



Regulatory Assessment

Presentation Overview

- Goal of Regulatory Quality Assessment
- Review of the case study
 - Considerations during regulatory evaluation
 - Areas of consideration by assessors will be presented in the form of questions for the assessor
 - The questions presented here are not necessarily the ones which are finally communicated in regulatory deficiency letters
 - API and Formulation
 - Manufacturing Process Development
 - Quality Risk Management
 - Design Space
 - Proposed Control Strategy and Real Time Release Testing
 - Assessors Inspector Interaction

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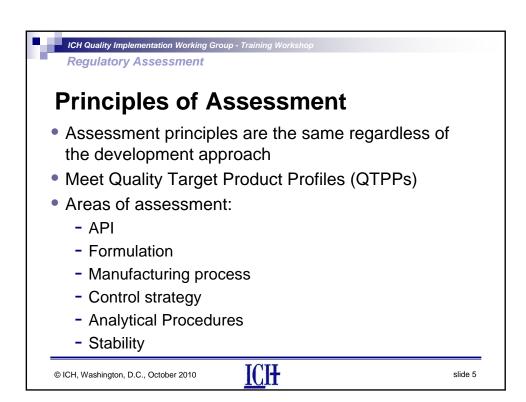
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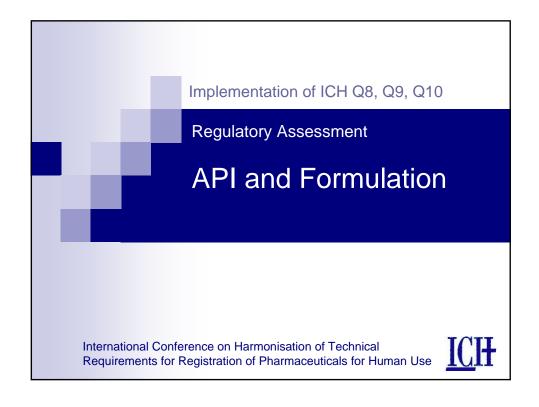
Goal of Regulatory Quality Assessment

- Assess
 - That the product is capable of consistently meeting the required quality
 - That the manufacturing process is capable of producing quality product
 - That throughout product shelf life and life cycle commercial batches will link to clinical batches in all relevant aspects
- These can be accomplished by
 - Process development and control strategy according to traditional standards
 - Process development and control strategy according to new paradigm

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API General Considerations

- QbD principles apply to APIs
- QbD principles can guide manufacturing process design and control strategy development
- Design space can be developed for API processes

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API- Assessors' Evaluation

- Have starting materials and process been adequately described?
- Are there toxicity concerns with degradants and/or related substances?
- Have adequate specifications and methods been proposed?
- Have adequate process controls been described?
- Was the design space adequately developed and data provided to support it?

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Formulation - General Considerations

- Design space formulation aspects
 - Variable composition or component attributes
 - Based on input raw material attributes
 - Lot to lot variability
 - Justified by data (Prior knowledge, DoE, etc)
- API attributes
 - To be considered in the development of formulation and choice of dosage form to meet QTPP
 - Additional information may be needed for the development of the formulation e.g. BCS, PK, stability, excipient compatibility

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Assessors' Evaluation of the Formulation

- Is dosage form designed to meet QTPP?
- Are the roles of ingredients identified?
- Have the safety and compatibility of ingredients been adequately addressed?
- Is the formulation adequately understood and specified?
- Does the proposed formulation differ from the formulation used in the pivotal clinical trials?

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Assessors' Evaluation of the Case Study Formulation

- Why was Calcium Hydrogen Phosphate Hydrate chosen with a water sensitive API?
 - Concern about compatibility and stability
- Has material variability effects been understood?
 - Adequacy of NIR testing
 - Adequacy of dissolution model and method
- What is the function of D-mannitol in the formulation?
 - Described only as excipient in the case study
 - Needs to be further explained

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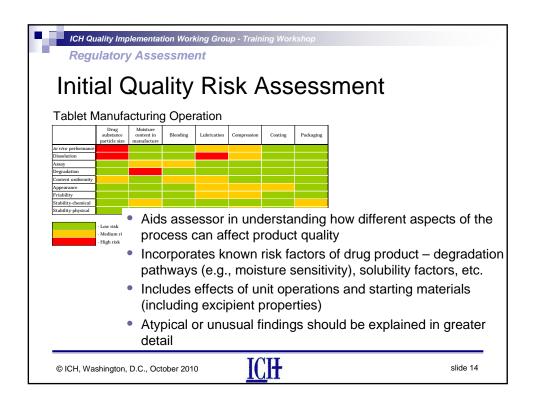
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Assessment of Manufacturing Process Development

- Production process description needs to have sufficient detail to enable assessment
- Assessment should evaluate
 - Process design
 - Use of risk management processes including risk assessments
 - Design space
 - Robustness

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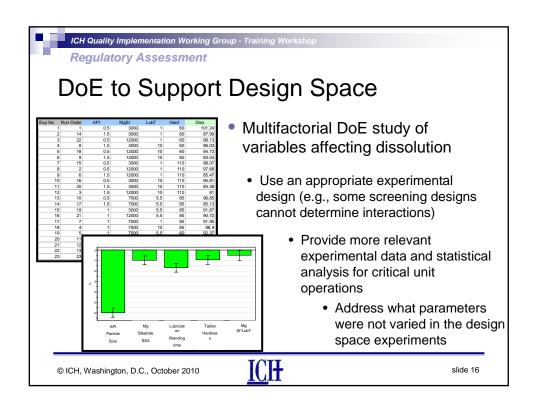
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Assessors' Evaluation of the Risk Assessment

- Assessors to evaluate methodologies and outcome
 - Explanation of risk ranking and score
 - Setting of risk threshold
 - Assurance that relevant factors have been considered
- Are results consistent with scientific principles and prior knowledge?
- Was there a linkage of results to the development of design space and control strategy?

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Assessors' Evaluation of Design Space

- Was a clear description of design space and its intended use provided?
- Has the proposed design space been appropriately established?
 - Demonstrated by data, supporting models and statistical evaluation
 - Understanding of interactions of variables
 - Multivariate vs univariate studies
 - Justified for the intended scale
 - Prior knowledge adequately summarised and/or referenced
- How could a design space built around one CQA (e.g particle size), affect other CQAs?
- Is the design space consistent with the control strategy?

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Example from the Case Study: Crystallization Design Space

- Goals of Crystallization Process
 - D90 between 5 20 microns
 - Target set by dissolution and formulation DoE
 - Degradant < 0.3% (qualified)
- Developmental knowledge
 - Water during crystallization causes degradation
 - Multiple parameters likely to influence PSD during crystallization

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Example from the Case Study: Crystallization Design Space – Cont.

- Univariate studies explored water content of solvent at max addition time and max temp
- DoE of 4 parameters established model for PSD:
 - PSD D90 = 19.3 2.51*A 8.63*B + 0.447*C 0.0656*A*C + 0.473*A^2 + 1.55*B^2
 - where A = Seed wt%, B = Agitator Tip Speed (m/s) and C = Temperature (C)
 - Statistical analysis shows that crystallization feed time does not impact PSD across the tested range.

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Assessors' Evaluation of the Crystallization Design Space

- Was the use of risk management processes acceptable?
 - Was adequate information provided?
 - Was there an appropriate use of prior knowledge?
 - Did the application include the risk assessments for the most important CQA/process parameter pairs e.g. Degradation/Crystallization?
- Was it appropriate to do separate studies on formation of degradant and PSD?
- Are the process parameters 'scale independent'?
- How can the proposed model be confirmed?
 - Case study relied on center point runs at scale

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Assessors' Evaluation of the Crystallization Design Space – Continued

- Is it appropriate to split out API PSD and impurity profile in risk assessment (Overall Risk Assessment for Process)?
 - Presented in the case study combined as "In Vivo Performance"
- Should crystallization have been classified as high risk in the risk assessment for degradation?
- How was process and/or method uncertainty accounted for in the model?
- Did the design space presented illustrate the interaction of parameters?
 - Case study showed two separate response surfaces for the two CQAs evaluated

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Regulatory Assessment Assessors' Evaluation Of the Control

Strategy

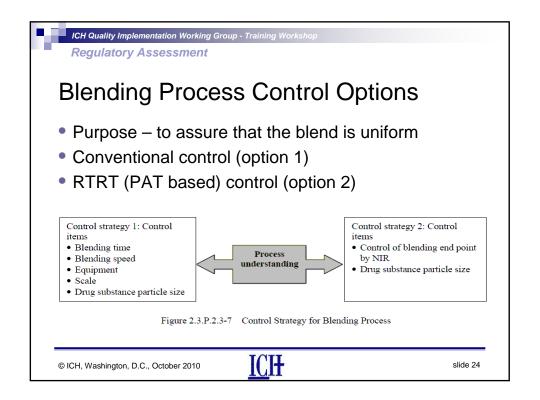
- Do the CQAs provide assurance that the QTPP will be met?
- Is the control strategy based on appropriate risk management?
- Is the placement of proposed controls maximally effective?
- Does the description of control strategy include down stream tests?
- Are the Specifications adequate?

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- What functional tests for excipients are needed? Were these included?
- Assessing some elements of control strategy such as RTRT, PAT, etc. may require assessors and inspectors with specialized training

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Blending Control Option 1

- Perform DoE to develop the design space
- CPPs involved blender type, blending speed, blending time, API particle size
- Assessors' evaluation
 - Were all CPPs properly identified during QRA?
 - Are the reference method and sampling procedure used to assess the blend uniformity adequate?
 - Is the design space developed from the DoE applicable at commercial scale?

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Blending Control Option 2

- Control of blending end-point by NIR
- Includes a chemometric model to predict the endpoint of the process
- Assessors' evaluation
 - Is the model properly developed and validated?
 - Do the model predictions correlate with standard blend uniformity measurements?
 - Are all sources of variation (e.g., excipients) included in the model?
 - Is the probe location adequate?

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Real Time Release Testing – Assessors' Evaluation General Considerations

- Have tests been verified at full scale?
- Have analytical procedures been validated? If the procedure contains a model, has it been validated and has an adequate maintenance plan been proposed?
- Have alternate traditional testing procedures been provided for any RTRT? To be used for
 - Stability testing
 - Regulatory testing
 - Break down of equipment when specified in dossier

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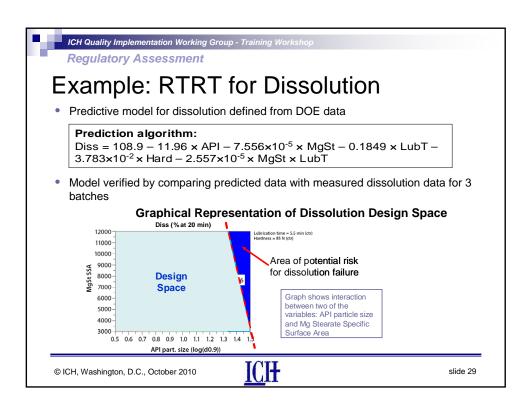
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Example from Case Study: RTRT for Dissolution

- Quality Risk Assessment shows that API particle size, lubrication and compression have potential to impact dissolution
- Analysis of in-vivo data also shows that API particle size impacts bioavailability
 - Larger particles have lower Cmax and AUC
- Multi factorial DoE carried out to estimate impact of factors on dissolution
 - Factors investigated: API particle size, magnesium stearate specific surface area, lubrication time and tablet hardness
 - Response measured: % dissolved at 20 min
 - DoE data analyzed to identify statistically significant factors affecting dissolution

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Dissolution Model Based on RTRT – Assessors' Evaluation

- Has a robust and discriminatory reference procedure (e.g. dissolution by HPLC) been provided?
- Has the dissolution model been validated with an independent data set (i.e. not just the DoE data)?
- Has model applicability been demonstrated across all variability proposed in the design space (e.g. change in scale, change in equipment type etc)
- Has process and/or method uncertainty been incorporated in the model?
 - Has a process been described for revision of design space on basis of prediction intervals?
- Has the applicant considered multivariate trend monitoring for the CQA and/or CPP that impact dissolution (e.g. API particle size, compression parameters etc)?
- Have plans been provided for model maintenance throughout the product life cycle?
 - Plans to revise the model (e.g. with change in API PSD outside the range that was evaluated via the DoE)
 - To be done under the company's quality system and subject to GMP inspection

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Dissolution Model based on RTRT -Assessors' Evaluation Continued

- Is the model prediction compared with the reference method for a statistically significant number of batches?
- Is the proposed acceptance criteria for dissolution appropriate?
- Given that there are more than 2 parameters that impact dissolution, should the dissolution design space be represented graphically as an interaction of more than one response surfaces?
- How capable is the model:
 - For taking into account variation in tablet hardness throughout the run?
 - For predicting failed batches?

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Dissolution Model based on RTRT -Assessors' Evaluation Continued

- Have details been provided on how the model would be used as a feed forward control, to adjust process parameters (e.g. compression parameters) depending on API particle size and/or magnesium stearate specific surface area?
- Could a routine in process disintegration test lower the risk of implementing this RTRT?

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Example from the Case Study: RTRT for Tablet Assay and CU

- Based on in-process tablet weight control
 - Part of compression operation
- Fill volume during compression adjusted by a feedback loop from the tablet weight measurement

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Example from Case Study: RTRT for Assay and Content Uniformity

- Risk Assessments as part of the QRM process shows four factors have potential to affect Assay and CU:
 - API Particle Size
 - Environmental moisture control
 - Blending and Lubrication
 - Absence of segregation before and during compression
- API Particle Size controlled by incoming materials testing and release
- Blend uniformity and absence of down stream segregation are key elements of control strategy

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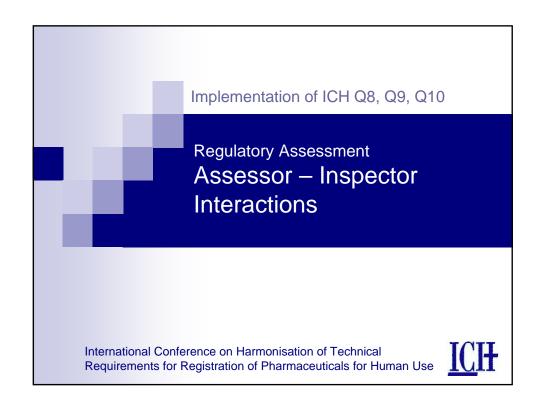


RTRT for Tablet Assay and CU: Assessors' Evaluation

- Are adequate data presented to demonstrate absence of segregation?
 - During compression, especially at beginning and end of run
 - When blend is held prior to compression
- Does the NIR method predict % active content of the blend (vs. indicating uniformity by variance change)?
- How is the use of the RTRT described in the specification?
- Is the information provided (e.g. data points, number of batches, comparison of individual tablets) adequate, to compare the assay calculated by weight to assay measured by HPLC?

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Assessor - Inspector Interaction

- Certain aspects of the application may need to be verified at site, such as
 - Has a statistically based criterion for release (e.g. acceptance limits, sample size, confidence intervals, outliers) been defined and addressed by the PQS?
 - Does the company's quality system have procedures to trend tablet weight during routine production and to accept/reject batches on the basis of RTRT?

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Assessor - Inspector Interaction Continued

- Certain aspects of the application may need to be verified at site, such as
 - Implementation of commercial manufacturing process
 - Implementation of design space, RTRT, control strategy.
 - Management of design space and models
 - Confirmation of data
 - Input for batch release strategy
 - Sampling plan especially for RTRT
- Communication between inspector and assesor is important

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Case Study Example of Interaction Between Assessors and Inspectors

Points to Consider

- For Crystallization Design Space
 - Conducting the inspection during the review period
 - Communication between Inspector and assessor prior to inspection
 - Including assessors and inspectors on inspection
 - May require specialized training for things like models and RTRT
 - Reviewing procedures for design space management within the company's quality system
- For future inspections after commercialization
 - Did verification of design space for crystallization at commercial scale support conclusion that the design space was scale independent?

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Conclusions

- Use of ICH Q8, Q9, Q10 will facilitate regulatory assessment
 - Knowledge rich applications provide transparency and facilitate assessment
 - Systematic development described in regulatory submissions will improve the regulatory assessment
 - Improve the efficiency of the review / assessment
 - Enable science and risk based regulatory decisions
 - Improve communication
 - Between Regulators and Industry
 - Between Assessors and Inspectors

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