Overview of January 2020 CASSS Sharing Science Solutions Workshop on Established Conditions

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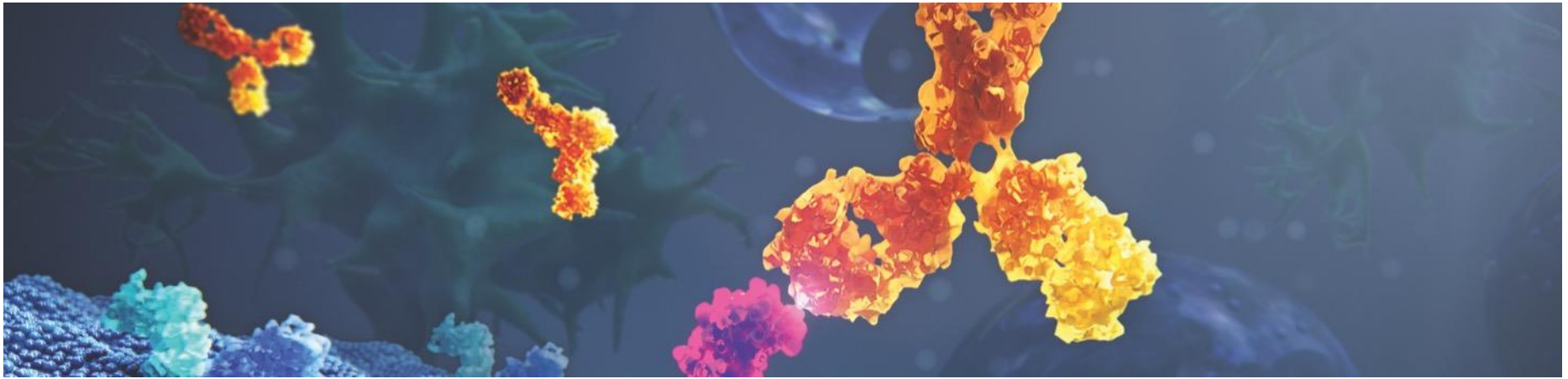


Overview

ICH Q12

- This guideline establishes a harmonized approach to defining which elements in an application are considered necessary to assure product quality and therefore would require a regulatory submission if changed post-approval. These elements are being defined in this guideline as “Established Conditions for Manufacturing and Control” (referred to as ECs throughout this guideline)

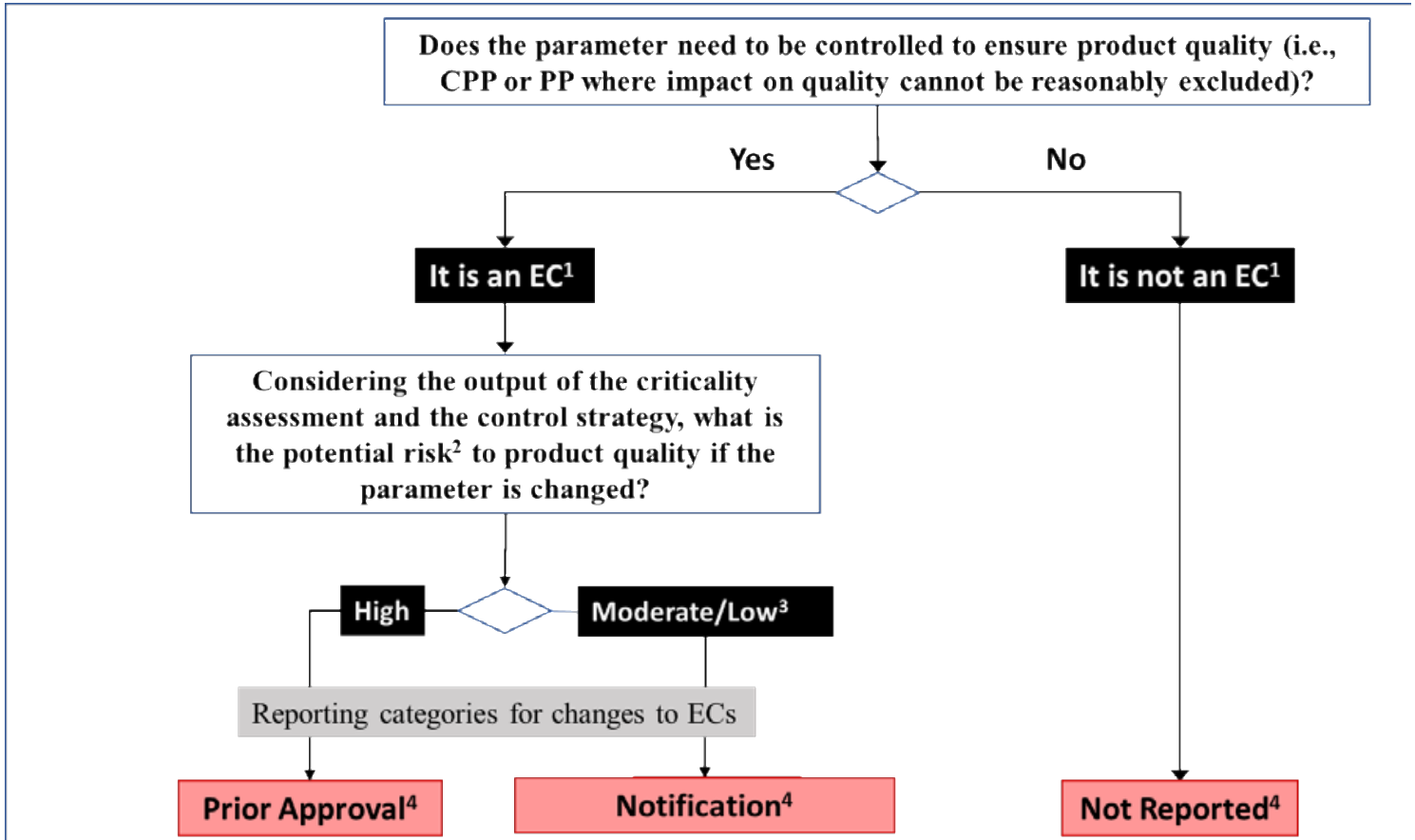
- ECs are legally binding information considered necessary to assure product quality. As a consequence, any change to ECs necessitates a submission to the regulatory authority.

January 27th EC Workshop

- Held in parallel with CMC SF US
- 50+ attendees (20+ companies, FDA CDER/CBER, PEI)
- Small and large companies
- Goal
  - To bring together US regulators and industry representatives to deliberate practical implementation of Q12

Format

- Morning: Level-setting
  - Intro: S. Kozlowski, CDER, FDA
  - 3 industry examples shared
  - Panel discussion
- Afternoon: Case Study
  - Small group exercises to identify ECs for a Case Study (CEX Chromatography)
- Discussion and questions



1 Appropriate justification is expected for parameters that are ECs and that are not ECs
2 Assessment of risk to quality using tools and concepts found in ICH Q9
3 In some cases, the regulator may determine that certain moderate risk changes proposed by the company may require prior approval
4 See Chapter 2 for further guidance on reporting categories and see section 3.3. regarding roles and responsibilities related to managing changes and maintaining an approved application

Summary – Morning Industry Examples

❖ **Sally Anliker, *Eli Lilly***
Overview of post approval changes and ways of globally working with EC's

- Change assessment for post approval
  - Using dossier content and guidance
  - Generate data to support change
  - Submit and track
  - Process can be lengthy and challenging
- Clarity can be provided via use of ECs
- Global harmonization can lead to simplification and greater speed
- ICH region approach
  - Ensure EC proposals are clear and complete
  - State all intended reporting;
  - Ensure Quality Unit is prepared for ECs

❖ **Vandana Chauhan, *F. Hoffman-La Roche Ltd*,** Experience of the FDA pilot program on EC's (defining for approved product)

- Used data from prior knowledge, multivariate and univariate studies
- Applied decision tree from ICH Q12, focus on inputs (parameters) and outputs (impact on PQ)
- Sequence of unit ops/flowchart, IPCs (microbial) and action limits were all ECs
- Cation exchange, most parameters were ECs
- #Cycles, regen/sanitization parameters were not ECs.

❖ **Amy Morrison, *Biogen***
Example of a potential performance based EC

- The example used Forward Feed control of % HMW upstream of the HIC to determine column loading parameters that led to improved impurity removal performance. This allowed for the final out put %HMW to be controlled to acceptable levels
- The example demonstrated the ability for manufacturing flexibility, while maintaining yield and product quality
- The example also made possible use of the CPV for future implementation as the worst case was not available during process validation

Key Points from AM Panel Discussion

- Is the EC concept appropriate in break-through applications?
- How much of the PQS part of the EC strategy needs to be in place?

  Not the intent of ICH Q12 to describe requirements (covered in Q10)
- Monitoring for bioburden is an EC but elements of the microbial controls also belong in inspection details.
- What is the true benefit as process parameters, if changes are infrequent?
- The overall level of detail and size of submission should not change.
- Reporting category is not a requirement to declare EC’s.

Afternoon Case Study: EC's for a CEX Chromatography Step

From ICH Q12

- Parameter-based approaches, including:
  - A minimal or ***traditional*** approach, with a limited understanding of the relationship between inputs and resulting quality attributes, will include a large number of inputs
  - An ***enhanced*** approach with increased understanding of interaction between inputs and product quality attributes together with a corresponding control strategy can lead to identification of ECs that are focused on the most important input parameters along with outputs, as appropriate
- ***Performance-based*** approach, ECs could be primarily focused on control of process outputs This is enabled by knowledge gained from an enhanced approach, a data-rich environment, and an enhanced control strategy (e.g., models, Process Analytical Technology (PAT).

Case Study

- Workshop attendees were divided into groups for case study
  - Traditional approach (2 group)
  - Enhanced approach (2 groups)
  - Performance approach (1 group)
- Identify ECs for mAb process CEX step
  - Data provided:
  - ✓ Basic product information MOA, drug product presentation, CQAs
  - ✓ Basic process information (e.g. process parameters)
  - ✓ Summary of results to support criticality of process parameters (for enhanced/performance approaches)

Output: Case Study Traditional Approach (2 groups)

- **Majority of the process parameters are ECs (approx. 15-19 parameters).**
  - Why? Limited product specific process development data. Hard to exclude the possibility of potential impact of process parameters on product quality.
  - Role of public literature and prior knowledge data from similar products? Data were provided for use in the case study. However, appropriate justification was not provided to support the applicability of this knowledge.

- **Reporting Category Observations:**
  - Most parameters will be EC and require a prior approval submission due to limited data and lack of process knowledge.

- **Additional Observations:**
  - Perhaps more challenging of an exercise than expected due to lack of data connecting parameter variation to attribute variation.
  - Lack of understanding made it challenging to make anything other than the most conservative decisions for criticality and reporting categories.
  - Prior knowledge and public literature could be considered; however, the applicability needs to be justified, which may require verification studies.

  - Could be an approach for breakthrough submissions, however benefits would need to carefully weighed

Output: Case Study Enhanced Approach (2 groups)

- **Fewer EC's were defined than for Traditional. 7-9 EC's were identified**
  - All CPPs were EC's / Some non-CPPs were EC's

- **Reporting Category Observations**
  - Reporting categories varied EC by EC and depended on several considerations such as:
    - **Magnitude of the future change:** That played a role in reporting category but -
      - Hard to define prospectively
      - Extrapolation beyond data was often hard to justify
    - **Directionality of future change:** Could be considered but also makes things more complex – e.g.
      - Protein load, high limit had higher risk than lower limit
    - **Size of the range studied in process characterization:** Also impacts interpretation of data
    - **Likelihood of changes**

- **Additional Observations**:
  - Diversity in assessments was not split by participant background (i.e. regulatory vs industry)
  - All parameters can become CPPs when varied over broad ranges, and many PPs become critical beyond upper or lower limit.
  - Discussion about PPs that impact non-CQAs (e.g., QAs, process performance)
  - Identification of ECs at filing and determination of reporting category later?
  - As a standard approach can reporting category for non-CPP ECs be NL/AR?
  - What can be used as and how to incorporate "prior knowledge?

Output: Case Study Performance Approach

- **Fewest number of EC's. 5 EC's were identified.**
  - Assumed that the process output could be controlled through feedback from a PAT sensor plus a model
  - The 3 Outputs were designated ECs as well as the Model and PAT sensor

- **Reporting Category Observations**
  - Minimal ECs were required compared to other groups but all ECs were prior approval in regards to reporting categories

- **Additional Observations**
  - Use of performance based ECs requires in depth process knowledge and full characterization
  - The group assumed for the case study use of PAT as well as model to determine process parameters and chromatography cut points
  - Models often evolve over time. If the model is an EC, how difficult will it be to update the model if prior approval?

Conclusions of Work Shop

Important Benefits

- Efficiency for Regulators and Industry!
  - More efficiency for regulators and industry (reduction in the number of submissions, regulatory flexibility, potential transparency for future CMC changes).
  - Harmonize change management (acknowledge the challenge to doing this).

Important Enablers

- Process data and knowledge, mature risk assessments, and a robust PQS!
  - The overall control strategy, risk assessments (critical vs noncritical, CQAs, etc.) , are important enablers
  - It is important to make data driven (science) based decisions. Your ECs and reporting category should be aligned with the science and data (knowledge/wisdom) that you have.
  - An enhanced approach is dependent on process understanding and if applicable appropriate analytical tools and statistical analysis.
  - It is valuable exercise to do an assessment by unit operation however the totality of the process control is needed context.
  - Determining downstream (overall) control must be defined
  - ECs and reporting categories assume the PQS is robust especially for change control and facility controls.

Observations

- This is not simple! Even attendees who have been immersed in this topic were challenged to think differently.
- There is a likelihood that the magnitude of change can influence the reporting category.
  - Understanding prior knowledge and studied parameters are important rationale to provide to provide guidance on how to measure magnitude of change.
- Deviations and perturbations are not to be confused with the justification to required to expand an EC prospectively.

Workshop Itself

- Mix of regulators, industry reps, CMC RA SMEs, process experts, small companies, large companies was beneficial.
- Let's do more of this!

Remaining Questions

- Are there parameters that are understood to “always” be critical?
- Is controllability of a parameter a factor?
- Is impact to a non CQA or a KPI a factor in determining ECs?

- What IPCs should be included as EC? Example bioburden, yield…

- Is it reasonable to propose different reporting categories for different magnitudes of changes for a given parameter versus PACMP?
- How much justification is required to support reporting categories?
- What will be the formality of the risk assessment for reporting categories?

- Are companies prepared to do this?
- What / when will we learn from the FDA pilot?