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Experiences with implementing ICH Q12 ECs and PLCM

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Established Conditions (ECs) and the Product Lifecycle Management Document (PLCM)

Established Conditions

ECs are legally binding information considered necessary to assure product quality. *As a consequence, any change to ECs necessitates a submission to the regulatory authority (ICH Q12)*

PLCM

*The **PLCM document serves as a central repository for the ECs** and the associated reporting category for changes made to ECs. The document also captures how a product will be managed during the commercial phase of the lifecycle including relevant post-approval CMC commitments and PACMPs*

Scope of Q12 implementation & BLA review experiences

- **Scope of Q12 implementation**
  - Focus on Established Conditions and PLCM
  - Q12 submission specific to DS manufacturing process (3.2.S.2.2 & 3.2.S.2.4) in the US market
- Utilization of **enhanced process development**, leveraging from prior and platform knowledge
- **No previous interaction with FDA on Q12** (e.g. FDA‘s pilot program, scientific advice)
- **Review of Biologics License Application (BLA) by FDA**
  - Majority of development requests received early in the process (within the first 2-5 months)
  - Majority of Established Condition (EC) requests received rather late in the process
  - Clear communication from FDA regarding expectations for reporting categories, mostly accompanied by explanations on their assessment of risk
  - 7 updates made to the PLCM for ECs (with 4 updates being triggered by control strategy requests); additional updates for protocols and post-approval CMC commitments
  - 18 information requests for upgrading EC reporting catagories, 3 requests on general EC section

PLCM

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Chapter on Established Conditions

- General section addressing scope, change management (link to PQS) and the mapping of Q12 reporting categories to FDA‘s reporting categories
- List of ECs, one table/page per unit operation (plus table for general non-parameter ECs)

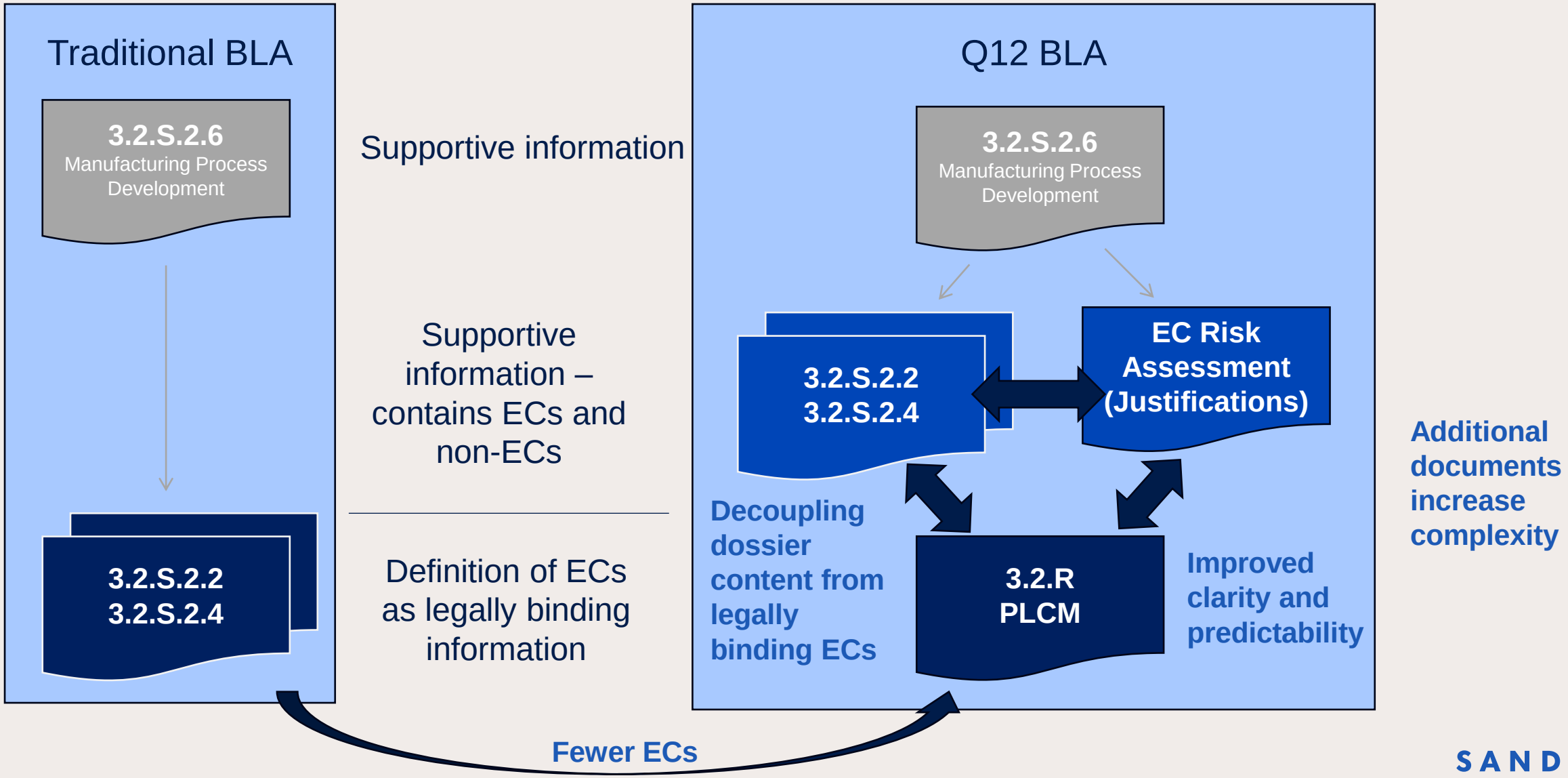
Chapter on „Protocols“

- Tabular overview referencing dossier module with reporting category for the data package
- Contains PACMP and other protocols (e.g. related to cell bank, reference standard, concurrent resin lifetime validation, reprocessing,...)

Chapter on Post-Approval CMC Commitments

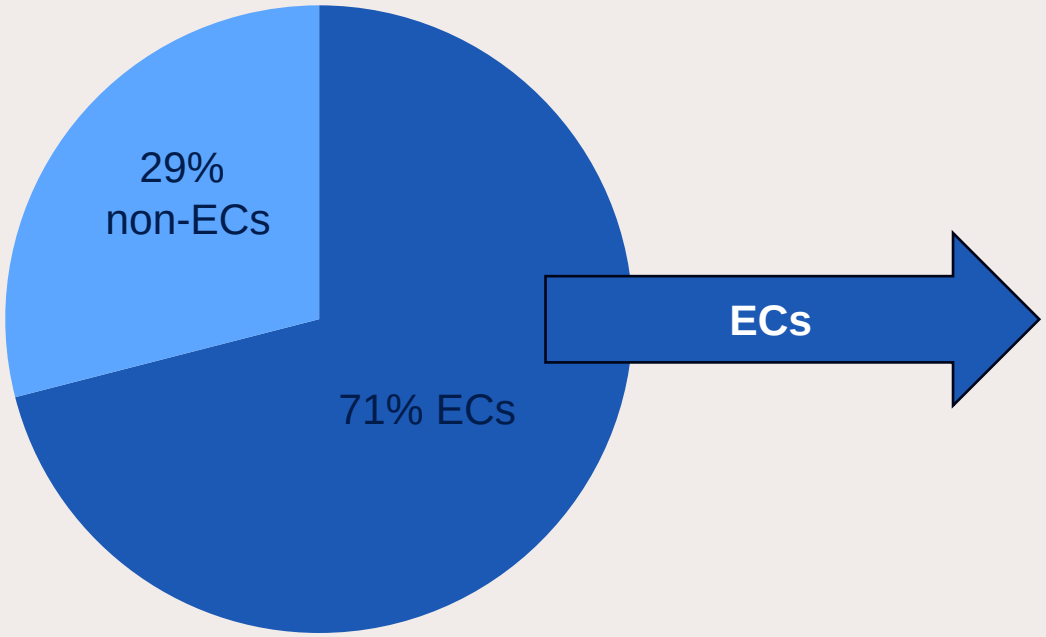
- Tabular overview with description of study/commitment, reporting category, sequence and submission timeline
- Populated during BLA review

Documentation Structure in the BLA



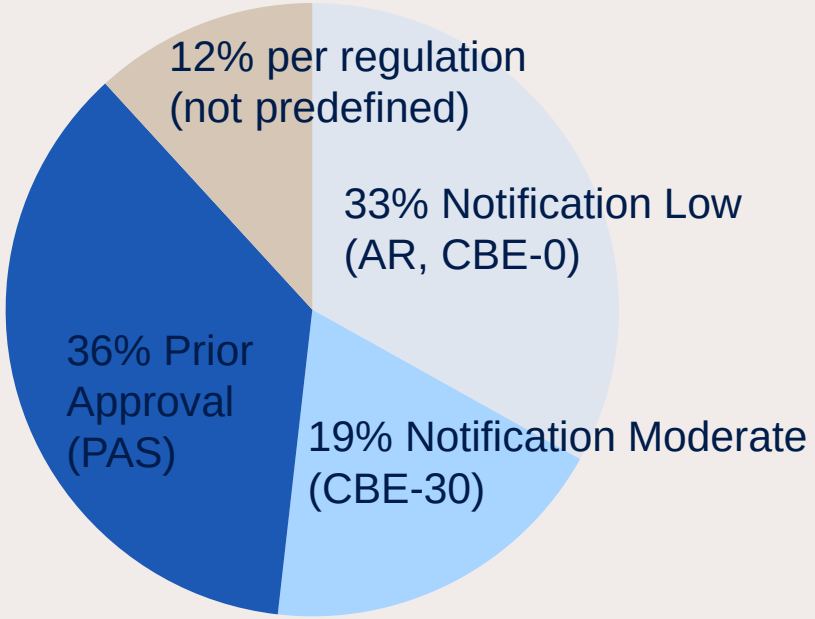
Agreed reporting categories provide transparency and predictability

ECs vs non-ECs for the assessed parameters



ECs

Reporting Categories for the ECs



- 15% increase in the number of assessed parameters* (vs traditional 3.2.S.2.2 and 3.2.S.2.4 submission)
- 19% reduction in the number of ECs (vs parameters* in a traditional 3.2.S.2.2 and 3.2.S.2.4)
- Significant number of ECs in low reporting category, but also a substantial number of ECs predefined as Prior Approval

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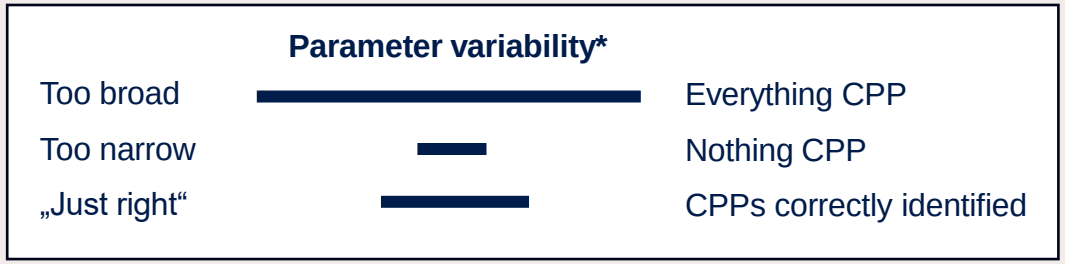
* Parameters include process parameters, IPCs & (descriptive) non-parameter ECs

What exactly is an EC? And what is a non-EC?

- **PLCM defines ECs only** – PLCM could not be used to define non-ECs
  - „Lowest risk“ parameters → non-ECs → not in PLCM
- **The parameter vs the limit** – what is the EC?
  - Can the e.g. lower limit for a parameter be a non-EC (lowest risk) despite the upper limit being an EC?
- **How to judge the impact on quality**
  - Very large (hypothetical) changes would almost always have an impact on quality → almost everything could become an EC (situation reminiscent of the CPP discussion from the Q8/Q11 implementation)



  - What is the role of data (that does not cover the change)?

- **Justification of lower risk ECs and non-ECs**: Typically in line with with ICH Q9 „Level of effort, formality and documentation [...] should be commensurate with the level of risk“
- **Performance indicators** (consistency) can be largely managed internally (e.g. test is EC, limit non-EC)

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* adapted from B. Rellahan SBE AccBio/QbD Conference Feb 2013 „Goldilocks Paradigm“

Take-aways

FDA has clear expectations for certain parameters

- For all other parameters, expectations may vary depending on the available data and justifications provided.
- Aligned with risk management principles outlined in ICH Q9 (effort is proportional to the associated risk)

Successful decoupling of dossier content from LCM relevance

Significant reduction in the number of ECs:

- Notable decrease in the overall number of ECs when compared to a conservative interpretation of sections 3.2.S.2.2 and 3.2.S.2.4. This reduction is particularly evident in the "tell, wait & do" ECs
- However, isolated changes to ECs of the DS process are not as frequent.

Enhanced predictability and transparency for future LCM:

- Consensus on categorizing certain changes as low-risk, which only require reporting in the annual report.
- On the other hand, notable number of predefined prior approval (PAS) ECs

Increased complexity during the review process

- The inclusion of ECs to the PLCM and the need for EC justifications have added complexity to the review process

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