Sharing the learnings from a Q12 case study:
The challenge and benefit of established conditions

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How we started our journey concerning established conditions and how we defined them for the first time for a biologic

What we learned out of it, which challenges we faced and which benefits we see in this concept

Why we as a company want to apply ICH Q12 and how our journey will continue
Starting the EC journey for a biologic

- **Product (biologic) marketed** since 2013

- **Proposed Established Conditions (ECs) acc. to ICH Q12:**
  - Combination of input and output parameters necessary to ensure product quality
  - Based on enhanced understanding of process parameter impact and prior knowledge (wherever applicable)

- **Product Lifecycle Management (PLCM) document, including EC definition and reporting categories, approved by U.S. FDA** (prior approval supplement, September 2020)
Selected CMC sections in scope of the EC definition

Module 2
- Quality Overall Summary

Module 3 sections containing ECs
- e.g., S.2.2/P.3.3, S.2.4/P.3.4, S.4.1/P.5.1, S.5 etc.

Module 3 sections containing only supportive information
- e.g., S.2.5/P.3.5, S.2.6/P.2.3, S.4.3/P.5.3, etc.

Product Lifecycle Management Document
- Section R (ECs & reporting categories, commitments)

Product Lifecycle Management Document - Addendum
- Section R (supportive information including justifications and non-ECs)
ECs were defined based on these principles

- Critical process parameters (manufacturing process) were considered ECs.
- Process parameters (e.g., non-critical process parameters) were assessed for their potential risk to impact critical quality attributes.
- Several non-critical process parameters have been identified as ECs.
- Differentiation between ECs and non-ECs was based on impact on product quality within and beyond approved range.
PLCM is a ‘living document’ used during lifecycle

- **Reporting categories** defined in Product Lifecycle Management (PLCM) document are default reporting categories.

- **Tightening of approved ranges** handled in pharmaceutical quality system only (if not implemented due to a quality issue).

- If multiple parameters are changed, associated risk level will be assessed → reporting at least at level of the highest parameter in scope of this change.
Overview of ECs & non-ECs - Manufacturing Process

- **Defined ECs (excerpt):**
  - Sequence of unit operations in manufacturing process
  - Majority of acceptable ranges for process parameters
  - Drug product batch size and batch composition

- **Defined non-ECs (excerpt):**
  - Harvest process parameter ranges
  - Selected buffers and corresponding volume used during purification process
  - Storage solution volume chromatography steps
Overview of ECs & non-ECs - In-process controls

Defined ECs (excerpts):
- Testing parameter
- Shift or broadening of:
  - Action limits for in-process control tests
  - Acceptance criteria for in-process control tests

Defined non-ECs (excerpts):
- Tightening of all action limits or acceptance criteria
- Shift of target for drug product fill weight checks
Closer look: Examples purification process (1 of 2)

- Critical process parameter:
  - low pH and incubation time at virus inactivation step: high risk (PAS) → ECs

- Non-critical process parameter:
  - Composition conditioning buffer for product composition: high risk (PAS) → ECs
  - Bed height and flow rate chromatography steps: moderate risk (CBE-30) → ECs
  - Column volume for regeneration: low risk (AR) → non-ECs
  - Storage solution volume chromatography steps: no risk (PQS only) → non-ECs

PAS = prior approval supplement, CBE-30 = changes being effected in 30 days, AR = annual report, PQS = pharmaceutical quality system.
Closer look: Examples purification process (2 of 2)

- non-critical process parameter
- pooling step chromatography
- start of pooling
- change to lower limit of approved range
- high risk (PAS)
- end of pooling
- change to upper limit of approved range
- low risk (AR)
- change to upper limit of approved range
- low risk (AR)
- change to lower limit of approved range
- high risk (PAS)

ECs

PAS = prior approval supplement, AR = annual report.
Key benefits of ECs (as approved by U.S. FDA)

Definitions of ECs can
- lower the number of regulatory-relevant submissions to health authorities
- give clarity regarding the regulatory filing categories
- enable more predictable and efficient post-approval change management

PAS = prior approval supplement, CBE-30 = changes being effected in 30 days, AR = annual report.
Key learnings & challenges of the first EC submission

- Overall **positive experience**, U.S. FDA was engaged and willing to gain understanding (verbal interactions helpful)

- **General strategy and documentation** to define ECs **accepted** by U.S. FDA

- Information Requests focused on **reporting categories** (rather than ECs vs. non-ECs)

- **Modulating reporting** in accordance with **magnitude of potential impact** was challenging
Key learnings & challenges of the first EC submission (continued)

- **Consistency**
  - Within agency
  - Across all agencies (harmonization)
  - Across product types

- **Global implementation** of ICH Q12 takes time

- How to build **trust** (especially regarding the **pharmaceutical quality system**) as basis for ICH Q12 deployment?
Why do we want to use ICH Q12?

Current state

Huge effort for post-approval changes for industry and regulators

Future state

ICH Q12 gives framework for post-approval CMC changes

Managing post-approval CMC changes in a more predictable and efficient manner
The EC journey will continue...

First EC definitions approved by U.S. FDA (individual products)

Uniform adoption and implementation of ICH Q12 in all ICH member states

Engagement with further health authorities on EC definitions for Roche products
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Doing now what patients need next