ICH-GCG ASEAN

Workshop B
Control Strategy

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Disclaimer

The information within this presentation is based on the ICH Q-IWG members expertise and experience, and represents the views of the ICH Q-IWG members for the purposes of a training workshop.
Introduction

• Objective:
  - Understanding about control strategy
  - Interactive workshop

• Structure of this session
  - Presentation of key messages in relation with Control Strategy
  - ICH Q&As on Control Strategy
  - Specific examples
  - Conclusions?
Key Messages - Definitions

• ‘Control Strategy’ is a
  - Planned set of controls,
  - Derived from current product and process understanding that assures 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)
Key Messages - Definitions

• **Critical Quality Attribute (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 (Q8(R2))

• **Critical Process Parameter (CPP):**
  A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality (Q8(R2))
Key Messages - Definitions

• **In-Process Control (or Process Control):**
  Checks performed during production in order to monitor and, if appropriate, to adjust the process and/or to ensure that the intermediate or API conforms to its specifications (Q7)
  Applies similarly to the drug product

• **In-Process Tests:**
  Tests which may be performed during the manufacture of either the drug substance or drug product, rather than as part of the formal battery of tests which are conducted prior to release (Q6A)
Key Messages - Definitions

- **‘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, which typically include a valid combination of measured material attributes and process controls’ (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 (Q8(R2))
Key Messages 1/5

• Control strategy derives from management of risk and should lead to assurance of consistent quality of product in alignment with the Quality Target Product Profile (QTPP)

• Control strategy is:
  - Not a new concept
  - Not just specifications
  - Based on product and process understanding and risk management
  - While design space is optional, control strategy is not.
Key Messages 2/5

• Every process and product has an associated control strategy.
  - There is one overall control strategy for a given product.
  - There are control strategies for unit operations
  - It could include some site specific aspects
• For a given product, different approaches for the control strategy are possible (e.g. in-process testing, RTRT, end product testing)
• Specifications for API and drug product are still needed for stability testing, regional regulatory testing requirements, etc.
Key Messages 3/5

• Control strategy and batch release should not be confused. *Control strategy is a key component, but not the only element needed for the batch release decision.*

• Scale-up, technology transfer and manufacturing experience can lead to refinements of the control strategy under the PQS considering regulatory requirements.
Key Messages 4/5

• Process for defining the control strategy
  - What are the quality criteria (QTPP)
  - Initial design of specific product & process
  - Assess prior knowledge to understand materials, process and product with their impact
    - Experience with different approaches to control
  - Risk assessment for process steps and variables
    - Assure all CPPs are identified during QRA
  - Development to further determine what type of controls are appropriate for each variable
  - Consider design space, if submitted
  - Specifications

• Scale-up considerations

• Quality system requirements of control strategy
  - Implementation, maintenance and updating
Key Messages 5/5

• Industry selects control approach based on multiple factors
  - Factors may include analytical testing sensitivity, equipment limitations, etc.
• Regulators (assessors) evaluate the control strategy and whether the risk has been adequately controlled
• Inspectors review the implementation of the control strategy at site, including adaptation at scale up, and the adequacy of the site quality system to support it
Q&As ICH Control Strategy

• What is the difference in a control strategy for products developed using the minimal approach vs. ‘quality-by-design’ approach?

Control strategies are expected irrespective of the development approach. Control strategy includes different types of control proposed by the applicant to assure product quality (Section 3.2.1 ICH Q10), such as in-process testing and end-product testing. For products developed following the minimal approach, the control strategy is usually derived empirically and typically relies more on discrete sampling and end product testing. Under QbD, the control strategy is derived using a systematic science and risk-based approach. Testing, monitoring or controlling is often shifted earlier into the process and conducted in-line, on-line or at-line testing.
Q&As ICH Control Strategy

• Are GMP requirements different for batch release under QbD?

No, the same GMP requirements apply for batch release under minimal and QbD approaches.
Q&As ICH Control Strategy

• What is the relationship between a Design Space and a Control Strategy?

A control strategy is required for all products. If a Design Space is developed and approved, the Control Strategy [see ICH Q8(R1), Part II, Section 4] provides the mechanism to ensure that the manufacturing process is maintained within the boundaries described by the Design Space.
Q&As ICH Control Strategy

- What approaches can be taken in the event of on-line / in-line / at-line testing or monitoring equipment breakdown?

The control strategy provided in the application should include a proposal for use of alternative testing or monitoring approaches in cases of equipment failure. The alternative approach could involve use of end product testing or other options, while maintaining an acceptable level of quality. Testing or monitoring equipment breakdown needs to be managed in the context of a deviation under the Quality System and can be covered by GMP inspection.
• Role of QTPP?
Example from ICH case study
Quality Target Product Profile (QTPP)
Safety and Efficacy Requirements

<table>
<thead>
<tr>
<th>Tablet</th>
<th>Characteristics / Requirements</th>
<th>Translation into Quality Target Product Profile (QTPP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>30 mg</td>
<td>Identity, Assay and Uniformity</td>
</tr>
<tr>
<td>Subjective Properties</td>
<td>No off-taste, uniform color, and suitable for global market</td>
<td>Appearance, elegance, size, unit integrity and other characteristics</td>
</tr>
<tr>
<td>Patient Safety – chemical purity</td>
<td>Impurities and/or degradates below ICH or to be qualified</td>
<td>Acceptable hydrolysis degrade levels at release, appropriate manufacturing environment controls</td>
</tr>
<tr>
<td>Patient efficacy – Particle Size Distribution (PSD)</td>
<td>PSD that does not impact bioperformance or pharm processing</td>
<td>Acceptable API PSD Dissolution</td>
</tr>
<tr>
<td>Chemical and Drug Product Stability: 2 year shelf life (worldwide = 30°C)</td>
<td>Degradates below ICH or to be qualified and no changes in bioperformance over expiry period</td>
<td>Hydrolysis degradation &amp; dissolution changes controlled by packaging</td>
</tr>
</tbody>
</table>

QTTP may evolve during lifecycle – during development and commercial manufacture – as new knowledge is gained e.g. new patient needs are identified, new technical information is obtained about the product etc.
• Role of Risk Assessment and Control Strategy

• Control Strategy derives from management of risk and product and process understanding
**Example from IWG Case Study:**
Risk Assessment (FMEA): Purity Control – API crystallization

<table>
<thead>
<tr>
<th>Unit Operation</th>
<th>Parameter</th>
<th>IMPACT</th>
<th>PROB</th>
<th>DETECT</th>
<th>RPN</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distillative Solvent Switch</td>
<td>Temperature / Time, etc.</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>5</td>
<td>Distillation performed under vacuum, at low temperature, minimizing risk of hydrolysis</td>
</tr>
<tr>
<td>Distillative Solvent Switch / Crystallization</td>
<td>Water content at end of Distillation (Crystallization Feed)</td>
<td>9</td>
<td>5</td>
<td>1</td>
<td>45</td>
<td>Higher water = higher degradation In process control assay should ensure detection and</td>
</tr>
<tr>
<td>Crystallization -- API Feed Solution</td>
<td>Feed Temperature</td>
<td>9</td>
<td>5</td>
<td>1</td>
<td>45</td>
<td>Higher temperature = higher degradation Temperature alarms should enable quick detection and control</td>
</tr>
<tr>
<td>Crystallization -- API Feed Solution</td>
<td>Addition Time</td>
<td>9</td>
<td>1</td>
<td>5</td>
<td>45</td>
<td>Longer time = higher degradation Detection of prolonged addition time may occur too late to prevent some degradation</td>
</tr>
<tr>
<td>Crystallization</td>
<td>Seed wt percentage</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>This parameters cannot impact impurity rejection, since no rejection of hydrolysis degradeate occurs.</td>
</tr>
<tr>
<td>Crystallization</td>
<td>Antisolvent percentage (charge ratio)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>This parameters cannot impact impurity rejection, since no rejection of hydrolysis degradeate occurs.</td>
</tr>
<tr>
<td>Crystallization</td>
<td>Crystallization temperature</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>5</td>
<td>Temperature is low enough that no degradation will occur.</td>
</tr>
<tr>
<td>Crystallization</td>
<td>Other crystallization parameters</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>These parameters cannot impact impurity rejection, since no rejection of hydrolysis degradeate occurs.</td>
</tr>
</tbody>
</table>
Example from ICH case study
Quality Risk Assessment
Impact on Assay and Content Uniformity CQAs

- QRA shows API particle size, moisture control, blending and lubrication steps have potential to affect Assay and Content Uniformity CQAs
  - Moisture is controlled during manufacturing by facility HVAC control of humidity (GMP control)

<table>
<thead>
<tr>
<th></th>
<th>Drug substance particle size</th>
<th>Moisture content in manufacture</th>
<th>Blending</th>
<th>Lubrication</th>
<th>Compression</th>
<th>Coating</th>
<th>Packaging</th>
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<tr>
<td><em>in vivo</em> performance</td>
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<td>Degradation</td>
<td></td>
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<tr>
<td>Content uniformity</td>
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<td>Appearance</td>
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<tr>
<td>Stability-physical</td>
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</tbody>
</table>

Key message: Initial QRA identifies where to focus Development efforts to understand and control Assay and Content Uniformity CQAs
Different control strategies

• What are the benefits in this blending example of the different control strategy options?
Example from ICH case study
Blending Process Control Options

Decision on conventional vs. RTR testing

Control strategy 1: Control items
- Blending time
- Blending speed
- Equipment
- Scale
- Drug substance particle size

Control strategy 2: Control items
- Control of blending end point by NIR
- Drug substance particle size

Process understanding

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

Note) In the case of employment of control strategy 1, it is possible that drug substance particle size as an input variable is combined with process parameters of blending time and blending speed to construct and present a three dimensional design space.

Key message: Both approaches to assure blend uniformity are valid in combination with other GMP requirements
RTRT of Assay and Content Uniformity

- What are the steps in building the control strategy elements for content uniformity?
  - Does this connect with the control strategy elements for another CQA (e.g. potency)?
- Is this control strategy adequate to assure assay and content uniformity of the final product? Can it replace end product testing for these CQA’s?
- What could be alternative approaches?
Example from ICH case study

Process Control Option 2: Blend uniformity monitored using a process analyser (ctd)

- On-line NIR spectrometer used to confirm scale up of blending
- Blending operation complete when mean spectral std. dev. reaches plateau region
  - Plateau may be detected using statistical test or rules
- Feedback control to turn off blender
- Company verifies blend does not segregate downstream
  - Assays tablets to confirm uniformity
  - Conducts studies to try to segregate API

Data analysis model will be provided
Plan for updating of model available

Acknowledgement: Adapted from Paul Stott (AZ) - ISPE POLITeam
Example from ICH case study

**Tablet Weight Control in Compression Operation**

Conventional automated control of Tablet Weight using feedback loop:
Sample weights fed into weight control equipment which sends signal to filling mechanism on tablet machine to adjust fill volume and therefore tablet weight.

**Control strategy:** Assay assured by control of weight of tablets made from a uniform powder blend that has acceptable API content by HPLC
RTRT of Assay and Content Uniformity

- Finished Product Specification – *use for stability, regulatory testing, site change, whenever RTR testing is not possible*
  - Assay acceptance criteria: 95-105% of nominal amount (30mg)
  - Uniformity of Dosage Unit acceptance criteria
  - Test method: HPLC

- Real Time Release Testing Controls
  - Blend uniformity assured in blending step (online NIR spectrometer for blending end-point)
  - API assay is analyzed in blend by HPLC
  - Tablet weight control in compression step

- No end product testing for Assay and Content Uniformity (CU)
  - Would pass finished product specification for Assay and Uniformity of Dosage Units if tested because assay assured by combination of blend uniformity assurance, API assay in blend and tablet weight control (if blend is homogeneous then tablet weight will determine content of API)
Further topics to be discussed

• How does control strategy evolve during life-cycle of product and process?

• Is there a relationship between control strategy and process validation?

• RTRT and certificate of analysis: how could a certificate of analysis look like in the future?