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
## Dates for implementation of ICH Q3D in Canada

<table>
<thead>
<tr>
<th>Implementation date</th>
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<tr>
<td>Submission of a new (A)NDS or DIN application for a drug product should include the content requirements as per Q3D</td>
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<td>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</td>
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<tr>
<td>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</td>
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<td>Completion of the risk assessment for elemental impurities</td>
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<td>Implementation of any manufacturing changes to control the levels of elemental impurities</td>
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<td>Updated drug product specifications with a statement confirming compliance with ICH Q3D</td>
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Training of Health Canada staff

- Additional emphasis on formal and informal training for Q3D
- Desire to have more formal training programs for new guidance to shorten the learning curve and improve consistency in application of ICH Q3D
- The ICH Implementation working group has developed all necessary training materials
- Health Canada training places all documents in an easy to access online training module and leads assessors through mandatory and optional training material
- There is a quiz at the end of the module to record completion of the training and to ensure a minimum level of understanding of the topic
Training module organization

- Training documents organized to suit Health Canada’s organization structure which includes:
  - Conventional Pharmaceutical Assessors
  - Biologic Assessors
  - Natural Health Product Assessors
  - GMP Inspectors
  - Toxicology Assessors
What do we want to emphasise in training

- Not all elemental impurities need to be considered in the risk assessment – training on what elements are included and when
- Most often, testing of all elements is not necessary - an initial risk assessment is performed to determine what testing is necessary
- Where to find information on analytical methods as necessary – targeted training for those who are not analytical specialists
- Training is targeted as needed – the goal is to aid staff to find the information fast
  - Where to find information on excipients and what elements they may be contaminated with
  - Presentations available and the relevance to each assessor’s daily tasks
- Have developed assessment tools such as worksheets to allow for easy calculation of PDEs or concentration based levels using formulation and excipient information
How assessor training will help

- Minimize comments to applicants by ensuring staff know where to find information quickly
- Minimize comments that are unnecessary – requests for testing of elements where there is no identified risk
- Ensure understanding of how to approach risk assessment of the Case 1 and 2a elements – this area has not been well understood prior to training
When to submit a risk assessment for a supplement?

Required from 1 January 2017

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

Ideally a risk assessment should be submitted prior to 2018 if:

• Updating specifications for a drug product

Defer till 1 January 2018:

• New manufacturing site or route of synthesis for a drug substance
• New specifications for a drug substance
• New stability information
• New container closures
ANDS (Generics)

- ANDS Screening Attestation form will be updated in December 2016 to include confirmation that a risk assessment has been included.

- For S(A)NDS – If no risk assessment or no justification for not including the risk assessment is included, this will be requested.

- After 1 January 2017, submissions which should have a risk assessment will be rejected as incomplete at screening.
Biologics

- Assessed by the Biologics and Genetic Therapies Directorate
- Scope of products requiring a risk assessment as per ICH Q3D
- “Cold kits” (for reconstitution with a radiopharmaceutical) do not meet the definition of a "radiopharmaceutical" and so are considered to be within the scope of ICH Q3D
What we’ve received to date

- Very few submissions have been received with a Risk Management Summary at this point as we haven’t reached the Health Canada implementation date
  - Majority of submissions come from 1 company
- No complete risk assessment summaries provided in accordance with ICH Q3D – 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
- Rationales are based on test results for extracted or leached elements
- Protocols for post-market studies received
- Information is generally acceptable for the elements considered, but wouldn’t be acceptable in accordance with ICH as Class 1 and Class 2a elements were not considered in the risk assessment
Risk Assessment Summaries

- Fall into two categories
  - Too brief to provide adequate information
  - Not a summary or a critical analysis of the information
- Use the case studies to get ideas before you start a risk assessment summary
- Risk summaries are living documents – they will need to be updated when changes are made to products
  - New sources of excipients
  - New manufacturers for container closure systems
  - New information about potential sources of contamination
Summaries that are too brief

- Summary contains statements that are not backed up with analysis or data
- Examples include general statements such as “The extraction study to determine impurities from container closure system indicated that there was no risk.”
- No information on what the study involved, what elements were considered, why the results indicated that there was no risk
- Don’t refer to specific studies performed
- Avoid broad statements without backing them up with information that supports the statement
- Ensure staff writing summaries are aware of what an assessor will be looking for:
  - How, why, what, results, gaps…..
- **Critical analysis** backed up by scientific information is necessary for the summary to be acceptable without further questions
Health Canada recommendations for summaries

• Be systematic
• Start with a table of the ICH Q3D elements
• Use tables, headings, hyperlinks and bookmarks to make information easy to find
• The risk assessment summary justifies the proposed controls and should be life-cycle managed. Appropriate to place this summary in P.5.6 Justification of specifications
• Use the summary to cross-reference to other areas in the submission rather than repeating information
  – Drug substance information – justification for catalysts
  – Excipient information could be in P.2 Development, P.4 Excipients
  – Container closure information may be in P.7 Container Closure System
  – Leachable information in P.8 Stability
Summaries with insufficient critical analysis

- Summaries that aren’t actually a summary at all
- Generally compiled by staff who are not specialists but have been provided with detailed reports
- Contain copious amounts of raw data usually cut and pasted from the analytical reports
- No filtering of information for relevance
- No critical analysis of the data or discussion of gaps in the information
- Experienced staff can often perform the analysis themselves but this will delay the submission due to the copious amounts of information and often leads to questions where gaps are identified but not discussed adequately
Other issues noted

• Worst case scenarios showed levels above PDEs. The discussion showed a poor connection between data submitted and proposed control strategy.

• No rationales submitted based on toxicology for elemental impurities which are greater than PDE but the product will only be used for short term exposure.

• Many elements of concern are not ICH Q3D elements – comments will still be asked to get justification for proposed controls, in particular data to support limits.
Use of third-party information

- Master files are expected to provide significant support for risk assessments if used judiciously
  - Information provided informs the initial risk assessment
  - Potential sources of elements identified (e.g. from extraction studies)
  - Identification of higher risk elements which may need to be tested in the drug product
- Information in Master Files is relevant but risk assessments should be specific to the actual product
  - While information on extractables may influence whether additional testing needs to be performed, the relevance of that information for your product should be taken into account
    - e.g., a risk assessment based on information on extractables determined using water it is not going be acceptable if your product uses an alcohol base
- When third-party information is used, justification needs to be sufficient to convince the assessor that there is no risk
Products regulated by the Non-Prescription and Natural Health Products Directorate

- OTCs are within scope of ICH Q3D so the guideline is applied
- Only certain products receive a quality assessment for licencing (DINAs)
- These are sterile products (generally ophthalmic or otic products)
- For other products, compliance with Q3D will be determined post-market

- Natural Health Products:
  - Herbal products
  - Vitamins and minerals

- “Quality of Natural Health Products” guide outlines the requirements for elemental impurity testing and compliance limits
Elemental Impurities in Natural Health Products

- Acceptance criteria for the elemental impurities - arsenic, lead, cadmium, mercury - in Natural Health Products (NHPs) are set out in the *Quality of Natural Health Products Guide*

- Ingredients derived from nature exposed to environmental elements contain elemental impurities through exposure to their environment
  - For example, plants absorb elemental impurities from the soil in which they grow

- NHPs are out of scope for ICH Q3D, however the health risks associated with elemental impurities are still relevant
Update on Elemental impurity limits for NHPs

• The Non-prescription and Natural Health Products Directorate is aware of the differences in the limits for elemental impurities imposed by various authorities and have started an exercise to examine current limits required for Natural Health Products.

• The following table reflects the initial examination of the differences in different jurisdictions.

• NHPD limits for elemental impurities are expressed in terms of body weight so depend on the patient population.
  – The limits in the following table reflect limits for products for adults.
Comparison of acceptance criteria for elemental impurities in the *Quality of Natural Health Products Guide*, USP <2232>, ICH Q3D and NSF/ANSI 173

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<tr>
<td>Total arsenic</td>
<td>&lt;10 µg/d</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Inorganic arsenic</td>
<td>&lt;2.1 µg/d*</td>
<td>15 µg/d**</td>
<td>15 µg/d</td>
<td>10 µg/d</td>
</tr>
<tr>
<td>Organic arsenic</td>
<td>&lt;1.4 mg/d*</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Lead</td>
<td>&lt;10 µg/d</td>
<td>5 µg/d</td>
<td>5 µg/d</td>
<td>20 µg/d</td>
</tr>
<tr>
<td>Cadmium</td>
<td>&lt;6 µg/d</td>
<td>5 µg/d</td>
<td>5 µg/d</td>
<td>6 µg/d</td>
</tr>
<tr>
<td>Total Mercury</td>
<td>&lt;20 µg/d***</td>
<td>15 µg/d***</td>
<td>-</td>
<td>20 µg/d</td>
</tr>
<tr>
<td>Inorganic Mercury</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>40 µg/d</td>
</tr>
<tr>
<td>Methyl Mercury</td>
<td>&lt;2 µg/d</td>
<td>2 µg/d</td>
<td>-</td>
<td>-</td>
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* Inorganic and organic arsenic speciation only required if total arsenic exceeds 10 µg/d.
**Arsenic speciation only required if 15 µg/d exceeded.
***Methylmercury determination is not necessary when the content for total mercury is less than the limit for methylmercury.
Responsibilities at Health Canada

- Risk assessments in marketing applications
  - Quality assessors at the Therapeutic Products Directorate (TPD) or Biologic and Genetic Therapies Directorate (BGTD)
- Risk assessments as part of the Quality Management System
  - Regulatory Operations and Regions Branch
- Information to support different PDEs or PDEs for routes of administration
  - Toxicology assessors at TPD or BGTD with support from clinical assessors as necessary
Contact information:

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NNHPD_DPSNSO@hc-sc.gc.ca (OTCs)
bgtd_ora@hc-sc.gc.ca (Biologics)

QUESTIONS?