Update on the Regulatory Considerations of Pharmaceutical Product Lifecycle Management (ICH Q12) from a Health Authority Perspective

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Established Conditions (EC)

Established Conditions are legally binding information (or approved matters) considered necessary to assure product quality.

Established Conditions are contained in a regulatory submission, submitted by the applicant, and approved, as necessary, by the regulatory authority. Established Conditions may be specifically proposed in a submission or they may be implicit based on existing regulation and guidance.

As a consequence, any change to Established Conditions necessitates a submission to the regulatory authority that is consistent with regional regulations or guidance; or as agreed upon during review and approval of the marketing application.
The EC chapter includes a list of “implicit” (i.e., “default/must have”) ECs & supportive info

<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.S</td>
<td>DRUG SUBSTANCE</td>
<td>There are implicit Established Conditions found in an application that can be linked to CTD sections found in ICH M4Q, however, only certain sections of the CTD contain Established Conditions. These implicit Established Conditions may be defined and managed consistent with regional regulations and guidance. Table 1 illustrates the sections where these implicit Established Conditions are generally found.</td>
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<tr>
<td>3.2.S.1</td>
<td>General Information</td>
<td>Supportive information</td>
</tr>
<tr>
<td>3.2.S.1.1</td>
<td>Nomenclature</td>
<td></td>
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<tr>
<td>3.2.S.1.2</td>
<td>Structure</td>
<td></td>
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<tr>
<td>3.2.S.1.3</td>
<td>General properties</td>
<td>Supportive information</td>
</tr>
<tr>
<td>3.2.S.2</td>
<td>Manufacture</td>
<td></td>
</tr>
<tr>
<td>3.2.S.2.1</td>
<td>Manufacturer(s)</td>
<td>Drug Substance Manufacturing Site (including testing)</td>
</tr>
</tbody>
</table>
| 3.2.S.2.2   | Description of manufacturing process and process controls | Individual unit operations and their sequence in the manufacturing process
For levels/details of Established Conditions for individual unit operations, input and output Reference is made to Section 3.2.3.2 – Identification of processes
Raw materials/reegens/solvent/critical controls
Source of materials (e.g. cell and seed source, raw materials) and |

NOTE: Additional granularity may be envisioned depending on risks, knowledge/understanding, etc.
Identification of Established Conditions for Manufacturing Processes

- The extent of Established Conditions will vary based on a number of factors, including product and process understanding, characterisation, and the firm’s development approach.

- Three approaches with regard to the level of EC detail are envisioned:
  
  - A **parameter based development** approach, not necessarily studying or understanding the relationship between inputs and resulting quality attributes, will include an extensive number of input parameters (e.g., process parameters and materials) along with outputs (including in-process controls).
  
  - An **increased understanding of interaction between inputs and product quality attributes** together with a complementary control strategy can lead to identification of Established Conditions that are focused on the most relevant input parameters (e.g. process parameters and materials) along with outputs, as appropriate.
  
  - In certain cases, (i.e., a **performance based** approach), Established Conditions could be solely focused on the control of intended outputs rather than process...
Identifying ECs for Manufacturing Processes

- As part of the identification a criticality assessment of input parameters should be performed based on their impact on CQAs (ICH Q8R2):
  - Parameters that **have impact on CQAs** (i.e., CPPs) are classified as Established Conditions.
  - Parameters for which the **impact on CQA cannot be reasonably ruled out** are classified as Established Conditions.
  - Parameters that **do not have impact on CQAs** and are only mentioned as supportive information are not classified as Established Conditions.
Changes to ECs for Manufacturing Processes

• Proposed reporting categories for changes to ECs should relate to the ability of the control strategy to mitigate their associated risks.
  – ECs related to **high severity of harm if control fails** (e.g., associated with viral safety and sterility), or **associated to high risks** are categorised as “prior-approval.” The “prior-approval” category is further commensurate with the potential risk based on regional considerations (i.e., Type II/PAS, vs Type 1B/CBE-30)
  – ECs **associated to moderate or low risks** are categorised as “notification” (e.g., Type 1A, 1Ain, CBE-0, Annual Report, MCN)

• Information regarding product-specific post-approval change activities, such as post change monitoring, may be provided as supporting information to aid in the determination of ECs and reporting category.
Updating ECs

• As experience with manufacturing of the product is gained through
  – continued product and process monitoring (e.g., PPPQMS concepts found in ICH Q10),
  – knowledge gained over the product lifecycle,
  it may be appropriate to update ECs (add, modify, subtract)

• Approaches to revise approved Established Conditions include:
  – Submit an appropriate post-approval regulatory submission describing and justifying the proposed change in ECs.
  – Submit a PACMP, in the original marketing application or as part of a post-approval submission, describing a change in ECs and how the change will be justified and reported.
Next Steps for EC Chapter

• Current version of Q12 under review by EWG constituencies to identify any significant issues
  – Interim meeting of EWG in April to discuss and address “showstopper” comments

• For EC chapter
  – EWG has developed several examples to help vet the text
  – Deciding which examples to include in the Q12 document
Product Specific Lifecycle Management Strategy (PSLCM)

- Intended as means to communicate the lifecycle strategy that will be used to manage the product post approval to the regulator.

- Key elements to be included in a regulatory document:
  - List of Established Conditions
    - Note: Change in ECs will trigger an update of PSLCM document
  - Reporting categories
  - PACMPs (post approval change management protocols)
  - Post-approval CMC commitments

- Anticipated Post-approval Changes Section
  - Optional
    - May identify changes anticipated for the immediate post-approval period (e.g., addition of a new supplier, change in manufacturing process or equipment to increase capacity)

- Example of PSLCM table to be included in future version
Pharmaceutical Quality System

- Considerably revised to avoid redundancy with Q10, while emphasizing the “best practices” of change management process
- Detailed recommendations provided for an effective change management system, including post-approval verification to avoid unintended consequences
- PQS topics covered in Q12 include: Change Management System, Management Review, use of Knowledge in Change management, Outsourcing and PQS, and......
- Relationship between Assessment and Inspection
  - Emphasizes that inspection information be made available to assessors, and dossier information be made available to inspectors
  - Allows for different regional approaches regarding how this information is communicated between assessors and inspectors
Next Steps

• April 2017 - Interim Meeting will be hosted by FDA to work through significant comments
• May/June 2017 - 5-day EWG Meeting to finalize the document and reach Step 1/2 Technical Document
Thank You!

Acknowledgments:

– Q12 Expert Working Group
– FDA Q12 Team – Bob Iser, Ingrid Markovic, Mahesh Ramanadham