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Health Canada's Experience When Implementing the ICH Q3D Elemental Impurity Guidance for NDSs and ANDSs

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PQRI/USP Elemental Impurities workshop

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Introduction

- Health Canada is now an official member of ICH
- We currently have representatives on several quality working groups – ICH Q3C, Q3D, Q11, Q12 as well as working groups for multidisciplinary topics.
- ICH guidance are adopted by Health Canada after they reach Step 4.

- Some Canadian terminology:

- NDS – New Drug Submission
- ANDS – Abbreviated New Drug Submission
- S(A)NDS – Supplemental (Abbreviated) New Drug Submission

Publication

- Published in Canada in January 2016
- Implementation guidance published in July 2016

Dates of implementation of ICH Q3D in Canada

	Implementation date
Submission of a new (A)NDS or DIN application for a drug product should include the content requirements as per Q3D	Submissions received after December 31, 2016
Submission of a new Supplemental (A)NDS or Post-DIN Change for a major change to an existing Drug Product as a result of the risk assessment per Q3D **Submission of a new Supplemental (A)NDS for a quality related major change to a marketed drug product should include the content requirements as per Q3D for a new drug product**	Submissions received after December 31, 2016
Completion of the risk assessment for elemental impurities **Implementation of any manufacturing changes to control the levels of elemental impurities** **Updated drug product specifications with a statement confirming compliance with ICH Q3D**	By January 1, 2018

Submission of risk assessments with supplements

Risk assessments were required from 1 January 2017

- New dosage form
- New formulation
- New manufacturing site of a drug product

Full implementation of ICH Q3D will be 1 January 2018:

- All marketed products will require a risk assessment unless the risk assessment was previously submitted and unchanged from earlier submission

What we've seen to date

- Great improvement in quality of risk assessments over the last 6 months
- Risk assessments are to be revisited if changes are made to the product – still too early to see if this is being achieved in practice

Few major deficiencies in recent submissions

- Reduction in number of submissions with no complete risk assessment summary provided in accordance with ICH Q3D
- Still a few risk assessments targeted to assessment of specific impurities
  - Submitted information simply uses principles of Q3D and limits to set controls for leached elemental impurities from container closure systems

- Reduced number of protocols for post-market studies received

Improving Risk Assessments

- Consider all possible sources of elements
- More communication between suppliers and manufacturers is needed to support component risk assessments
- Rationales for not screening elements should be scientific
- Analytical data alone without risk assessment is not sufficient as it does not give assurance that variability has been considered in the risk assessment

Common areas of weakness

- Appropriate documentation of elements considered should be improved
- Information is generally acceptable for the elements considered, but often missing complete compliance with ICH Q3D as Class 1 and Class 2a elements were not considered in the risk assessment

Use this table in the risk summary

Element	Class	If intentionally added (all routes)	If not intentionally added		
			Oral	Parenteral	Inhalation
Cd	1	yes	yes	yes	yes
Pb	1	yes	yes	yes	yes
As	1	yes	yes	yes	yes
Hg	1	yes	yes	yes	yes
Co	2A	yes	yes	yes	yes
V	2A	yes	yes	yes	yes
Ni	2A	yes	yes	yes	yes
Tl	2B	yes	no	no	no
Au	2B	yes	no	no	no
Pd	2B	yes	no	no	no
Ir	2B	yes	no	no	no
Os	2B	yes	no	no	no
Rh	2B	yes	no	no	no
Ru	2B	yes	no	no	no
Se	2B	yes	no	no	no
Ag	2B	yes	no	no	no
Pt	2B	yes	no	no	no
Li	3	yes	no	yes	yes
Sb	3	yes	no	yes	yes
Ba	3	yes	no	no	yes
Mo	3	yes	no	no	yes
Cu	3	yes	no	yes	yes
Sn	3	yes	no	no	yes
Cr	3	yes	no	no	yes

Drug Product risk management summaries

- Ensure the summary appropriately and accurately reflects the process and product
- Is the product solid or liquid? Will it be reconstituted?
- What is the maximum daily dose?
- Are limits for EI in excipients taken into consideration?
- Limits not in line with ICH Q3D may need toxicological justification
- Overall: 3.2.P.5.5 and P.5.6 should not contain detailed information, but sufficient summary to provide assurance the appropriate approach is taken

Risk assessment vs Analytical testing

- Which EI should be included in the screening?
  - Not all elements need to be screened for – the risk assessment can influence the decision to screen materials
  - Literature data, knowledge of components, data from suppliers should influence the decision to conduct screening – reasons for screening or not screening components should be transparent and well documented

Component analysis

- Risk assessment for the drug product should influence whether component approach or finished product approach is used
- Controls are often not required to ensure that elemental impurities are less than 30% of the PDE
- Where controls have been required, it has been sufficient to have a control on the particular elemental impurity in the component
- Rationales are based on test results for extracted or leached elements
- No routine testing of drug products has been seen to date

Controls most usually seen

- Arsenic for glass vials
- Controls for class 1 elements in mined and natural excipients
- Reduction in routine controls for catalysts in APIs as a result of Q3D (levels are significantly less than 30% of the PDE)

Elements not intentionally added

- Elements that should be considered in the risk assessment are mentioned and adequately justified
- Rationale for not considering elements is poorly documented - Class 1 elements are reasonably well documented
- Class 2A elements poorly documented
- Class 3 elements for parenteral products poorly documented

Elements often not adequately considered

- Insufficient rationale for contributions from manufacturing equipment
  - As – glass lined reactors
  - Co, Ni, V – stainless steel equipment
  - API contribution as synthetic processes are harsher than drug product formulations
- Even if the drug product is a solid hence the risk is low, this needs to be documented as the rationale

Using component analysis to estimate element levels

- Worst case scenarios are often used to estimate levels of impurities in risk assessments, e.g. contribution from glass to a liquid parenteral product
- The values of the element in the finished product should be calculated on an cumulative basis considering also excipients, container closures, catalysts, etc.
- Where multiple elements could be present, separate tables for components (e.g. the API) can be prepared and then consolidate the potential contaminants from components into a single table for the drug product

Health Canada acceptance of CEPs and how EDQM policies be used to support the Drug Product risk assessment

- Health Canada accepts EDQM CEPs with minimal data since August 2017
- EDQM policies therefore influence assessment practices at Health Canada
- EDQM policies will be covered in a presentation this afternoon
- Communicate with API supplier to get brief risk management information on the API
- Use conclusions to decide on what controls may be needed or if further screening is needed

Questions?

- All questions on chemistry and manufacturing issues can be directed to the email address:
  bps_enquiries@hc-sc.gc.ca

  BPS has a correspondence
  coordinator who either answers the questions directly or directs them to the appropriate quality or bioequivalence expert

  Administrative questions on ASMFs can be directed to:
  dmf_enquiries@hc-sc.gc.ca