The complexity of post approval changes for legacy products

CASSS Strategy Forum Seville, Spain 2019

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15.05.2019
For legacy products, files were established without the well defined control strategies now expected for initial registration eg. CQA assessments, QbD but...

- Outdated / superseded methodologies still need to be replaced to maintain production
- Improvements required over time e.g. process improvement
- Specification changes inevitable – very challenging post approval

Can we incorporate ICH Q12 principles now into old files to manage anticipated changes?
Post approval changes for analytical activities: Why and impact

- **Improvement of analytical technologies**: Faster, more sensitive, accurate and robust methods, methods combining several parameter → Revision of method and, potentially the specification limits/parameters.

- **Continuous characterization with improved analytical tools**: Provide additional understanding of the critical quality attributes of the molecule and which parameter monitor them → Revision of the control strategy accordingly.

- **Obsolescence of material**: Need to validate more recent material (e.g., HPLC column) → Method revision and, potential revision of specification limits.

- **Change in regulation (e.g., ICH or country specific regulation)**: Need to assess, implement new methods and/or specification parameters.

- **Implementation of company strategy regarding new QC lab**: Confirm compliance of method validation to ICH prior method transfer → Transfer to new lab.

Doing no change is not an option in analytical life cycle management to guarantee long term supply of pharmaceutical products to patient!
Replacement of analytical method

*Main steps and main information requested by regulatory authorities*

- Method development and validation
- Method transfer to all laboratories where the method should be implemented
- **Evaluation of method equivalence:**
  - Method characterization and comparison to previous method
  - Generation of data with the old and new method on several samples (incl. Release, stability, forced degraded samples)
  - Statistically evaluate the agreement and correlation between the two methods.
- **If the methods are not equivalent: set up new specification limits with the new methods with objective to keep same level of control!**
Case study 1: Obsolescence of material – replacement with an equivalent method

Replacement with an almost equivalent method

HPLC Chromatogram prior to change

Regression and agreement between current and new method

A good correlation but constant bias (with a variability around the bias) is observed ➔ To be taken into consideration to evaluate specification limits.
Case study 1: update to analytical method and specification

Replacement with a method with improved resolution

HPLC Chromatogram prior to change

Regression and agreement between current and new method

HPLC Chromatogram after change

A good correlation but variable bias is observed ➔ To be taken into consideration to evaluate specification limits
Case study 1: Timelines for regulatory approval and impact on supply activities

Example

- 2020: EU/US submission and approval
- 2021: Regulatory roll out
- Approval letter available
- Testing with initial methods/specification
- Testing with new methods/specification
- Release and ongoing stability analysis to be performed with the approved method and specification in the different countries
  ➔ Need to choose between supply chain complexity and several years of double testing for release or stability
Case study 2: implementation of a new QC lab

For release and stability of Drug product

Analytical method transfer

- Laboratory set up
- Protocol/experiment/report

Regulatory submission

- Major variation in most country (prior approval)
- For product registered WW: lead time of several years – starting with EU/US

Routine implementation

- Progressive implementation upon country approval

Use of Change management protocol help decrease the timelines but is not available in all countries.

Several years
How can ICH Q12 principles help?

PACMPs:

- Used routinely ➔ very useful to reduce timelines to approval BUT only recognised by a few countries

Life cycle management plan (LCMP) with Established Conditions (EC):

- The benefits for a new registration are clear but there are limitations for legacy products
- Pros: The LCMP will allow introduction of CMC commitments (e.g. monitoring of performance and adjustment parameters) and regulatory requirement are defined upfront
- Cons: Overhaul of the files would be required to redesign… and this would only be available for a few accepting ICH member countries, the classical approach would still be required for many ROW countries.
- Reassessment of the justifications for EC would be required to meet current expectations
- EU approval letters are required for many ROW countries ➔ using the company QMS doesn’t help with ROW variation roll out.
Conclusions

• In the current framework of ICH Q12 – limited scope for legacy products as control strategies are less extensive than now expected for new products
• It could be used for minor specific changes but not applicable to major changes such as cell-based assays changes or specifications
• PACMPs have been very useful for accelerating approval timeframes allowing faster ROW variation roll out for legacy products
• There still remains significant draw backs for ROW files – classical approach will still only be recognised in many ROW countries & EU approval letters still required for many countries
Questions?
Thanks!