Implementation of ICH Q3D in the CEP procedure

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Hélène BRUGUERA

Head of the Certification Division, EDQM

edqm
European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé
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Certification (CEP) procedure

- Managed by EDQM, Council of Europe (Strasbourg)
- Centralised assessment of the quality of substances for pharmaceutical use covered by Ph. Eur monographs
- Contributes to updating Ph. Eur monographs

Current policy for metal catalysts in pharmaceutical substances

- EU gdl on “Specification limits for residues of metal catalysts” (General Chapter 5.20 of Ph. Eur) and related Q&A
- Catalysts used to be declared in the dossier, together with control strategy
  - Limits as in the EMA gdl
  - Class 1 catalysts introduced in the last synthetic step to be limited in the specification of the API
  - Class 1 catalysts used earlier in the synthesis to be limited in an intermediate or in the API
  - Other classes => flexibility possible when absent

Current policy and CEPs

- CEPs carry:
  - Test & limit for catalysts introduced in the last synthetic step (whatever levels found)
  - Test & limit for catalysts (class 1) used in earlier in the synthesis, and not absent in the API or not limited in an intermediate
  - Skip testing not addressed in Certification

Q3D: a shift in mindset

Q3D: General Principles for CEPs

- No mandatory implementation of ICH Q3D at the level of pharmaceutical substances
- Same basic principles for ASMF & CEPs
- Define an appropriate quality for APIs and excipients
- Serve the Component Approach of Q3D:
  - ➢ Provide necessary information to MAH for their Risk Assessment on the Drug Product
- Be useful for substances manufacturers and MAH and keep the benefits of the centralised assessment

EI in Ph. Eur monographs

- Heavy Metals test (2.4.8) will be removed from Ph. Eur monographs (within scope of Q3D)
- Some individual Ph. Eur monographs will contain test & limit for specific elements
- Expectation that the test of the monograph is included in the specification of the substance (if relevant)

In the CEP application

- 2 possible options:
  - ➢ Risk Assessment (RA) is made at the level of the substance (Component Approach)
  - ➢ No Risk Assessment is made
- **EDQM encourages the submission of a RA in the CEP dossier**

RA is performed

- In the CEP dossier, submission of a summary of the Risk Assessment by the substance manufacturer
  - Include the 4 Class 1 (As, Cd, Hg, Pb) and Class 2A (Co, V, Ni) elements
  - Include Class 2B intentionally added
  - Include any Class 3 intentionally added, and other Class 3 if relevant for the use of the substance (parenteral, inhalation)
  - Include potential contribution of raw materials (incl. water if used as solvent), equipment, facilities, & packaging

RA is performed (2)

- Control strategy:
  - Address absence/presence of EI
  - Describe any controls applied
    - Specification
    - Method validation elements as needed
- CEP assessors will look at:
  - Completeness and relevance of the RA
  - Controls applied, if any

No RA performed

- In the dossier, describe Class 1, 2, 3 elements intentionally added, as part of process description
- For elements intentionally added in early steps (all but the last synthetic step), data showing levels in the final substance, and controls applied if any

No RA is performed (2)

- For elements intentionally added in the last chemical step, a specification in the final substance is expected
  - Specific validated test
  - Limit to be determined based on batch data, PDE of ICH Q3D **may** be used as reference
  - Flexibility for no test if EI is **consistently** absent
- CEP assessors will look at:
  - Controls applied, specification, batch results, methods validation

Controls of EI in the final substance

- Control threshold: Possibility to demonstrate that an element is **consistently and convincingly** removed (< 30% of PDE, option 1, worst case scenario of ICH Q3D) ➔ no test in the final substance
- CEP assessors will NOT question the proposed limits for EI (unless they are obviously not acceptable)

To be further developed

- Definition of “absence”
  - Final use and daily dose of the final substance may not be known
  - Basis: conservative scenario < 30% of PDE, option 1 worst case - other options??
- Replacement of the Ph. Eur Heavy Metals test (2.4.8) by screening of X elements by ICP-AES/ICP-MS
  - Routine testing in the substance is not required by ICH Q3D
  - Results from 3 batches not enough if not accompanied with RA

On the CEP

- If RA submitted:
  - Info on the CEP that RA has been performed, and summary annexed to the CEP
  - Specification of the final substance with regards EI as proposed by the manufacturer (limit + test appended)
- If RA not submitted:
  - “No EI is intentionally introduced” or a “list of EI intentionally introduced”
  - Proposal NOT to mention which EI considered absent
  - Specification of the final substance with regards EI as proposed by the manufacturer (limit + test appended)

Update of existing CEPs

- No requirement for existing substances
- Deletion of reference to Ph. Eur 2.4.8 from monographs
  - ➢ No or little impact
- CEPs which refer to "*option 2a of Chapter 5.20 of Ph. Eur*" to be revised (n=14)

Update of CEPs (2)

- At renewal, good opportunity to update the CEP dossier in line with Q3D:
  - Submission of RA (preferred!)
  - Update of control strategy: Data + justification to be provided
- Request for revision: up to CEP holder to decide
  - Type of revision and conditions to be defined
  - Will lead to revised CEP granted
- Transparency in case CEPs are revised for other reasons: under discussion

Use of a CEP in Marketing Applications

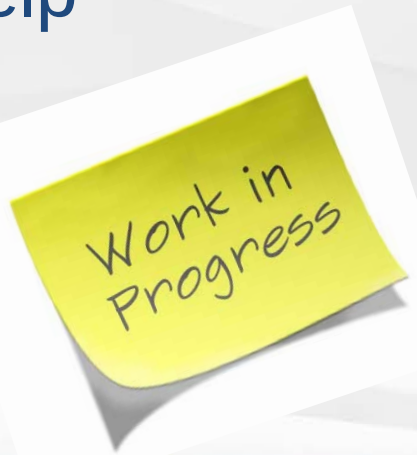
- For “new” CEPs
  - In a **new** MA, include info carried by the CEP in the Drug Product Risk Assessment
  - In a **variation** to a MA, use info carried by the CEP to determine **impact** on the Drug Product ➔ impact on type of variation!

Use of a CEP in a Marketing Application (2)

- For “old” CEPs
  - Use info from CEP: metals present or introduced in the last step, according to EMA guideline
  - Drug Product manufacturers to get info from CEP holder, to feed the Risk Assessment of the Drug Product, or use Drug Product approach

Next steps...

- Policy to be endorsed by the CEP Steering Committee (April 2016)
- Details of implementation
- Substances outside scope of ICH Q3D
- Preparation of template of RA to help manufacturers



Next steps (2)

- Revisions of existing CEPs
- Inspections (documentation when RA is submitted)
- **Need to gain practical experience…**

Deadline June 2016

WATCH THIS SPACE!

Acknowledgements

S-e Hillver

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COMMENTS WELCOME!

THANK YOU FOR YOUR ATTENTION

www.edqm.eu

cep@edqm.eu