Global Implications – ICH Q3D

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The Perfect World

- Global adoption of ICH Q3D
  - New and Legacy products

Q3D	Heavy Metals
Based on sound scientific & risk based approach	> 100 years old!
Focuses on patient safety	Unable to detect some toxic elements
Updated, accurate, specific analytical methodology	Known issues with method (loss of analyte during ignition)
	Lack of sensitivity and reproducibility
	Known issues with method since at least 1998!

The Reality

- **Adoption is NOT universal**
- Majority of countries outside US/EU/Japan are NOT on board
- Retention of Heavy Metals Test still expected

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The Reality:

- Health Canada – implementing Q3D (NEW SUBMISSIONS)
  - Submissions after 31Dec2016 – required inclusion of Risk Assessment
  - Details of risk assessment are to be documented and made available upon request
  - Elemental Impurities related information should be included in submission
    - –Module 2.3.P.5 - Control Of Drug Product of the Quality Overall Summary – clear summary
    - –Module 3.2.P.5.6 – Justification of Specifications – overall risk assessment summary
  - Compliance with Q3D should be documented after risk assessment is complete and any necessary controls have been implemented
  - A statement confirming Q3D compliance should be included on the drug product specifications and reflected in CPID (Certified Product Information Document)

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The Reality:

- Health Canada – implementing Q3D (Marketed Drug Products)
  - A risk assessment should be performed according to the ICH guideline **AND any training materials published on ICH Website**
  - If any previously manufactured (unexpired) lots may have levels that could pose a potential risk to health – HC should be notified, and appropriate corrective action taken
  - ICH Q3D compliance should be included in drug product specifications and reflected in CPID (Certified Product Information Document)

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The Reality:

- Health Canada – implementing Q3D (Marketed Drug Products) (01 JAN 2018)
  - Possible outcomes of Risk Assessment
    - –Additional controls added to specifications to ensure levels meet Q3D
      - »Non-specific compendial method is NOT acceptable
    - –No further controls or updates to specifications needed
    - –No replacement or change of the quality of materials
    - –No change to manufacturing process
    - –Replacement of API, API starting materials , synthesis intermediates, or excipients in order to comply
    - –Major changes to manufacturing process
  - Periodic re-assessments of the risks may be appropriate throughout lifecycle

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The Reality:

- Australia: TGA
  - Implementation aligned with EU (June 2016 New Products; December 2017 New Products containing existing Drug Substances)
- Swiss Medic
  - New Drug Products – 01 July 2016
  - Marketed Products – 01 January 2018
    - Must comply with Ph. Eur. Supplement 9.3
    - During transition companies should preform risk assessment covering all potential sources of elemental impurities
- Taiwan FDA & CDE (Center for Drug Evaluation)
  - New Products – 01 July 2017
  - Marketed products – unknown (but expect companies to perform risk assessments)

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The Reality:

- International Markets
  - Difficult to remove existing heavy metals test and limits
- How can this work?
  - USP/Ph Eur heavy metals chapters were typically referenced
  - What happens once they are completely removed?
    - Temporary switch to JP?
    - Requiring companies to validate the old method?
    - **Can it even be validated!?**

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The long road ahead

- Burden on industry to drive change
- Can we collaborate to drive adoption in international markets ?
  - Demonstrating the better controls and assurance on product quality and patient safety

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