Implementation of ICH Q8, Q9, Q10

Breakout B
Control Strategy

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

ICH

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.

© ICH, Washington, D.C., October 2010

ICH

Introduction

- Structure of this session
  - Discussion of key messages on Control Strategy
  - Examples from the Case Study
  - Wrap up
    - Feedback on barriers to implementation
    - Feedback on issues where further clarification is required
  - Breakout report

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))

© ICH, Washington, D.C., October 2010

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)

© ICH, Washington, D.C., October 2010

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))

© ICH, Washington, D.C., October 2010

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 space is optional, control strategy is not.

© ICH, Washington, D.C., October 2010

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

© ICH, Washington, D.C., October 2010

Key Messages 5/5

- Industry selects control approach based on multiple factors
  - Factors may include analytical testing sensitivity, equipment limitations, etc.
- Regulators evaluate the control strategy and whether the risk has been adequately controlled
- Inspector reviews the implementation of the control strategy at site, including adaptation at scale up, and the adequacy of the site quality system to support it

© ICH, Washington, D.C., October 2010

Examples from the Case Study

- Review of QTPP and Drug Product Risk Assessment
- Blending Process Control Options
  Decision on conventional vs. on-line testing
- Tablet weight control during compression

Quality Target Product Profile (QTPP) Safety and Efficacy Requirements

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

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.

Breakout B: Control Strategy

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)

	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 risk
- High risk

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

© ICH, Washington, D.C., October 2010

Breakout B: Control Strategy

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

Process understanding

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

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 partcle 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

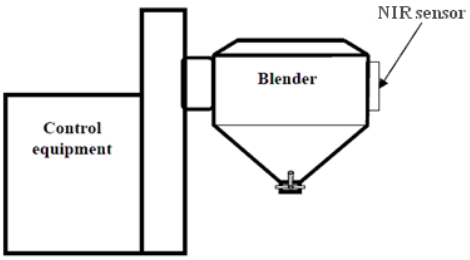
© ICH, Washington, D.C., October 2010

Process Control Option 2

Blend uniformity monitored using a process analyser

- Control Strategy to assure homogeneity of the blend
  - Control of blending end-point by NIR and feedback control of blender
  - API particle size

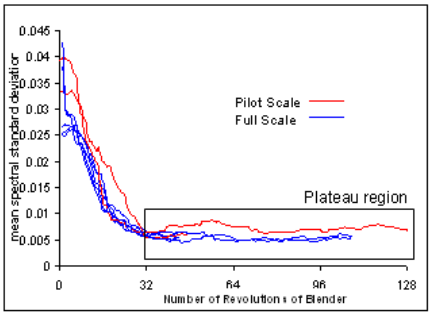
Equipment: XXXXX
Location of sensor attachment: Side position of the blender
Wavelength: XXXX cm^{-1} (Range of wave number: XXX to XXX cm^{-1})
Spectral Acquisition mode: diffuse reflectance



In this case study, the company chooses to use online NIR to monitor blend uniformity to provide efficiency and more flexibility

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

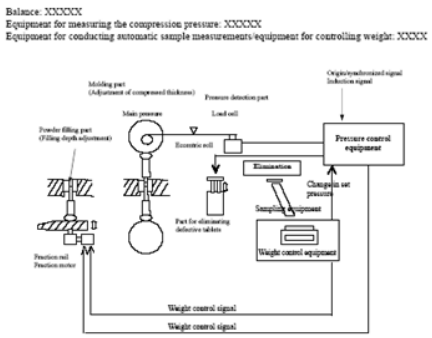
- On-line NIR spectrometer used to confirm scale up of blending
- Blending operation complete when mean spectral std. dev. reaches plateau region
  - Plateau may be detected using statistical test or rules
- Feedback control to turn off blender
- Company verifies blend does not segregate downstream
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

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)

Topics to discuss using this Case Study

- 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)?
  - How does this fit into the overall control strategy of the product CQA's?
- What are the benefits in this blending example of the different control strategy options?
- 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 to the proposed control strategy?

Additional discussion questions

- What could the drug product specification be presented in the application file when RTRT is employed?
- What might a certificate of analysis look like for a product that is released via RTRT?

Acknowledgement

This presentation has been developed by members of the ICH Quality Implementation Working Group (Q-IWG)

- Jean-Louis Robert (rapporteur)
- Diana Amador-Toro
- Robert G. Baum
- Nicholas Cappuccino
- David Cockburn
- Georges France
- Richard L. Friedman
- Nigel Hamilton
- Hirotada Nagai
- Yukio Hiyama
- Fusashi Ishikawa
- Takao Kiyohara
- Urs Kopp
- Akira Kusai
- Yoshihiro Matsuda
- Motoaki Mitsuki
- Elaine Morefield
- Jacques Morénas
- Masatoshi Morisue
- Markus-Peter Müller
- Tamiji Nakanishi
- Moheb Nasr
- Kazuhiro Okochi
- Anthony Ridgway
- Rachael Roehrig
- Stephan Rönninger
- Swroop Sahota
- Hideki Sasaki
- Tetsuhito Takarada
- Shigeki Tamura
- Krishnan Tirunellai
- Mats Welin
- Jean M. Wyvratt
- A J van Zyl

© ICH, Washington, D.C., October 2010

Implementation of ICH Q8, Q9, Q10

Breakout: B Control Strategy Discussions

Bob Baum
Jean-Louis Robert

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

Acknowledgement

Facilitators

- Regulator:
  - Steve Kozlowski
  - Terry Ocheltree
  - Elaine Morefield
  - Jacques Morenas
  - Grace McNally
- Industry:
  - Jeff Blumenstein
  - Eric Ahuja
  - Chi-wan Chen
  - Mark Schweitzer

Disclaimer

General on this presentation

- Feedback from the facilitated discussions
- See it as a brainstorming from the breakout discussion

Are we clear with the key messages? Yes / No

- **IWG messages are generally understood and accepted**
  - Recognition that concepts are applicable to biologics and small molecules
- **Further clarification of link between control strategy and pharmaceutical quality systems and cGMPs. Control strategy does not replace cGMPs**
- **Need to emphasize overall product control strategy**
  - Includes:
    - Lifecycle approach
    - Justification of decisions
    - Verification of linkages
    - Consideration of material properties and suppliers

Are there **practical concerns** on implementation?

(e.g. on harmonisation among regions needed, by region/local issue)

- Clarify relationship between control strategy and batch release decision
- Further clarification on process for determining criticality
- Clarifying the linkages between QTPP, CQAs and specifications
- Clarify difference between RTRT and in-process tests
- RTRT environment requires robust quality system

Practical concerns / Clarification required for practical harmonised implementation?

- How do we describe RTRT in specification?
  - Relationship to Pharmacopoeial standards
  - Certificate of Analysis
- Foundation built during product development activities
- Control strategy and continuous process verification
- Harmonised approach to RTRT and avoidance of import testing
- Expectations for confirming suitability of control strategy at different scales

Practical concerns / Clarification required for practical harmonised implementation?

- **Importance of risk assessment and management**
  - Output included in application files
  - How much information in an application file?
- **Description of control strategy in a submission**
  - Is current CTD format adequate?

Practical concerns / Clarification required
for practical harmonised implementation?

- **RTRT and advanced control systems**
  - Adoption by Industry?
  - Global acceptance by Regulators?
  - Training and understanding of concepts and technology
  - Increase in regulatory queries?
  - More submissions will help learning (industry and regulators)
  - How to deal with unforeseen events?
  - RTRT requires adaptive quality system

© ICH, Washington, D.C., October 2010

Practical concerns / Clarification required
for practical harmonised implementation?

- **How does Control Strategy evolve during lifecycle?**
  - Maintenance and update of models
    - Clarification of role of Assessors and GMP Inspectors
    - Linkage of model to change control procedures (PQS)
  - Requires access to knowledge
- **Role of QTPP to be clarified**
  - Dynamic nature of QTPP during development

© ICH, Washington, D.C., October 2010

Practical concerns / Clarification required
for practical harmonised implementation?

- **Acceptance of alternative control strategies for the same product**
  - Fall-back testing for RTRT equipment failure
  - Different facilities
  - Approved for different countries

Practical concerns / Clarification required
for practical harmonised implementation?

- Continue dialogue between industry and regulators
- Continued assessor and inspector collaborative interactions
- Recognition that we are all in the midst of a culture change as we move to the new quality paradigm