Perspectives on Q12 Lifecycle Management and Established Conditions / Approved Matters

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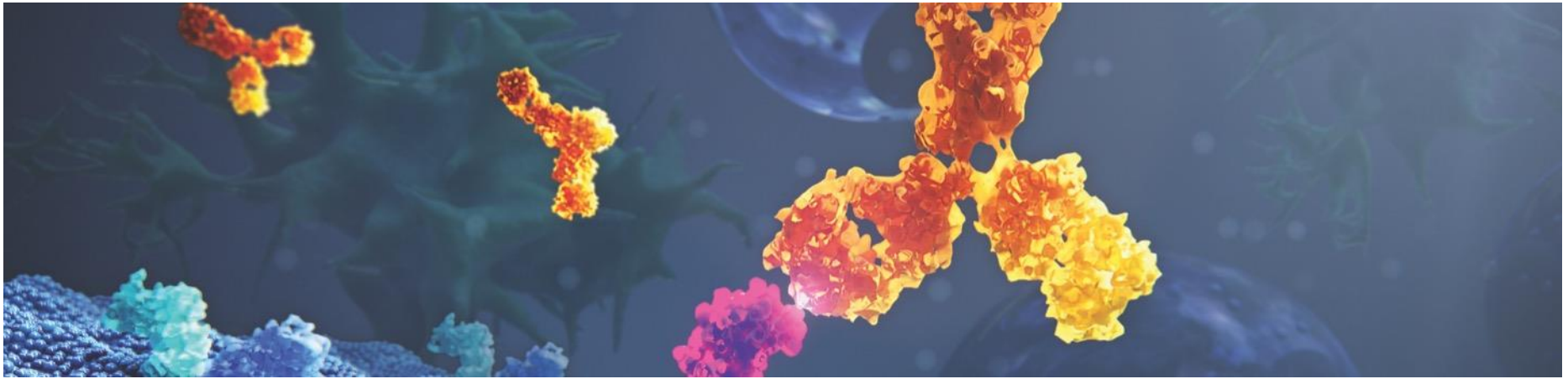


Overview

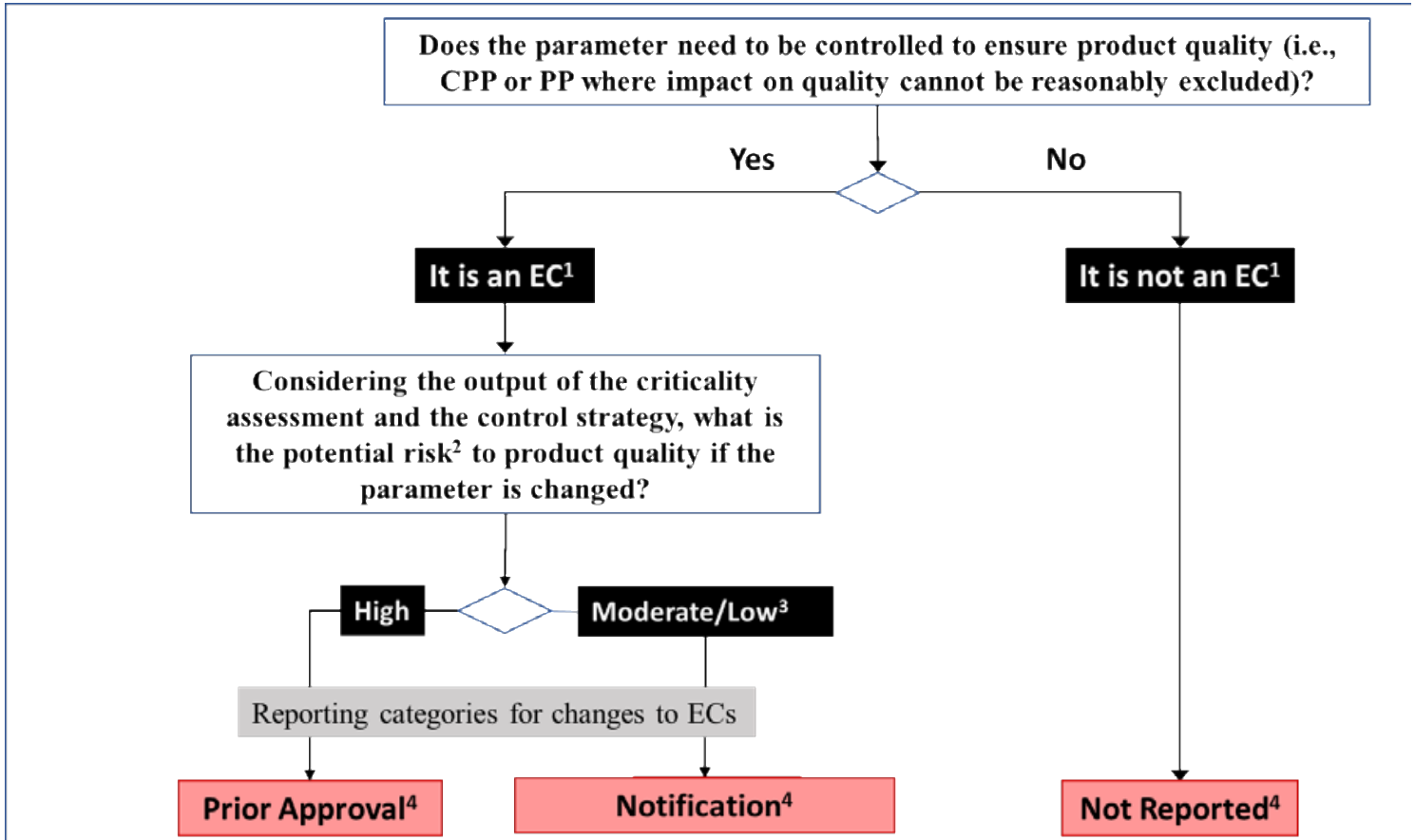
- Background
- Work Shop Session Goals
- Summary of presenters
  - traditional
  - enhanced
  - performance
- Case study read outs
  - Traditional
  - Enhanced
  - Performance
- Discussion and questions

Background

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.



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

Overview

- 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).

Workshop Overview

- Sharing Science Solutions Working group 27 January
- The goal of the workshop was to bring together US regulators and industry representatives to deliberate practical implementation of Q12
- Opening remarks were provided by Steve Kozlowski, *CDER, FDA* and 3 industry examples were presented
- An ECs case study for cation exchange chromatography unit operation using a traditional, enhanced and performance approach was conducted and a discussion followed

Workshop Overview

- Sally Anliker, *Eli Lilly* provided an overview of post approval changes and ways of globally working with ECs
- 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

Enhanced Approach Example

Vandana Chauhan, *F. Hoffman-La Roche Ltd*, presented their experience of the FDA pilot program on Established Conditions (to define ECs for an 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.

Performance Approach EC Example

- Amy Morrison, *Biogen* provided an example of a potential performance based established condition
- 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

Panel Discussion

- Is EC 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 ECs

Brief Summary of Case Study Set-up

- Workshop attendees were divided into groups for case study
  - Traditional approach
  - Enhanced parameter based approach
  - Performance based approach

- Case study to identify ECs for CEX unit operation for a mAb
  - Process parameters
  - MOA, drug product presentation, CQAs,
  - Basic information and summary of results to support criticality of process parameters for enhanced/performance based approach

Case Study Traditional Approach

- Majority of the process parameters are ECs (approx. 15-19 parameters):
  - limited product specific process development data are available to exclude the possibility of potential impact of process parameters on product quality.
  - Public literature and prior knowledge of the manufacture of other similar products, were used in the case study. However, appropriate justification/verification results were not provided to support the applicability of this knowledge.
- As mainly PPQ data is available, this may provide limited benefits as most parameters will be EC and require a prior approval submission due to limited data and lack of process knowledge.

Case Study Traditional Approach

- Additional notable discussions:
  - An unforeseen challenging exercise where information and data are limited to understand the risk and the relationship between process parameters and product quality attributes
    - Challenging to determine criticality for parameters due to limited understanding of the relationship between process parameters and quality attributes
    - Challenging to determine reporting categories due to limited understanding of potential risk to product quality for changes to the process parameters.
  - 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

Case Study Enhanced Approach Groups 1 and 2

- 7 ECs and 5 non-ECs versus 9 ECS and 3 non-ECs
  - All CPPs were ECs
  - Some non-CPPs were ECs
- Considerations for assessment include:
  - **Likelihood of changes**, are there practical limits for parameters ranges.
  - **Magnitude of the change** played a role in reporting category but:
    - Hard to define prospectively
    - Extrapolation beyond data was often hard to justify
  - **Directionality of change** could be considered but also make things complex
    - Protein load, high limit had higher risk than lower limit
  - **Size of the range** studied also impacts interpretation of data
- Diversity in assessments was not split by participant background

Points to Consider for EC identification

- All parameters can become CPPs when varied over broad ranges.
- Many PPs become critical beyond upper or lower limit.
- How about PPs that impact non-CQAs (e.g., QAs, process performance)?
- Identification of ECs at filing and determination of reporting category later?
- Reporting category for non-CPP ECs is NL/AR?
- What can be used as “prior knowledge?

Case Study Performance Based Approach

- 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

- Summary of ECs
  - Performance based approach was controlled via the outputs
  - Minimal ECs were required compared to other groups but all ECs were prior approval in regards to reporting categories
  - 3 Outputs were designated ECs as well as the Model and PAT sensor
  - Total of 5ECs

Conclusions of Work Shop

- 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.
- Determining downstream (overall) control must be defined
- 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.
- ECs and reporting categories assume the PQS is robust especially for change control and facility controls.
- An enhanced approach is dependent on process understanding and if applicable appropriate analytical tools and statistical analysis.

Conclusions of Work Shop

- Deviations and perturbations are not to be confused with the justification to required to expand an EC prospectively.
- 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).
- It is valuable exercise to do an assessment by unit operation however the totality of the process control is needed context.
- Let’s do more of this!

Questions

- Are there parameters that are understood to “always” be critical?
- What ICPs 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?
- Quality impact in change control
- Are companies prepared to do this?
- Any updates on the pilot?
- Is controllability of a parameter a factor?
- Is impact to a non CQA or a KPI a factor in determining ECs?