Medicines Evaluation Board

Some regulatory reflections on ICH Q14

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Personal views only, meant to initiate further (scientific/regulatory) discussion

Innovation

Innovation is mandatory

- Article 23 of Dir 2001/83, as amended:
  - *After a marketing authorisation has been granted, the marketing authorisation holder shall (..) take account of scientific and technical progress and introduce any changes that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods.*
- Analytical procedures (especially in realtion to specifications) are the cornerstone of any control strategy for Medicinal Products.
- Regulators support (balanced) innovation
  - See e.g. EMA's commitment to Quality Innovation Group
  - Innovation not a goal in itself; but a way to adapt to a changing environment
    - See e.g endotoxins (3Rs, sustainability, LER)
  - Balanced approach
    - If it works, it ain't stupid...
    - Regulators always remain cautious

ICH Q14 analytical procedure development

- ICH Q14 adopted by CHMP december 2023
  - EU disclaimer regarding Established Conditions
- ‘*Science and risk-based approaches for developing and maintaining analytical procedures [for DS/DP]*’
- Key points (for this session)
  - Analytical Target Profile (section 3)
  - Analytical procedure control strategy (section 6)
  - Lifecycle management and post-approval changes of analytical procedures(section 7)
  - Submission of analytical procedure related information (section 10)

Analytical Target Profile (ATP)

- Conceptual core of ICH Q14 (and its true innovation)
- ‘*A prospective summary of the performance characteristics describing the intended purpose and the anticipated performance criteria of an analytical measurement*.’
- Structured approach to development
- QTPP/(Product and process) characterization >> Critical Quality Attribute identification >> analytical measurement for control needed (>> development&validation)
  - CQA takes centre stage!
  - CQA ‘objective’, i.e. exists independent of the method (ideally…).
  - However, CQA itself often based on characterization with specific methods

Analytical Procedure Control Strategy

- *An analytical procedure control strategy should ensure that the analytical procedure is fit for the intended purpose during routine use throughout its lifecycle*.
  - What is ‘fit for purpose’?
- Based on development data
  - Evaluation of robustness and parameter ranges (ICH Q14 section 5)
- Comprises:
  - Analytical procedure parameters needing control
  - System Suitability Tests (SST)
  - Sample suitability assessment may be required/useful
- <u>Rational/lean Control Strategy</u>

Analytical Procedure LCM

- Stepwise process
  - Analytical procedure development based on ATP (linked to QTPP); ATP first step in development process and facilitates the technology selection.
  - Analytical procedure development and validation
  - During routine use, ongoing analytical procedure monitoring is performed to ensure that the quality of the measured results remains as expected. Analytical procedures should be continually evaluated against the performance characteristics and criteria in the ATP.
    - Stability data (a form of repeat measurements) offer interesting insights.
  - As part of continual improvement, a new analytical procedure or adjustments to an existing analytical procedure may be implemented.
- Structured approach; think before you do.
- Development never truly stops!
  - Analytical procedures further mature after development and validation.

Analytical Procedure replacement

- The big question: Are the old and new method ‘equivalent’?
  - See e.g. Ph. Eur. General Notices: *(..), alternative methods of analysis may be used for control purposes, provided that the methods used enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official methods were used.*
    - Formal requirement for compendial methods; scientific principle has broader relevance
  - Numerical equivalency may be appealing, but is not a must
- Different principle/reagents/instruments may lead to different results;
  - Which result is ‘correct’ (accurate) for that CQA?
    - Difference between MS and HILIC for glycosylation

Analytical Procedure replacement ctd.

- New method may actually measure a (slightly) different CQA!
  - SE-HPLC versus other methods for dimers/aggregates
  - SDS-PAGE vs CE-SDS
    - E.g. due to improved separation of NGHC (reducing conditions)
  - IEF vs IEC vs capillary IEF
  - Host Cell Proteins
    - Different antisera recognise different HCPs (qualitatively or quantitatively)

Submission of regulatory information

- *'The analytical procedure should describe the steps in sufficient detail for a skilled analyst to perform the analysis (including SST).'*
  - This might sometimes be a difficult standard to meet/assess
- The description should be such, that reliable performance of the procedure is assured/can be assessed
  - See also section 6 which lists:
    - *Performance characteristics and associated criteria (e.g., included in an ATP);*
    - *Analytical procedure principle (i.e., the physicochemical basis or specific technology);*
    - *SST and sample suitability assessment criteria [Objective criteria for valid and invalid results];*
    - *Set points and/or ranges for one or more analytical procedure parameters.*
  - Reportable result is accurate and precise; unsuitable batches do not pass

A regulatory reflection

- ICH Q14 addresses both technical/regulatory issues and technical/business issues.
  - Technical/business issues (including logistics, budget, workplace safety, sustainability) affect method selection;
  - Regulators should be aware of and acknowledge such considerations.
- Ultimately, method should be ‘fit for purpose’ and ‘generally accepted’
  - Which reflects a balance between mature and innovative

Concluding remarks

- Innovation is a must, but not a goal in itself
- Structured development supports scientifically sound analytical procedures and rational/lean analytical procedure control strategies
- ATP innovative concept and useful tool
  - But CQAs may not be fully method-independent
- Replacement of methods remains a critical step
  - Are results ‘equivalent’?
- ICH Q14 is valuable, but no panacea
  - Distinguish between regulatory expectations and business considerations (logistics, budget, HSE) – ICH Q14 not always clear in this respect
- Use your brain – that’s what it’s for!

Routine application can be challenging…

Thank you

Backup/useful EMA links

- Q&A for Biologicals
  - https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/biologicals/questions-answers-biological-medicinal-products
- Analytical Method Transfer
  - https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/pre-authorisation-guidance
    - See e.g. section 3.3.3
  - https://www.ema.europa.eu/en/human-regulatory/post-authorisation/classification-changes-questions-answers
    - See e.g. section 7.2.14.