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Quality by Design (QbD) in Process Analytical Technology (PAT) and Real Time Release Testing (RTRT)

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Outline

- Clarification of QbD, PAT and RTRT Terminology
- Examples of PAT and RTRT
- Regulatory Considerations for RTRT
- Concluding Remarks

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New Quality Terminology

Real Time Release Testing (RTRT)

Critical Quality Attributes (CQAs)

Design Space

Quality by Design (QbD)

Process Analytical Technologies (PAT)

Control Strategy

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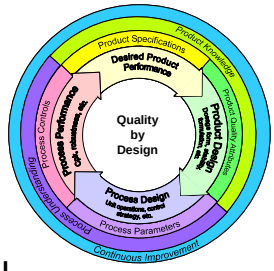
What is Quality by Design (QbD)?

- Systematic approach to pharmaceutical development and manufacturing
- Begins with predefined objectives
- Emphasizes product and process understanding and process control
- Based on sound science and quality risk management



From ICH Q8(R2)

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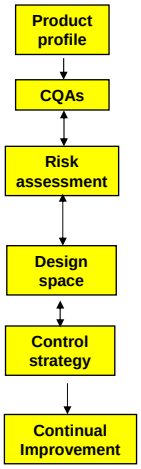
Example QbD Approach - ICH Q8(R2)



- Target the product profile
- Determine critical quality attributes (CQAs)
- Link raw material attributes and process parameters to CQAs and perform risk assessment
- Develop a design space
- Design and implement a control strategy
- Manage product lifecycle, including continual improvement

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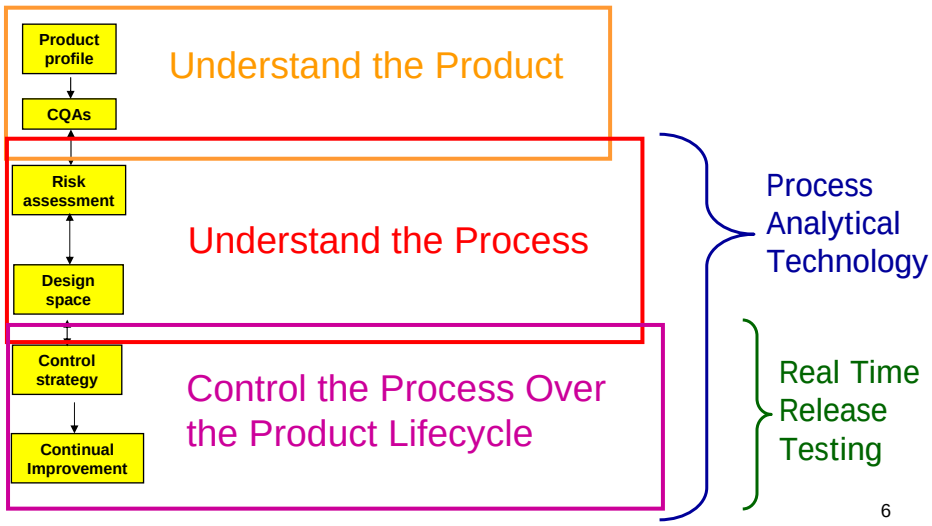
QbD Approach



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FDA's View of Process Analytical Technologies

- Process Analytical Technology (PAT)
  - a system for designing, analyzing, and controlling manufacturing
  - through timely measurements of critical quality and performance attributes of raw and in-process materials and processes
  - with the goal of ensuring final product quality
- PAT Fundamental Tenets
  - ***Quality cannot be tested*** into the product; it should be built-in or ***should be by design***
- PAT Goals
  - Enhance understanding and control of processes

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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)

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Examples of PAT

- During Development
  - In-line laser light scattering analyzer to monitor and understand nucleation during crystallization
  - At-line particle size distribution monitoring
  - NIR to understand & design blending process
- In Manufacturing
  - Table compression weight check and adjustment
  - Endpoint determination of blending
  - Weight check and adjustment of powder filling operation
  - Adjustment of process parameters based on starting material attributes

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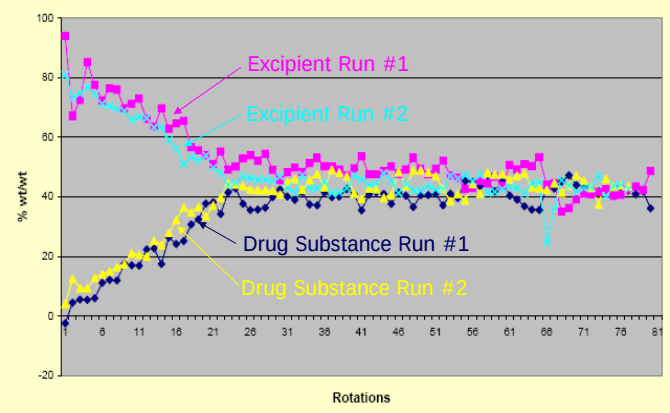
Endpoint Control Example for Blend Uniformity



Uniformity of excipients and blend determined by on-line process monitoring by NIR

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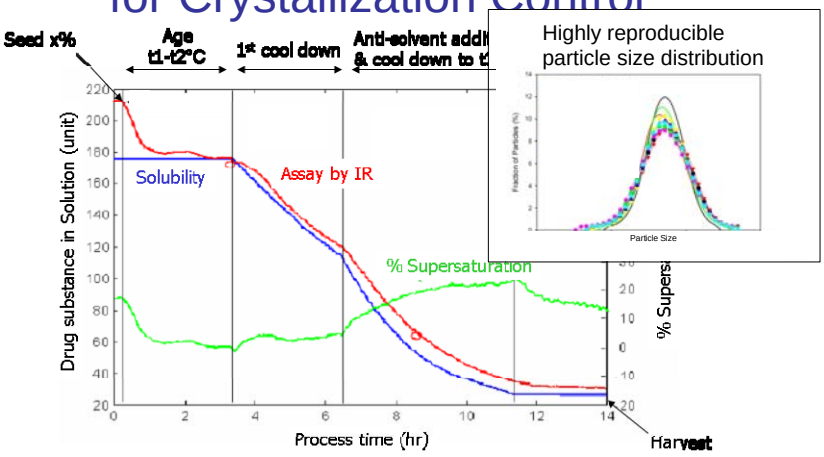
Example Monitoring and Modeling for Crystallization Control



- Controlled crystallization with seeding
- Processing occurs entirely in thermodynamically favored regime

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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*

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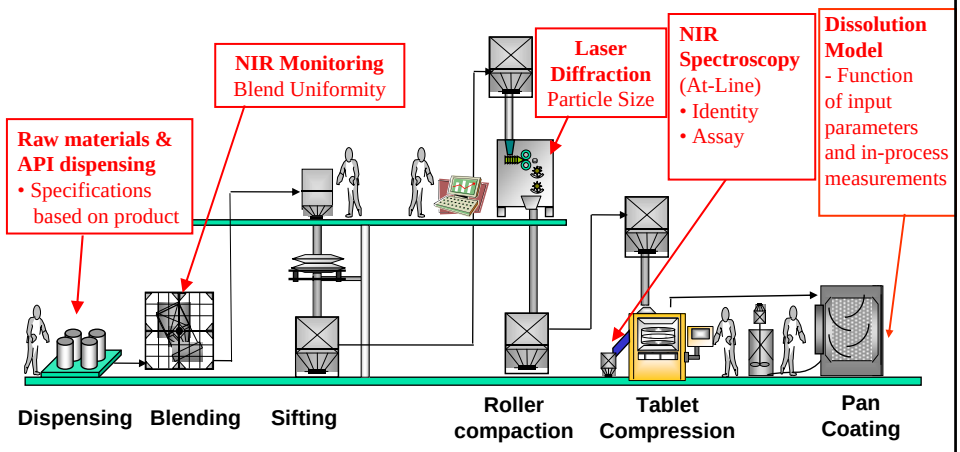
Example of An Unified Approach for RTRT



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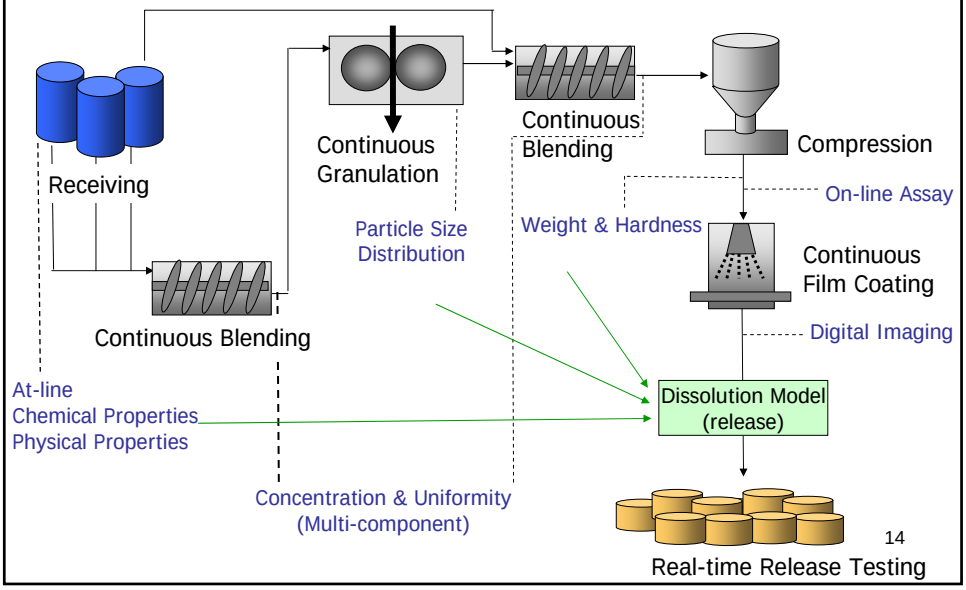
Conceptual Example of Control Strategy for RTRT in Continuous Manufacturing



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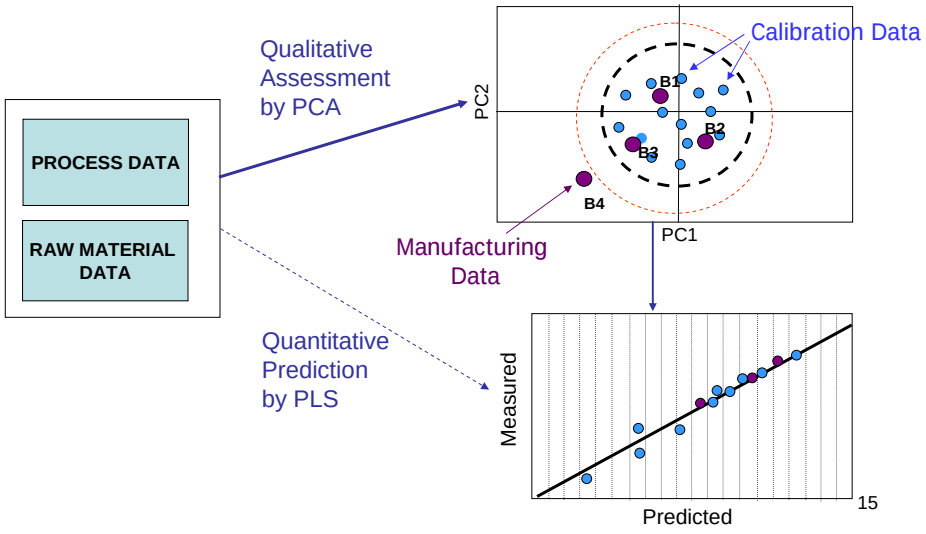
Multivariate Model for Predicting Dissolution



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Considerations for Real Time Release Testing Approaches

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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

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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

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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?

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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

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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)

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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

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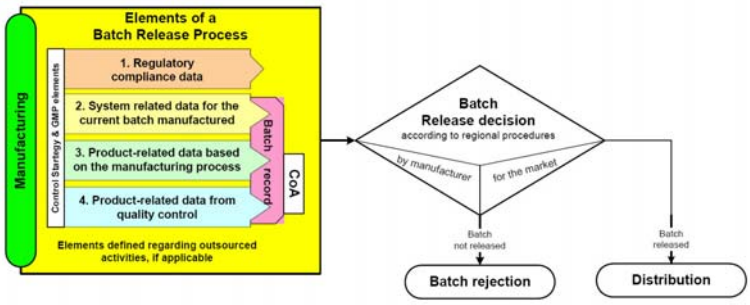
Batch Release Decision for RTRT



- 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.

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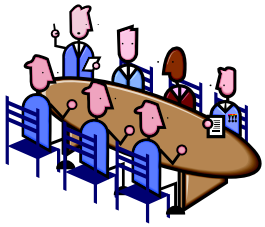
Communicate Early and Often!



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

- PAT and 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

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Thank you!

Questions, comments, concerns:

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