normally scaled
- Acceptable envelope based on historical data around process average

Consideration for Development of MSPC models (2)

- Variables typically included in the model
  - Process parameters important for quality
  - Critical Quality Attributes
  - Material attributes
- Critical variables may be assigned higher weights
- Sufficient variance captured by the model
- Capability to detect “bad” batches

Consideration for Development of MSPC models (3)

- Outliers may be detected by cross-validation
- If using MSPC model in RTRT approach
  - Parameters not included in the model are typically reviewed as a part of batch release decision
- Values outside NORs typically trigger an investigation

MSPC and Design Space (DS)

- If MSPC model is not developed over DS
  - MSPC model for routine monitoring likely needs to be re-developed and re-validated upon movement to another region of DS
- If MSPC model is developed over entire DS
  - Depending on risk (mode of implementation/ impact) of the model movement to another region of DS may call for verification of model predictions

Considerations for Setting Acceptance Criteria for MSPC RTRT models

- Allowable deviation from the historical process average
  - What is the highest deviation experienced so far?
- Based on scientific rationale
- Address risk of accepting marginal batches and rejecting good batches

Validation of MSPC models for RTRT

- Comprehensive validation using batches not used for model development (i.e., external validation)
- Scope of validation
  - Number of batches
  - Time span of collecting validation data
- Demonstration that model rejects bad batches
  - Ideally validation data of MSPC models for RTRT should include data outside of expected normal ranges (e.g., potential failure modes)

Points to Consider for MSPC Implementation

- Is MSPC model still valid after scale-up or site transfer?
- Is MSPC model specific to the equipment it has been developed on?
- Can MSPC model be developed for new products or only for legacy products?
- Scope of external validation of MSPC model

Maintenance considerations

- MSPC models can require verification, and possible update upon
  - Process condition changes
  - Equipment replacement/modification
  - Change in material characteristics
  - Shift or drift of model diagnostic parameters or predictions as shown by trending
- Approach for maintenance documented in firm's site Quality System

Conclusions

- MSPC is an element of control strategy
  - Can enhance process understanding
  - Can be used for real time analysis and control of processes
  - Supports continual improvement
- FDA supports implementation of MSPC using a science and risk based approach
  - Recommend discussions with the Agency before implementation of MSPC as part of an RTRT approach
  - MSPC considered as a tool to enhance quality for traditional pharmaceutical manufacturing

Thank you!

Questions, comments, concerns:

NewDrugCMC@fda.hhs.gov