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

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Bianca Omasreiter, Ph.D., Pharma Technical Regulatory, Roche

Outline

- ★ 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

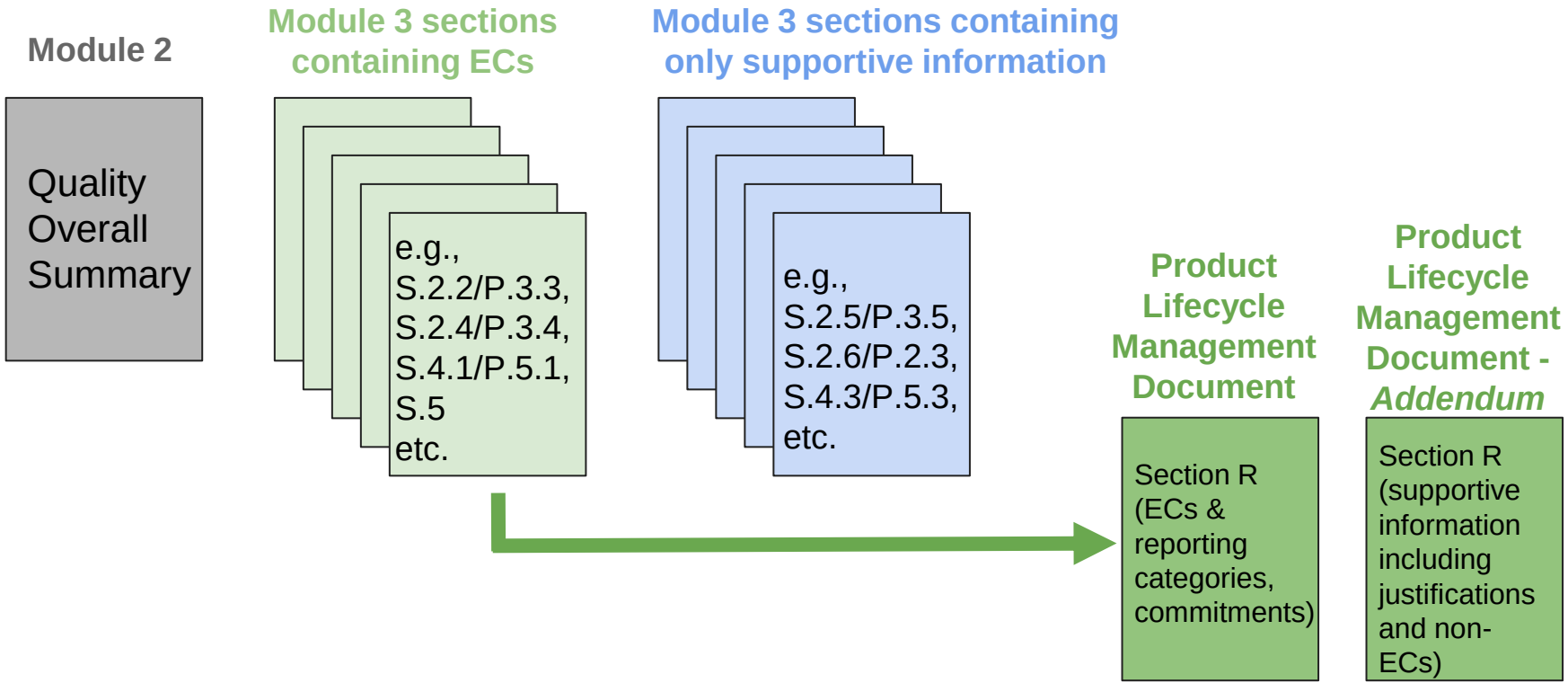
Starting the EC journey for a biologic

- **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



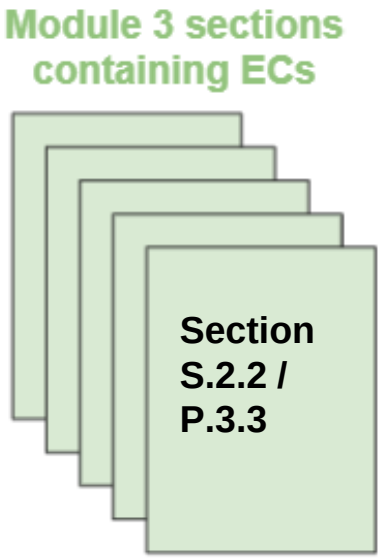
ECs were defined based on these principles

- **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

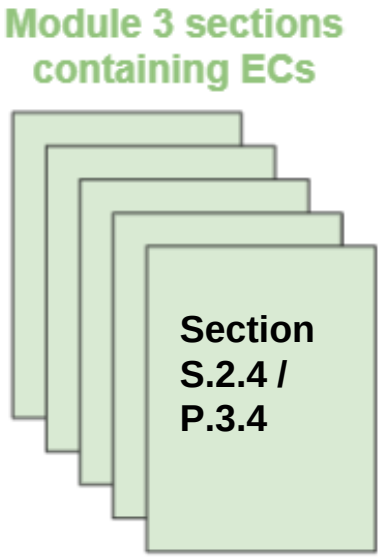
Overview of ECs & non-ECs - Manufacturing Process



- **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



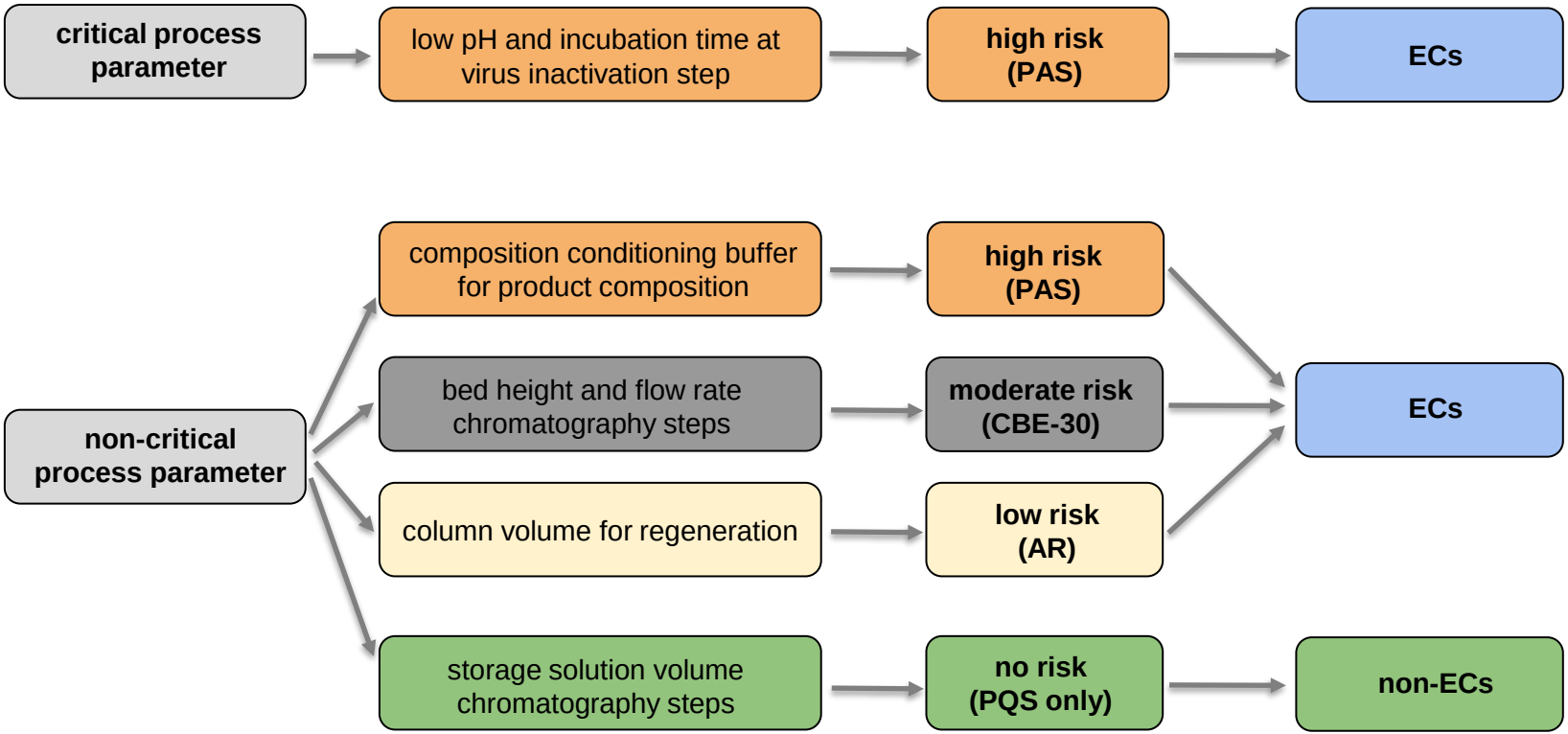
Defined ECs (excerpt):

- Testing parameter
- Shift or broadening of:
  - Action limits for in-process control tests
  - Acceptance criteria for in-process control tests

Defined non-ECs (excerpt):

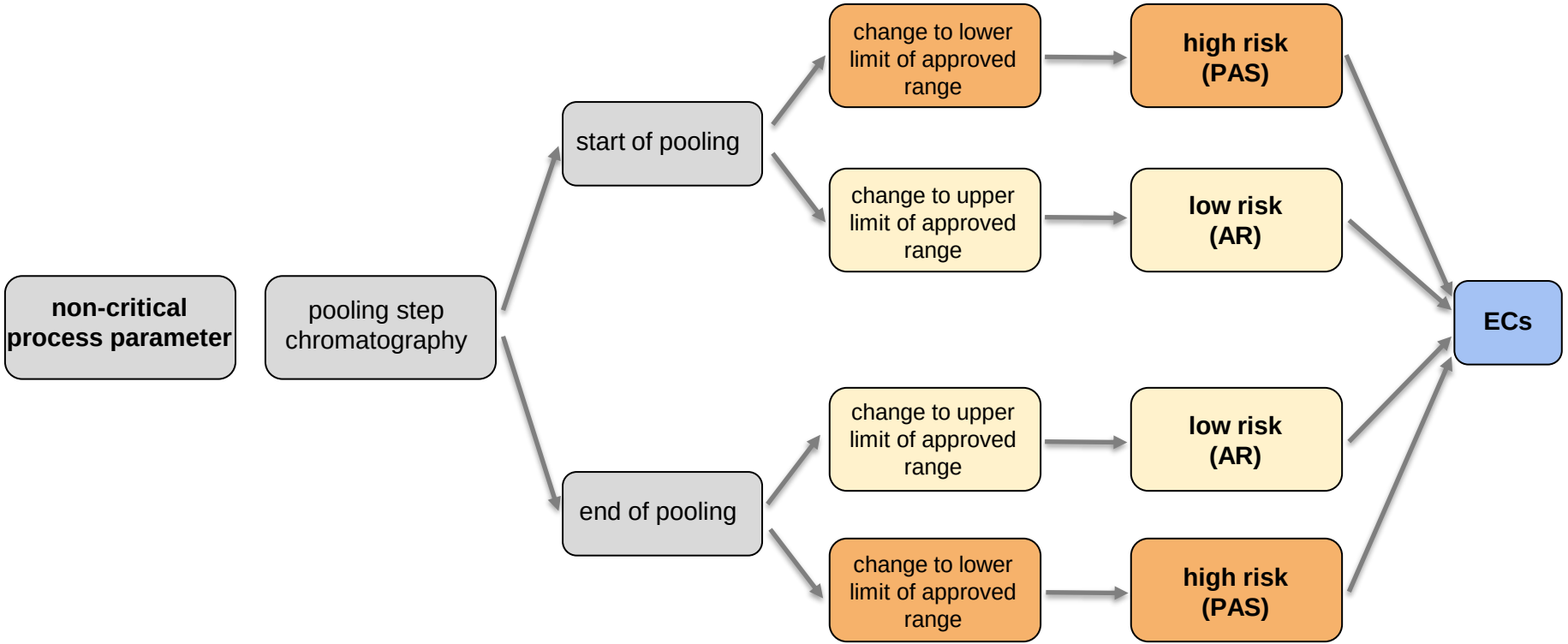
- Tightening of all action limits or acceptance criteria
- Shift of target for drug product fill weight checks

Closer look: Examples purification process (1 of 2)



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)



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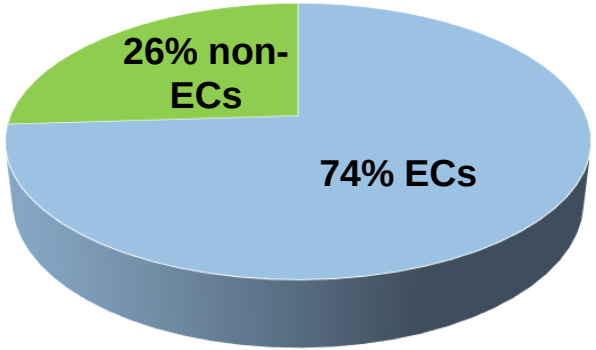
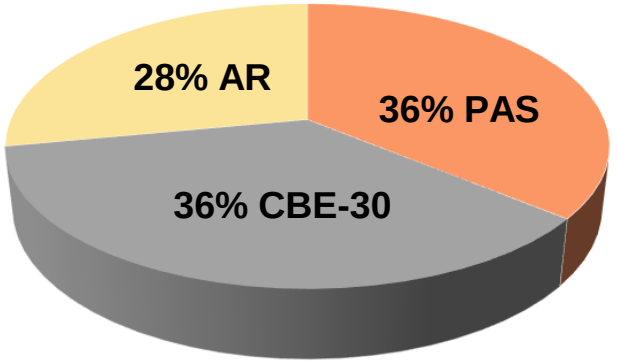
Key benefits of ECs (as approved by U.S. FDA)





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

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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

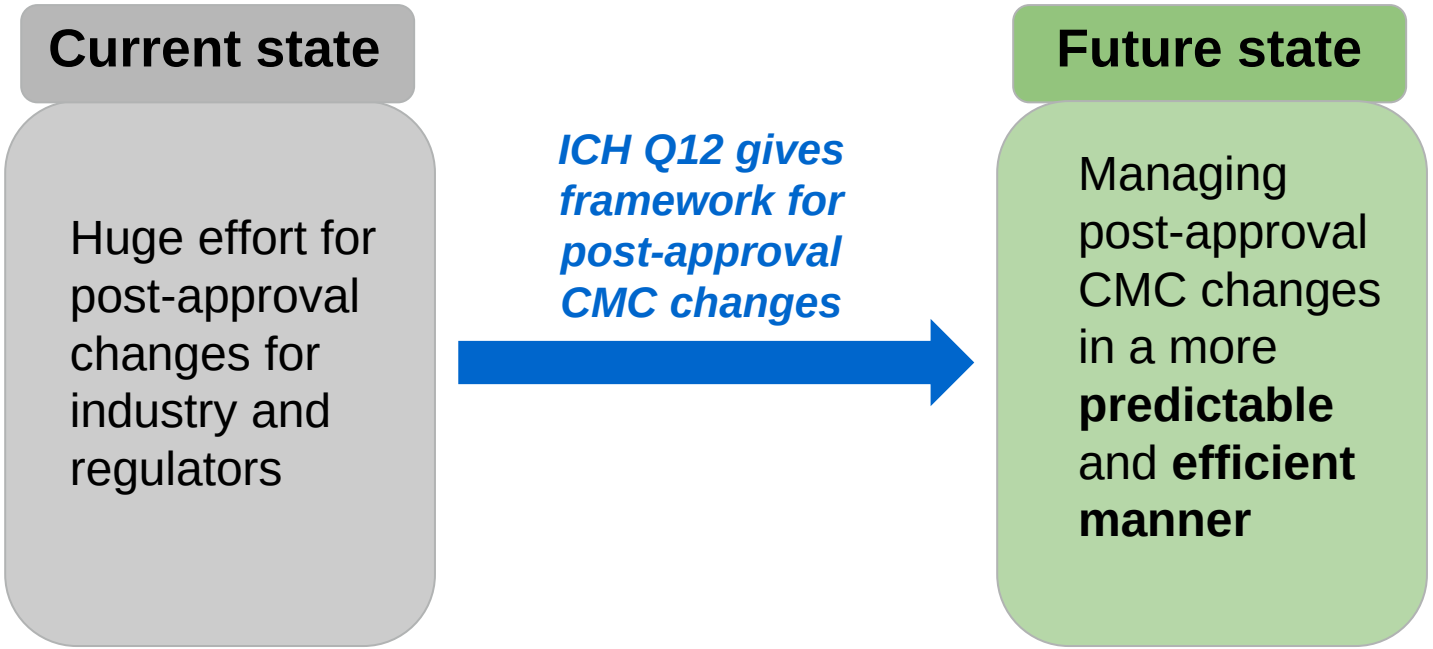
Key learnings & challenges of the first EC submission *(continued)*

- **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?



The EC journey will continue...

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

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

Engagement with further health authorities on EC definitions for Roche products

Acknowledgements

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Doing now what patients need next