Industry Perspective on ICH Q12 Progress and Direction

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ICH Q12 - The Challenge

• How to create a transformational guideline to enable effective lifecycle management of medicines

• Maintain sufficient regulatory oversight

• And bring benefit to patients
How can we achieve this?

- Transfer more responsibility to manufacturers who have demonstrated enhanced product knowledge & control who are able to implement this effectively at the sites
  - Reduce the number and speed up the implementation of post approval changes
  - Focus on those areas with most potential to impact patients

- More consistency in how post approval changes are assessed within ICH region

- A guideline that can support global regulatory convergence
The role of Established Conditions in achieving this

• EC may vary in their level of detail and change category based on a sponsor’s product and/or process understanding, extent of characterization and risks/impact tied to product quality and performance

  – E.g. Established Conditions, in certain cases, could simply be the method principle and the performance characteristics of a monitoring or testing method
Background

• Many “details” are provided in regulatory dossier to enhance understanding of the manufacturing process and/or control strategy. Maintenance of those “details” is a burden.

• EU Module 3 is the legally binding section of the dossier

• Examples of a recent variations for a drug substance (small molecule):
  – Change in starting material quantity: from 200-235 kg’ to ‘195-235kg’
  – Use of lower concentration of NaOH leading to higher volume loaded into the reaction (stoichiometry respected)
  – Lower amount of class 2 solvent used (from ‘2200-5650 kg’ to ‘2000-5650 kg’)
  – Stirring time changed from ‘approximately 2 hours’ to ‘at least 1 hour’ based on process experience (completion of reaction)

• Agreement on established conditions (EC) (to be maintained proactively) and non-established conditions (non-EC) should help to focus on change(s) with a potential quality impact.
  – Non-EC would not be subject to proactive reporting to Health Authorities (HA) as stand alone
Difficult areas to be resolved

• Where more of the “details” are not considered EC how will this be managed in the dossier?
  – If included in EC containing granules Mod 3 they may still need to be maintained?
  – If not included in EC containing granules will HAs be comfortable with this?
• What is the current status of the process?
• What are the current analytical methods?

• Although these are low risk aspects of process and methods they are important to ensure patient safety
  – Surveillance of product in the market
  – Routine and non-routine investigation of site activities
## Post-Approval Change Reporting Categories

<table>
<thead>
<tr>
<th>Impact on quality</th>
<th>Japan</th>
<th>US</th>
<th>EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Partial change Application (approval of variation)</td>
<td>Major change (Prior approval supplement)</td>
<td>Type II variation (Application for approval of variation)</td>
</tr>
<tr>
<td>Moderate</td>
<td>Minor change Notification (within 30 days after implementation or shipping)</td>
<td>Moderate change 1)Supplement-changes being effected (CBE) in 30 days</td>
<td>Type IB variation (Notification before implementation and MAHs must wait a period of 30 days)</td>
</tr>
<tr>
<td></td>
<td>2)Supplement-changes being effected (CBE)</td>
<td></td>
<td>Type IA&lt;sub&gt;IN&lt;/sub&gt; variation (Immediate notification)</td>
</tr>
<tr>
<td>Low</td>
<td>SOP (Under GMP change control)</td>
<td>Minor change (Annual report)</td>
<td>Type IA variation (Notification within 12 months after implementation)</td>
</tr>
</tbody>
</table>

### ECs/AMs
- Japan
- US/EU

**Questions**
- Will we end up in the same place regionally?
  - Different notification Categories & legal frameworks
- Will it make a difference in practice?
EC considerations – Identification and location

• Clear and unambiguous identification of established conditions (EC) and consequently things that are not established conditions in the dossier is critical.

• ICH Q12 will provide guidance and multiple examples on how to identify and present the ECs in the dossier.

• Separate annex is proposed as an example based on draft FDA guidance (Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products).

• Location: part of CTD Module 2 and/or 3 (tbd, e.g. QOS or 3.2.A), as all ICH regions should apply the same rules. This is critical for Industry to have as much as possible one single set of EC and in all ICH regions.

• For the majority of modules, identification of EC should not be problematic. Difficulties are mainly expected for S.2.2, S.2.3-S.4.2, P.3.3-P.5.2 or 3.2.A.1.
<table>
<thead>
<tr>
<th>Must Have ECs</th>
<th>Opportunity to Negotiate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name/structure/composition</td>
<td></td>
</tr>
<tr>
<td>Manufacturing site (DS, DP, packaging) and testing sites</td>
<td></td>
</tr>
<tr>
<td>Specifications (DS, DP, excipients, reference material)</td>
<td>Tests and acceptance criteria and elements of the procedure</td>
</tr>
<tr>
<td>Unit operations and their sequence</td>
<td></td>
</tr>
<tr>
<td>Source material including specifications and storage conditions</td>
<td></td>
</tr>
<tr>
<td>Raw material of biologic origin including specifications</td>
<td>Other raw materials and specifications</td>
</tr>
<tr>
<td>Generation of a working cell bank from a master</td>
<td></td>
</tr>
<tr>
<td>In-process testing linked to a rejection limit</td>
<td>other in-process controls</td>
</tr>
<tr>
<td>Process parameters</td>
<td>Based on development approaches (traditional, enhanced…)</td>
</tr>
</tbody>
</table>

- Change category for EC by default would follow regional norms
- Opportunity to propose lower reporting category
  - Justification in application file and/or through a PACMP
Case Study: Raw Materials

- High administrative burden for HAs and MAHs due to submission of every (minor) change in the control of raw materials

Regulatory framework

High level of detail required for initial application assessment
No differentiation between critical and non-critical raw materials
EU: for some changes same reporting categories for DS, starting materials, intermediates and reagents → same data requirements

Criticality of control is different for e.g. starting materials, media for biotech processes vs. standard reagents
RM manufacturer/supplier often slightly change RM specifications
Large number of (minor) changes with no impact on quality

Regulatory burden
Definition of “Established Conditions”

- By applying the tools of ICH Q12 regulatory binding information will be defined more clearly in the quality part of the dossier

**Established Condition**
- Quality control of „critical“ raw materials
- Definition based on risk assessment, process and product understanding
- Regulatory binding
- Change management via established reporting categories or reduced categorisation proposed

**Not Established Condition**
- Additional, supportive information
- Quality control control of „non-critical“ raw materials
- Definition based on risk assessment, process and product understanding
- Not regulatory binding
- Change management within PQS

- Overall less regulatory burden for low impact changes in raw material controls
## Changes in Specification for Raw Materials Defined as “Non-critical” → i.e. not Established Condition

<table>
<thead>
<tr>
<th>Change</th>
<th>Classification acc. to applied ICH Q12 tools</th>
<th>EU classification acc. to current procedure</th>
<th>US classification acc. to current procedure</th>
<th>Canadian classification acc. to current procedure</th>
<th>JP classification acc. to current procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Octanol</td>
<td>Managed within PQS</td>
<td>Type IB by default B.I.b.1 z) Change in specification parameters and/or limits of a reagent</td>
<td>Annual report</td>
<td>Notifiable change submission (annual report only if change within approved limits)</td>
<td>PCA</td>
</tr>
<tr>
<td>Refractive index n 20/D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.4291 – 1.4300 to 1.4285 – 1.4303 (widened limit)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-Butanol</td>
<td>Managed within PQS</td>
<td>Type IA B.I.b.1 d) Deletion of a non-significant specification parameter</td>
<td>Annual report</td>
<td>Annual report</td>
<td>PCA</td>
</tr>
<tr>
<td>Deletion of test parameter „Odor – alcoholic, irritating”</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2- Butanol</td>
<td>Managed within PQS</td>
<td>Type IA B.I.b.1 b) Tightening of specification limits</td>
<td>Annual report</td>
<td>Annual report</td>
<td>Minor change notification</td>
</tr>
<tr>
<td>Residue on evaporation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NMT 10 mg to NMT 9 mg (tightening of limit)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
Scope of the case study - Control of fragments

- Antibody fragments (Fab, Fab/c, light chain, heavy chain, and others) are identified for this case study as Critical Quality Attributes (CQA).
- Case study on lifecycle of capillary electrophoresis sodium dodecyl sulfate (CE-SDS) under non-reducing conditions:
  - Option 3: method changes follow existing regulatory pathways (e.g. regulatory submission)
  - Option 2: method changes within a given technology (e.g. vendor, operating conditions, reagents, instruments…) will be performed in accordance to agreed criteria
  - Option 1: enhanced method development
    - changes across technologies (e.g. microchip electrophoresis, mass spectrometry, chromatography, AUC…) will be performed in accordance to agreed criteria/preapproved protocols.
Case study 2 - Key concepts

• Method description and validation will be submitted in all cases
• Different options define the extent of information that will be part of EC
  – EC option 1: method capability / performance commitment
  – EC option 2: capability performance commitment for a specified technology
  – EC option 3: method description (including operating conditions)
• Method changes:
  – Amount of information will be the same for all 3 options at the time of implementation
  – Difference in availability sequence and timing (i.e. pre or post approval)
    • Frontloading of lifecycle relevant information for option 1 and 2
    • Use of agreed criteria or protocols without reporting of implementation for option 1 and 2
## EC for control of fragments

<table>
<thead>
<tr>
<th></th>
<th>Option 1</th>
<th>Option 2</th>
<th>Option 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Method Description</strong></td>
<td>Analytical target profile: capability to measure fragments</td>
<td>Analytical target profile restricted to a technology: capability to measure fragments with CE</td>
<td>Detailed description</td>
</tr>
</tbody>
</table>
| **Development approach** | - Method Operable Design Region  
- Risk analysis (e.g. structured method factor analysis) | Targeted development, dependent of risk assessment | Classical       |
| **Predefined assay comparability protocol** | - Acceptance criteria aligned with the claim  
- Study design (e.g. number and type of samples…)  
- Stability indicating property  
- Characterization of signals including use of orthogonal methods | - Acceptance criteria aligned with the claim  
- Study design (e.g. number and type of samples…)  
- Stability indicating property | Not applicable |
| **Claim / Performance verification** | yes | yes | none |
# EC for control of fragments (2)

<table>
<thead>
<tr>
<th></th>
<th>Option 1</th>
<th>Option 2</th>
<th>Option 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Technology</strong></td>
<td>None*</td>
<td>- Capillary Electrophoresis</td>
<td>- Capillary Electrophoresis</td>
</tr>
<tr>
<td><strong>Instrument / Critical Material</strong></td>
<td>None*</td>
<td>None*</td>
<td>- Capillary system manufacturer X, type Y</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Detection mode</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Capillary</td>
</tr>
<tr>
<td><strong>Conditions</strong></td>
<td>None*</td>
<td>None*</td>
<td>Comprehensive description (e.g. Inject voltage, Injection duration, sample preparation, system operating conditions …)</td>
</tr>
<tr>
<td><strong>Buffers / Critical Reagents (EC)</strong></td>
<td>None*</td>
<td>None*</td>
<td>Comprehensive description (e.g. sodium bicarbonate, pH)</td>
</tr>
</tbody>
</table>

* Information equivalent as the one presented in option 3 would be presented in the filing as non-EC
Summary
What would success for ECs look like?

• ECs based on science
  – Aspire that output could be achieved for aspect of the process or controls in the future
  – Reduce the level of detail of ECs within the dossier
• More consistency in change categories across the regions
  – Shift in balance of risk transferred to MAH
• Focus regulatory compliance activities on areas with potential to impact patients
  – Clear, simplified and better managed
• Legacy products
  – Use understanding of “negotiable” ECs to enable more do and tell
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