ICH Q12 Update
Does Japan need ICH Q12?

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Challenges in Japan

- Reviewers expect very detailed J-AF
  - High number of variations for low/no impact changes
  - Compliance with J-AF has proved very difficult
    - But no impact to patient safety experienced!
- Most variations are PCAs
  - Long review approval times
  - Large amount of resources needed
- Little/no benefit on LCM for implementation of Q8-11
- No PACMP procedure

- But change is coming……….we hope!
What should Q12 do?

...could mitigate drug shortages related to manufacturing and quality issues

Support continual improvement...which can result in decreased product variability and increased manufacturing efficiency

Facilitate the introduction of innovations...

...Facilitate risk-based regulatory oversight...harmonized expectations across the ICH regions...in a more transparent and efficient manner...

Emphasize...control strategy as a key component of the dossier...clarify and simplify J-AF....enable more change only within PQS

Enhance use of regulatory tools for prospective change management...

...enabling strategic management of post-approval changes...
Progress in Geneva (Nov, 2017)

- Regulators legal review of Step 2a document identified some concerns for implementation

- Q12 was endorsed to proceed to Step 2b with the added text: "In certain ICH regions, the current ICH Q12 guideline is not fully compatible with the established legal framework with regard to the use of explicit Established Conditions ('EC') referred to in Chapter 3 and with the Product Lifecycle Management ('PLCM') referred to in Chapter 5 as outlined in this guideline. These concepts will, however, be considered when the legal frameworks will be reviewed and, in the interim, to the extent possible under the existing regulation in these ICH regions."

- Imminent regional publication for 12 Mo commenting period
Steps in the ICH Process

- **Step 1**: Consensus building - Technical Document
- **Step 2**: a. ICH Parties consensus on Technical Document / b. Draft Guideline adoption by Regulators
- **Step 3**: Regulatory consultation and Discussion
- **Step 4**: Adoption of an ICH Harmonised Guideline
- **Step 5**: Implementation

WHO and IFPMA as Standing Observers
ICH, International Council for Harmonisation (from 2015)
WHO and IFPMA as Standing Observers
Observer Regional Harmonisation initiatives
Convergence toward risk-based categorization of post-approval changes is encouraged as an important step toward achieving the objectives of Q12

- Prior-approval: Changes with sufficient risk to require regulatory authority review and approval prior to implementation
- Notification: Moderate- to low-risk changes that do not require prior approval and generally require less information to support the change
  - These changes are communicated to the regulatory authority as a formal notification that takes place within a defined period of time before or after implementation, according to regional requirements.
- In addition, the lowest risk changes are only managed and documented within the Pharmaceutical Quality System (PQS) and not reported to regulators, but may be verified on routine inspection
Established Conditions (EC)

ECs are legally binding information (or approved matters) considered necessary to assure product quality
• As a consequence, any change to ECs necessitates a submission to the regulatory authority
• All regulatory submissions contain a combination of ECs and supportive information
  • Supportive information is not considered to be ECs, but is provided to share with regulators the development and manufacturing information at an appropriate level of detail, and to justify the initial selection of ECs and their reporting category

ECs in a submission are either implicit or explicit:
• Implicit ECs are elements that are not specifically proposed by the applicant but are derived from and revised according to regional regulation or guidance related to post-approval changes.
• Explicit ECs are specifically identified and proposed by the applicant together with their proposed reporting category as part of a regulatory submission
## CTD Sections That Contain ECs

<table>
<thead>
<tr>
<th>CTD SECTION</th>
<th>SECTION TITLE</th>
<th>ESTABLISHED CONDITIONS – General List with notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.2.P.3.1</td>
<td>Manufacturer(s)</td>
<td>Drug Product Manufacturing (including: testing, primary packaging, device assembly for drug product-device combination products) sites</td>
</tr>
<tr>
<td>3.2.P.3.2</td>
<td>Batch Formula</td>
<td>Drug Product Batch Formula (Qualitative and Quantitative)</td>
</tr>
<tr>
<td>3.2.P.3.3</td>
<td>Description of manufacturing process and process controls</td>
<td>Individual unit operations and their sequence in the manufacturing process. For levels/details of ECs for inputs (process parameters and material attributes) and outputs of individual unit operations, reference is made to <a href="#">Chapter 3.2.3.1 – Identification of ECs for the Manufacturing Processes</a></td>
</tr>
<tr>
<td>3.2.P.3.4</td>
<td>Controls of Critical Steps and Intermediates</td>
<td>Specifications (e.g., test, elements of analytical procedure and acceptance criteria) for critical steps and intermediates including storage conditions of critical intermediates</td>
</tr>
<tr>
<td>3.2.P.3.5</td>
<td>Process validation and/or evaluation</td>
<td>Supportive information</td>
</tr>
<tr>
<td>3.2.P.4</td>
<td>Control of Excipients</td>
<td></td>
</tr>
</tbody>
</table>
| 3.2.P.4.1   | Specifications | Excipient Specification. For each Quality Attribute on the specification  
  - Test Method  
  - Acceptance Criteria  
  Or, if applicable reference to pharmacopoeial monograph |
| 3.2.P.4.2   | Analytical Procedures | Reference to pharmacopoeial monograph and if none exists, refer to [Chapter 3.2.3.2 – Identification of ECs for Analytical Procedures](#) |
| 3.3.P.4.3   | Validation of analytical procedures | Supportive information |
Identification of ECs

- EC and reporting category may vary based on a sponsor’s product and/or process understanding, ease of characterization and/or risks tied to product quality and performance.

- Appropriate justification should be provided to support the identification of ECs and proposed reporting categories.

- Opportunity to simplify many aspects of dossier to focus ECs on those elements of process important to assure product quality.
  - Raw materials, Intermediates, IPCs, reference materials etc.
  - *Reduce and clarify the compliance commitment*
Analytical Procedures

• ECs related to analytical procedures should include elements which assure performance of the procedure.
  – Where method performance has not been fully studied, ECs will incorporate details of operational parameters incl. system suitability
  – Convergence on regional requirements is happening as a consequence of discussions
    • Simplification away from JP style under discussion in Japan

• With an increased understanding, ECs are focused on high level method description and method-specific performance criteria.
  – Not established conditions: Method details needed to run the method effectively

Concerns
• Availability of current method for surveillance and in country testing
  – Some progress on using alternate mechanism to facilitate this
AZ Example for Analytical Procedures

1. CQA Acceptance criteria

2. Method Description

The quantification of degradation products of ‘Product name’ tablets Y mgs is achieved by preparing a sample solution that is analysed by liquid chromatography with UV detection at using a suitable column and chromatographic conditions. Levels of individual degradation products are determined by relative peak areas.

3. Method specific performance verification tests and criteria

<table>
<thead>
<tr>
<th>Method Attribute</th>
<th>Acceptance criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity</td>
<td>No interference with the main peak or known degradation products</td>
</tr>
<tr>
<td>Linearity</td>
<td>$r^2 \geq 0.99$</td>
</tr>
<tr>
<td>Accuracy</td>
<td>Mean recovery at each level 90% to 110%</td>
</tr>
<tr>
<td>Repeatability</td>
<td>RSD of $\leq 20%$ for each specified degradation product (performed in accordance with ICH Q2)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>Quantification limit (QL) $\leq 0.05%$</td>
</tr>
<tr>
<td>Method equivalence</td>
<td>Statistical equivalence demonstrated</td>
</tr>
</tbody>
</table>
Identification of Established Conditions for Manufacturing Processes

- The extent of ECs will vary based on a number of factors, including product and process understanding, characterization, and the firm’s development approach.
  
  - A **parameter based approach**, in which product development prior to regulatory submission provides a limited understanding of the relationship between inputs and resulting quality attributes, will include a large number of inputs (e.g., process parameters and material attributes) along with outputs (including in-process controls).
  
  - An **enhanced approach** with increased understanding of interaction between inputs and product quality attributes together with a corresponding control strategy can lead to identification of ECs that are focused on the most important input parameters along with outputs, as appropriate.
  
  - In certain cases, applying knowledge from a data-rich environment enables a **performance based approach** in which ECs could be primarily focused on control of unit operation outputs rather than process inputs (e.g., process parameters and material attributes).
Manufacturing Process

• ECs proposed in a manufacturing process description should be those inputs (e.g., process parameters, material attributes) and outputs (that may include in-process controls) necessary to assure product quality.

• These should include critical process parameters (CPPs), and key process parameters (KPPs)

• KPP - parameters that may not be directly linked to CQAs, but need to be tightly controlled to assure process consistency as it relates to product quality.

  – A suitably detailed description of the manufacturing process is important to provide a clear understanding of what is and is not necessary to assure product quality.

  – This guidance should not lead to a less detailed description of the manufacturing process in Module 3 of the CTD.
ECs for Manufacturing Processes

Is the process parameter either a CPP or a KPP?

Yes

It is an EC

Reporting categories for changes to EC

What is the level of potential risk associated with the proposed change, taking into consideration the Control Strategy?

High

Prior Approval

Moderate to low

Notification

No

It is not an EC

Not Reported

3

4

5
### ECs for Manufacturing Processes (Bio)

The table below summarizes the acceptable ranges and reporting categories for various inputs and outputs during the production bioreactor process. **White boxes** indicate ECs, while **grey ones** indicate non-ECs.

<table>
<thead>
<tr>
<th>Unit operation</th>
<th>Input/Output</th>
<th>Acceptable ranges and reporting categories</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Production bioreactor (XXX L)</td>
<td>Inoculum Cell Density</td>
<td>Parameter Based Approach: 4.0-6.0 x10^5 cells/mL KPP (NM)</td>
<td><strong>Enhanced Approach:</strong> 2.0-8.0 x10^5 cells/mL PP</td>
</tr>
<tr>
<td></td>
<td>Temperature</td>
<td>Parameter Based Approach: 37.0 – 38.0°C CPP (PA)</td>
<td><strong>Enhanced Approach:</strong> 36.0 – 39.0°C CPP (NM)</td>
</tr>
<tr>
<td></td>
<td>Input Z</td>
<td>Parameter Based Approach: ### CPP (PA)</td>
<td><strong>Enhanced Approach:</strong> ### CPP (PA)</td>
</tr>
<tr>
<td></td>
<td>Viability at harvest</td>
<td>Parameter Based Approach: ≥ 70% IPC (NM)</td>
<td><strong>Enhanced Approach:</strong> ≥ 50% IPC inline automatic counting (NM)</td>
</tr>
<tr>
<td></td>
<td>Titer</td>
<td>Parameter Based Approach: ≥ 4.0 g/L IPC (NM)</td>
<td><strong>Enhanced Approach:</strong> ≥ 4.0 g/L Predicted through process model</td>
</tr>
<tr>
<td></td>
<td>G0-F oligosaccharide (CQA)</td>
<td>Parameter Based Approach: Included in release specification</td>
<td><strong>Enhanced Approach:</strong> Included in release specification</td>
</tr>
<tr>
<td></td>
<td>Microbiological tests</td>
<td>Parameter Based Approach: ### IPC (PA)</td>
<td><strong>Enhanced Approach:</strong> ### IPC (PA)</td>
</tr>
</tbody>
</table>

**Enhanced Approach:**

- Similar DOEs as described for seed train step were performed. These studies showed that:
  - Temperature and input Z can impact CQAs (classified as CPP)
  - Inoculum cell density (tested at wider ranges than traditional parameter based approach) do not impact CQAs and process consistency.

*Downgraded reporting for Temperature is proposed (NM) because statistical models predict that when operating beyond the tested acceptable ranges, CQAs would remain within their acceptance criteria.*

**Performance Based Approach:**

- In addition to parameter based:
  - Outputs of this step were linked to subsequent steps
  - Inline tests are used to control outputs in a real time manner
  - Relevant inputs are monitored through Multivariate Statistical Process Control (MSPC) defining a process signature that is not considered EC.

*Inputs are adjusted realtime based on a model accounting for the inline measurements of outputs.*
Post Approval Change Management Protocols (PACMPs)

- A PACMP provides predictability and transparency in terms of the requirements and studies needed to implement a change.

- An approved PACMP needs to be maintained and assessed routinely:
  - ensure that the outcomes of the initial risk assessment are still valid
  - confirm that the control strategy continues to ensure that the product will be produced consistently following implementation of the change(s)

- The use of a PACMP is enabled through an effective PQS that incorporates quality risk management principles and an effective change management system.

- Whenever a CMC change is to be introduced under a PACMP regulatory requirements with respect to GMP compliance, and inspection or licensing status should be considered.
The PLCM document outlines the specific plan for product lifecycle management, includes key elements:

- Summary of Product Control Strategy
- Proposed ECs for the product
- Reporting category for making changes to approved ECs
- PACMPs to prospectively manage and implement one or more post-approval changes
- Post-approval CMC commitments

Use of a PLCM encourages prospective lifecycle management planning and facilitate regulatory assessment and inspection.

The PLCM document should be updated throughout the product lifecycle, as needed.
An effective PQS as established in ICH Q10 and in compliance with regional GMPs is the responsibility of a firm. Q12 does not require a specific inspection assessing the state of the PQS before the principles can be used. In the event that the PQS is found not to be compliant, it may result in restrictions on the ability to utilise flexibility in this guideline. Consistent with the basic requirements of ICH Q10, an effective change management system is necessary for implementation of this guideline.

Relationship between Regulatory Assessment and Inspection
- Regulatory assessment and inspection are complementary activities
- Communication between assessors and inspectors can facilitate regulatory review of a specific product submission
Q12 includes tools for changes to marketed products

- **Structured Approach to Analytical Procedure Changes**
  - Incentivizes structured implementation of equivalent analytical procedures that are fit for purpose (some complex products and methods would be out of scope)
  - Specific criteria are defined for changes to analytical procedures used to test marketed products is described
  - If followed, the analytical procedure change can be made with immediate or other post-implementation notification, as appropriate

- **Data Requirements to Support CMC Changes**
  - Stability Data Approaches to Support the Evaluation of CMC Change
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