European reflections on reviewing NDAs and ANDAs for ICH Q3D elemental impurity compliance

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Introduction

• Although ICH Q3D applies equally in all regions, the regulatory framework may differ

• This presentation is focused on the implementation in the European Union (EU)

• However, EU regulators still have to work hard on how to apply ICH Q3D in practice

• This presentation is an attempt to further clarify issues

• First, some background information is given on EU regulatory setting (request PQRI)
The USE do not exist

European Union is
28 member states
> 40 national authorities (NCA)
1 centralised EU body (EMA)
≠ Europa
Countries following EU drug rules
Observer countries
Countries that want to join EU
EU main legislative structure

- Directives > to be included national legislation member states
- Regulations > immediately apply
- Both further detailed by e.g. EMA/ICH guidelines
- EU is a member of the Ph. Eur. convention (legally binding)
- Confirmation suitability active substance by e.g. ASMF, CEP

Directive 2001/83

- Essential aim to protect public health
- Not to hinder trade within the Union
Role of product quality in marketing authorisation (MA)

consistent & adequate product quality

clinical trial

clinical batches tox. batches

in principle

same requirements for innovator & generic medicines

same EMA quality guidelines* and pharmacopoeial monographs applicable to adults & children

trade

commercial batches

Medicines Evaluation Board
MA in EU - two license types

1) European marketing authorisation
   - Granted by European Commission (EC)
   - To allow marketing medicine over EU (all 28 countries)
   - EC obtains support from European Medicines Agency (EMA)
   - EMA scientific opinions drawn by scientific committees
   - Scientific committees supported by working parties
   - Committee & Working Party experts appointed and usually also employed by EU National Competent Authority
MA in EU - two license types

2) National marketing authorisation
   - Granted by national competent authority (NCA)
   - To allow marketing medicine in its territory
MA in EU: four procedures

1) Centralised procedure
   - obtained by majority voting in CHMP
   - CHMP supported by Quality Working Party (QWP); work may also apply to other procedures
   - European license

2) Decentralized procedure
   - scientific assessment RMS & CMSs in single procedure
   - national license in several member states
MA in EU: four procedures

3) Mutual Recognition Procedure
   - MA already granted in Reference Member State (RMS)
   - prior to start MRP: update Module 3 required
   - Concerned Member State (CMS) reviews RMS assessment report and where appropriate MA dossier
   - each CMS expected to recognise MA granted by RMS; if negative at end of procedure, then a referral starts; outcome referral binding to all countries, including RMS

4) National procedure > national MA
Increased attention to patient needs

- further discussion on regulatory expectations essential
- some measures already adopted
  - Orphan legislation
  - Paediatric Regulation
  - ICH Q8: product should be fit for its intended purpose
Regulators challenges ICH Q3D

• A shift in paradigm
• Q9 Risk Management to be assessed with every application
• Leaving stricter rules for more flexibility – harmonised assessment?
• Challenges for ASMFs and CEPs?
The EU Guideline EMEA/CHMP/SWP/4446/2000

• Took 10 years and 3 consultations from start until coming into effect
• Addresses intentionally added elements (metals) in drug substance
  – because they are of the greatest concern
• Other sources of these elements also mentioned
  – the concentration limits in this guideline are in principle also applicable to residues from other sources than catalysts and reagents. However, for these other sources adoption of a concentration limit and a validated method in the specification is only necessary in the very exceptional cases where these residues are known to be insufficiently limited by GMP, GDP or any other relevant provision.
Differences at a Glance

ICH Q3D

- All sources of elemental impurities
- Focused on drug product contamination
- PDE:s for 24 elements
- Classification based on safety and occurrence
- Focused on risk management in line with ICH Q8-11

EU Guideline

- Catalysts and reagents
- Focused on drug substance contamination
- PDE:s for 15 elements
- Classification based on safety
- Does neither mention nor contradict the use of risk assessment
Risk based approach vs. strictly defined rules

• ICH Q3D adopts a scientifically sound approach
• It will however be more challenging to assess
• There is an increased risk for divergent views between EU assessors; in worst case leading to referrals
• QWP is dedicated to facilitate the implementation
• We still lack practical experience of assessing elemental impurities according to ICH Q3D
When should products comply with ICH Q3D in the EU?

• CHMP has decided that
  – New MA for new product (new active substance)
    • June 2016
  – New MA for product with existing active substance
    • June 2016
  – Marketed products including new MR applications of already approved products
    • December 2017
New Marketing Authorisations should comply from June 2016

• This means
  – Compliance with the Q3D PDEs
  – The applicant should document the Risk Assessment and the control approaches in an appropriate manner

• On site
  – The documentation of the Risk Assessment should be kept available for inspection

• In file
  – A summary of the Risk Assessment and any measures taken to ascertain compliance
  – The overall Control Strategy for elemental impurities including any specifications as needed
Existing marketed products should comply from Dec. 2017

- Risk Assessment should be performed, documented and be kept available.
- No variation is necessary if the Risk Assessment show that for compliance:
  - No further controls on elemental impurities to materials such as the designated active substance starting material, synthesis intermediates, active substance, excipients or the finished product are needed.
  - No replacement or change of quality of materials such as the designated active substance starting material, synthesis intermediates, active substance, excipients or of the manufacturing equipment is needed.
  - No change of the manufacturing process is needed.
- In other cases a variation is needed.
  - Categorised according the Variation Guidelines (Official Journal 2013/C 223/01)
  - Accompanied with the documentation required in the Variation Guideline.
  - In addition contain a summary of the Risk Assessment and the conclusions drawn.
Expectations during the products Lifecycle

• Product and process knowledge gained during the lifecycle to be used for improvements (ICH Q10)

• Risk Assessment to be re-evaluated upon changes e.g.
  – Synthetic routes
  – API or Excipient suppliers
  – Raw materials
  – Processes
  – Equipment

• Subject to internal Change Management process (ICH Q10) and where applicable regulatory Variations.
Submission expectation

• A Summary of the Risk Assessment to be submitted
  • Full documentation of Risk Assessment available at site
• What should the Summary look like?
  • Should follow the principles lined out in ICH Q3D
  • Contain what is needed to evaluate the appropriateness and completeness of the elemental impurities Risk Assessment.
  • Tell a story to the assessor on what has been considered, done and concluded
  • Raw data not expected, but summary of findings may be necessary
  • The justification for the Control Strategy (what to control and not to control)
Where to be put in the dossier?

- The ICH CTD format not adopted to this new information but QWP considers a suggestion could be
  - Summary of Risk Assessment
    - 3.2.P.5.5 Characterisation of impurities (DP) (rather than 3.2.P.2 Pharmaceutical development)
  - Depending on the outcome, data may also go into e.g.:
    - 3.2.S.3.2 Impurities (DS)
    - 3.2.S.4.5 Justification of specification (DS)
    - 3.2.P.4 Control of Excipients
    - 3.2.P.5.6 Justification of specification
Implementation of ICH Q3D in the Ph.Eur.

- **General text 5.20**
  - ICH Q3D replaces the EMA guideline on metal catalysts and reagents

- **General method 2.4.20**
  - Wording to be aligned with ICH Q3D

- **General monographs**
  - **Pharmaceutical Preparations** cross reference to 5.20
  - **Substances for pharmaceutical use** to clarify how to handle substances used in drug products outside of the scope of ICH Q3D
Implementation of ICH Q3D in the Ph.Eur. cont.

• **Suppression of heavy metals test (2.4.8)**
  – From all individual monographs (except vet. use only)
  – Implemented from January 2017 for practical reasons
  – Does not preclude substance manufacturers from controlling elemental impurities in their products
  – 2.4.8 is still acceptable until ICH Q3D comes into force for a given product
Implementation of ICH Q3D in the Ph.Eur. cont.

- Specific metal tests in monographs – suggested strategy
  - To be decided case by case if kept or not
  - To be deleted when intentionally added (catalyst or reagent)
  - To be kept when not intentionally (mined excipients)
    - Delete only confirmed superfluous tests
    - Collect data and revise monograph if necessary
    - This would represent a Ph.Eur. minimum quality. Applicant would still have to assess if that quality is sufficient in the drug product
Application of Control Threshold

• In ICH Q3D, compliance should be ascertained by testing when necessary
  – The concept of Control Threshold (consistently < 30 % of PDE) facilitate the decision on when it is necessary
• Assurance of negligible likelihood of exceeding the PDE
  – For many elements the observed or predicted levels will be far below this threshold and the decision will be easy
  – The closer the levels are to the threshold, the more difficult to judge whether no further controls are needed.
• All sources of variability and uncertainty must be considered
Application of Control Threshold – Number of batches

- The guideline states
  - *At the time of submission, in the absence of other justification, the level and variability of an elemental impurity can be established by providing the data from three (3) representative production scale lots or six (6) representative pilot scale lots of the component or components or drug product.*

- This is a minimum that may be sufficient
  - To allow the absence of controls, regulators must be convinced that the threshold will never be exceeded.
  - Being close to the Control Threshold means that more batches may be necessary for concluding ”consistently below”.
Intentionally added elements – EMA guideline

• Until now – in line with the EMA guideline a specification has been needed (except for Fe and Zn)
  
  – “If the synthetic or manufacturing processes have shown to result in the removal of a potential metal residue, routine testing of that metal residue may be replaced by non-routine (skip) testing. A metal residue can be considered adequately removed if, in 6 consecutive pilot scale batches or 3 consecutive industrial scale batches less than 30 % of the appropriate concentration limit was found. A change from routine to non-routine testing does not mean that the test may also be deleted from the specification.”
Intentionally added elements – ICH Q3D

• To comply with Q3D
  – Intentionally added elements must **always be included** in the Risk Assessment

• The need for a specification will **depend on the outcome** of the Risk Assessment

• It is preferred that the applicant, also for outsourced active substances, are fully **informed by the supplier** on the use of any sources of elemental impurities in the synthesis of the active substance.
Intentionally added elements – ICH Q3D

• Intentionally added elements in active substance should be known to authorities (and normally to applicants) since
  – Details of the synthetic route including the use of catalysts or reagents are mandatory either
    • in the dossier for an in-house synthesised substance
    • in an ASMF or
    • in a CEP dossier for an outsourced substance
• Need to find ways that this information known to authorities also can inform the overall Risk Assessment
Intentionally added elements – catalyst used in the last step of the synthesis

• This constitutes an elevated risk
  – *Impurities introduced or created early in the manufacturing process typically have more opportunities to be removed in purification operations (e.g., washing, crystallisation of isolated intermediates) than impurities generated late in the manufacturing process, and are therefore less likely to be carried into the drug substance* (ICH Q11).

• Special considerations are warranted
Intentionally added elements – catalyst used in the last step of the synthesis

• Less reassurance from purging compared to a synthesis with multiple subsequent steps
• Possibly greater impact of any unexpected events
• Due to this elevated risk
  – The normal expectation will be to have a specification in either the drug substance or drug product; skip testing may be possible
  – The absence of a specification must be justified by evidence of robust purging
  – To apply the Control Threshold to eliminate a testing, borderline results will most likely not be accepted
  – More than minimum number of batches may be needed
Mined material – originating from the Earth Crust

- In some geological environments certain elemental impurities may be abundant
- Needs to be taken into account in Risk Assessment when material is sourced from minerals
Mined material

- **Directly mined material, e.g.**
  - Sodium chloride
  - Titanium dioxide
  - Calcium carbonate
  - Talc

- **Inorganic salts derived from mined material e.g.**
  - Calcium hydrogen phosphate

- **Simple organic salts made with mined material e.g.**
  - Ferrous fumarate
Mined material – special considerations

• The natural level of elemental impurities may vary from one mine/quarry to another
  – It may even vary within a pit

• Compliance with Q3D may require
  – Specifications with routine testing
  – Selection of vendors
  – Selection of batches
Role of API and excipient suppliers

• It is acknowledged that the choice of a Drug Product vs. a Component approach is at the discretion of the DPM

• From a science and a transparency point of view, manufacturers & suppliers are encouraged to cooperate
  – To facilitate the Risk Assessment by exchanging information
    • Information from DPM on intended use (dose, RoA)
    • Information from supplier on possible elemental impurities
  – To use the ASMF or the CEP procedures whenever possible as a way to supply information useful for the Risk Assessment
Role of ASMF and CEP

• No mandatory implementation of ICH Q3D at the level of pharmaceutical substances

• Same basic assessment principles should apply for in-house made substances as well as outsourced with ASMFs & CEPs

• ASMFs and CEPs to be useful for substance manufacturers and MAH also in the future
  – A mechanism for exchanging information that can inform the DPMs Risk Assessment
In the CEP application – two options

- **Risk Assessment is made** by the substance manufacturer at the level of the substance (Component Approach)
  - Submission of a summary of the Risk Assessment on elemental impurities originating from the manufacture of the substance including equipment, utilities and packaging

- **No Risk Assessment is made**
  - Describe Class 1, 2, 3 elements intentionally added, as part of process description
On the CEP

• If Risk Assessment is submitted
  – Info on the CEP that a Risk Assessment has been performed
    • the Summary annexed to the CEP
  – Any specification of the final substance as proposed by the manufacturer (limit + test appended)

• If Risk Assessment is not submitted
  – “No EI is intentionally introduced” or a “list of EI intentionally introduced”
  – Proposal not to mention which EI considered absent
  – Any specification of the final substance as proposed by the manufacturer (limit + test appended)
CEP assessor will look at

- If a Risk Assessment is submitted
  - Completeness and relevance of the Risk Assessment
  - Controls applied, if any
- If no Risk Assessment is submitted
  - Controls applied, specification, batch results, methods validation
- CEP assessors will generally not question the proposed limits
Drug Product scanning

• It is recognized that sometimes the most reasonable way of complying with the guideline would be to decide on a control strategy based on scanning of Drug Product batches

• From a regulatory point of view
  – ICH Q3D compliance include performing Risk Assessment
  – Analytical data only will not be sufficient to justify the omission of testing for an element
  – Without an acceptable Risk Assessment, only full routing scanning of all elements can ensure compliance with the guideline
Thank you for your attention

Please ask any questions either now / lunch

Being a member of the European Union implies
Being united in diversity
Sharing the good and preventing the worse
Harmonization is key: it is not My Rules Apply to all