Implementation of ICH Q8, Q9, Q10

Regulatory Assessment

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

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 are not representative of what is commonly 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

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

Principles of Assessment

- Assessment principles are the same regardless of the development approach
- Meet Quality Target Product Profiles (QTPPs)
- Areas of assessment:
  - API
  - Formulation
  - Manufacturing process
  - Control strategy
  - Analytical Procedures
  - Stability

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API and Formulation

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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

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?

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

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?

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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Manufacturing Process Development

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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

Initial Quality Risk Assessment

Tablet Manufacturing Operation

	Drug substance particle size	Moisture content in manufacture	Blending	Lubrication	Compression	Coating	Packaging
in vivo performance							
Dissolution							
Assay							
Degradation							
Content uniformity							
Appearance							
Friability							
Stability-chemical							
Stability-physical							

- Low risk
- Medium r
- High risk

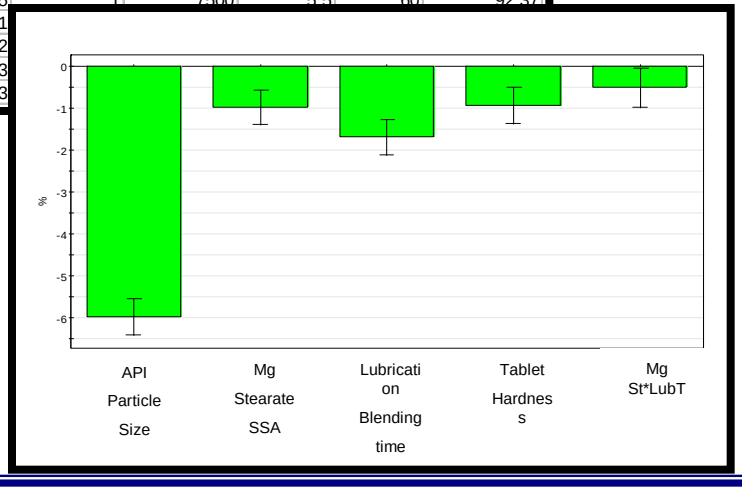
- Aids assessor in understanding how different aspects of the process can affect product quality
- Incorporates known risk factors of drug product – degradation pathways (e.g., moisture sensitivity), solubility factors, etc.
- Includes effects of unit operations and starting materials (including excipient properties)
- Atypical or unusual findings should be explained in greater detail

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?

DoE to Support Design Space

Exp No	Run Order	API	MgSt	LubT	Hard	Diss
1	1	0.5	3000	1	60	101.24
2	14	1.5	3000	1	60	87.99
3	22	0.5	12000	1	60	99.13
4	8	1.5	3000	10	60	86.03
5	18	0.5	12000	10	60	94.73
6	9	1.5	12000	10	60	83.04
7	15	0.5	3000	1	110	98.07
8	2	0.5	12000	1	110	97.68
9	6	1.5	12000	1	110	85.47
10	16	0.5	3000	10	110	95.81
11	20	1.5	3000	10	110	84.38
12	3	1.5	12000	10	110	81
13	10	0.5	7500	5.5	85	96.85
14	17	1.5	7500	5.5	85	85.13
15	19	1	3000	5.5	85	91.87
16	21	1	12000	5.5	85	90.72
17	7	1	7500	1	85	91.95
18	4	1	7500	10	85	88.9
19	5	1	7500	5.5	60	92.37
20	11					
21	12					
22	13					
23	23					



- Multifactorial DoE study of variables affecting dissolution
  - Use an appropriate experimental design (e.g., some screening designs cannot determine interactions)
  - Provide more relevant experimental data and statistical analysis for critical unit operations
    - Address what parameters were not varied in the design space experiments

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?

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

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.

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

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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Proposed Control Strategy and Real Time Release Testing

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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?
- 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

Blending Process Control Options

- Purpose – to assure that the blend is uniform
- Conventional control (option 1)
- RTRT (PAT based) control (option 2)

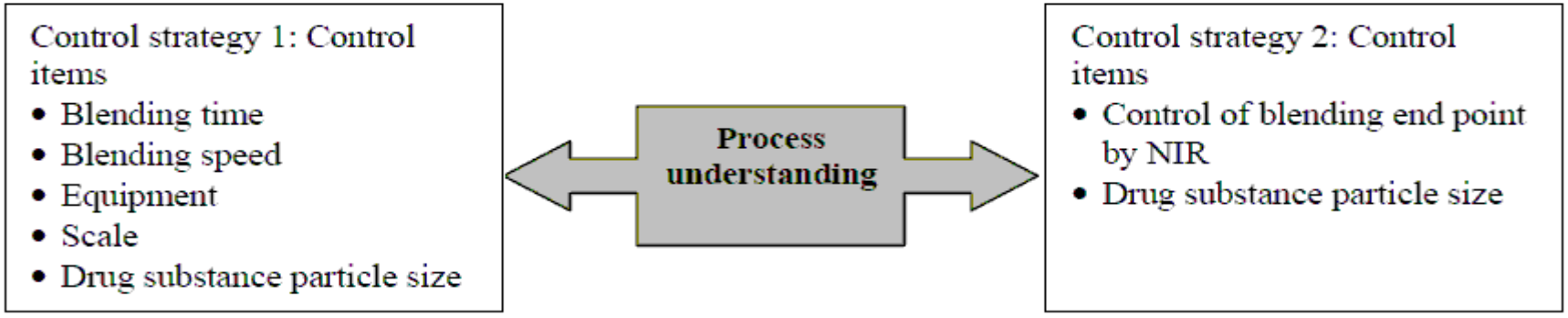


Figure 2.3.P.2.3-7 Control Strategy for Blending Process

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?

Blending Control Option 2

- Control of blending end-point by NIR
- Includes a chemometric model to predict the end-point 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?

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

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

Example: RTRT for Dissolution

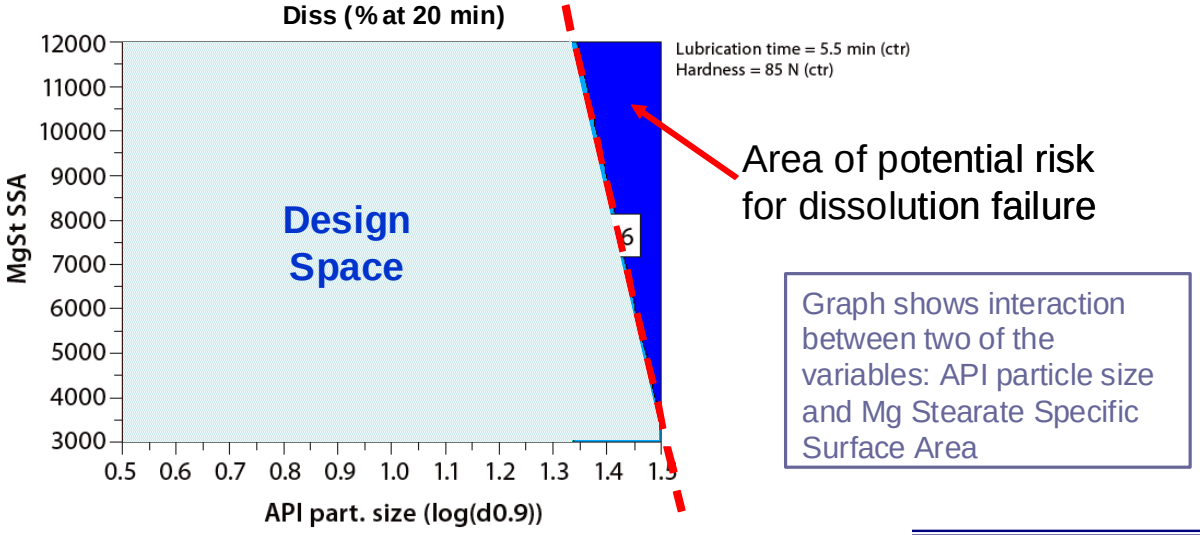
- Predictive model for dissolution defined from DOE data

Prediction algorithm:

$$Diss = 108.9 - 11.96 \times API - 7.556\times10^{-5} \times MgSt - 0.1849 \times LubT - 3.783\times10^{-2} \times Hard - 2.557\times10^{-5} \times MgSt \times LubT$$

- Model verified by comparing predicted data with measured dissolution data for 3 batches

Graphical Representation of Dissolution Design Space



Area of potential risk for dissolution failure

Graph shows interaction between two of the variables: API particle size and Mg Stearate Specific Surface Area

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

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?

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?

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

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

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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Regulatory Assessment Assessor – Inspector Interactions

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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?

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

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?

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