Harmonization of Requirements Between ICH Q3D and Pharmacopeias

Kahkashan Zaidi, USP
PQRI/USP Workshop on Elemental Impurities
March 31 – April 1, 2015
USP
Rockville, Maryland
20 year Journey

Elemental Impurities

Heavy Metals
Metals and Pharmacopeias:

- **Where we started from:**
  - **USP**
    - **<231> Heavy Metals**
      - 3 wet chemistry methods all involving
      - Sulfide precipitation of metals
      - Visual comparison to lead standards
  - **Ph.Eur.**
    - 2.4.8. Heavy metals
      - 8 wet chemistry methods
  - **JP**
    - 1.07 Heavy Metals Limit Test
      - 4 wet chemistry methods
• 1995 – First stimuli article identified issues with <231> method II (K. Blake)

• 2000 – Second stimuli article proposed ICP-MS as an instrumental alternative (T. Wang)

• 2004 – Third Stimuli article by USP’s PA6 EC recommended abandonment of the existing <231> for the first time.
2008

- **Stimuli Article** in PF 34(5) [Sept.—Oct. 2008] - General Chapter on Inorganic Impurities: Heavy Metals

- List of 31 elements with limits for Oral and Parenteral

- EMEA Guideline on the Specification Limits for Residues of Metal Catalysts (CPMP/SWP/4446/00) {enforced Sept. 2008}

- ICP Procedures
• EMEA Guideline on the Specification Limits for Residues of Metal Catalysts (CPMP/SWP/4446/00) {enforced Sept. 2008}

– Chapter 5.20 Metal catalyst or metal reagent residues
– 14 catalysts used in pharmaceutical synthesis
– Potential contaminants not address
– PDEs for Oral, Parenteral and Inhalation
**Concept Paper**

- **Establishment of appropriate limits for specific metals**, without necessarily providing details on the analytical procedures to be used.

- **Interested parties** participate in the effort to achieve initial agreement on metal impurities, *rather than the regulators and the pharmacopoeias reaching independent decisions which would necessitate subsequent harmonization.*

- **Harmonized analytical procedures** should be established by the pharmacopoeias for determining levels of metal impurities, with allowance for use of any appropriate validated procedure for a particular application.
2010

- USP published the following for comment in *PF 36*(1):
  - Chapter <232> Elemental Impurities-Limits
    - List of 16 elements with PDEs for Oral and Parenteral (EMA Elements minus Zn, Fe, and Mn)
    - Element Classification as Class 1 and Class 2
  - Chapter <233> Elemental Impurities-Procedures
  - Dietary Supplement chapter <2232>
  - Stimuli article with rationales for limits
  - Stimuli article with responses to comments on *PF 34*(5) stimuli article

- ICH Q3D EWG meeting
• June 2013, ICH Q3D reached step 2

• September 2014, ICH Q3D reached step 4
  – ICH released it on its website on Dec 16, 2014
USP Chapter <232>:

PF 37(3), May-June, 2011

- Revision proposed to align with Q3D (pre-stage 2 draft)
- No element classification
- Comment letter
  - Pb, Cd, Ni, Hg, Platinum Group of elements, Co, V, Cu, and Mo
Harmonization with Q3D

- **PF 40(2), March-April 2014**
  - Proposed revision to align with Q3D Step2
    - Comment Letter
      - PDEs
        - Hg, Mo, Cd, and Platinum Group (Pd, Os, Ir, Ru, and Rh)
        - Large Volume Parenterals (LVPs)
        - Topical and Mucosal Products (other products)
        - Rounding PDEs

- **USP-- Q3D EWG Discussions**
  - Jan 2014—March 2014
Harmonization with Q3D

Where are we today?

- Terminology
- Scope
- List of Elements
- PDEs
- Other Routes of Administration
- Options
- Implementation
## Harmonization

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<tr>
<th></th>
<th>Q3D</th>
<th>USP</th>
<th>Ph.Eur</th>
<th>JP</th>
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<tbody>
<tr>
<td><strong>Terminology</strong></td>
<td>Elemental Impurities</td>
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<tr>
<td><strong>Scope</strong></td>
<td>Harmonized</td>
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<td></td>
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<td>(Exception: TPNs)</td>
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<tr>
<td><strong>List of Elements</strong></td>
<td>24</td>
<td>15 Exception: Ti, Au, Se, Co, Ba, Sn, Li, Sb and Ag</td>
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<td><strong>PDEs</strong></td>
<td>Harmonized</td>
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<td><strong>Other Routes</strong></td>
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<td><strong>Options</strong></td>
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## Implementation in Europe

<table>
<thead>
<tr>
<th>Date</th>
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<tbody>
<tr>
<td>Dec 16, 2014</td>
<td>ICH Q3D step 4 published</td>
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<tr>
<td>December 2014</td>
<td>Adopted by CHMP, issued as EMA/CHMP/ICH/353369/2013</td>
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<tr>
<td>June 2016</td>
<td>ICH Q3D applicable to New Drug Products</td>
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<tr>
<td>Dec 2017</td>
<td>ICH Q3D applicable to Authorized Drug Products</td>
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<td></td>
<td>Delete cross-references to chapter 2.4.8 Heavy metals from all individual monographs</td>
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<tr>
<td>April 2015</td>
<td>Pharmeuropa- Publish list of all impacted monographs (Jan 2015)</td>
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**Q3D---** Application of Q3D to existing products is not expected prior to 36 months after publication of the guideline by ICH.
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<tr>
<td>Implementation of (&lt;232&gt;) and (&lt;2232&gt;)</td>
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<tr>
<td>○ Jan 1, 2018 Via USP General Notices</td>
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<td>○ Revision Bulletin March 27, 2015 official date of April 1, 2015</td>
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<tr>
<td>USP to publish list of monographs with cross reference to (&lt;231&gt;)</td>
<td><strong>Accomplished---July 2014 and Jan 14, 2015</strong></td>
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<td>Delete cross-references to <strong>General Chapter (&lt;231&gt;)</strong> <strong>Heavy metals</strong> from all individual monographs</td>
<td><strong>Accomplished---USP 38 and following publications with delayed implementation on Jan 1, 2018</strong></td>
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<tr>
<td>Publish Omission of General Chapter (&lt;231&gt;)</td>
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<td>○ Published in USP 38–NF 33 with an official date of December 1, 2015</td>
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<td>Flexible Procedures</td>
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USP Update

• March 27, 2015:

USP announces a revision to General Notices section 5.60.30 Elemental Impurities in USP Drug Products and Dietary Supplements, establishing **January 1, 2018** as the new date of applicability of General Chapters <232> Elemental Impurities—Limits and <2232> Elemental Contaminants in Dietary Supplements. USP also announces a revision to General Chapter <231> Heavy Metals and its references to **delay their omission until January 1, 2018**. Through these revisions, USP specifies that users could either continue to utilize the current <231> approach or implement the new <232>/<2232> approaches until January 1, 2018, at which time General Chapters <232> and <2232> will be made applicable to drug product and dietary supplement monographs as described in General Notices 5.60.30 and will be required unless specified otherwise in a monograph.
USP Website

- **March 27, 2015**
- General Chapters and Related Information
- To be Published in *Second Supplement to USP 38-NF 33*: (official on December 1, 2015)
  - <232> Elemental Impurities—Limits
  - <233> Elemental Impurities—Procedures

- **Revision Plan** (updated March 27, 2015)

- **Frequently Asked Questions**

Thank You!