USP <2232> Elemental Contaminants In Dietary Supplements

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Dietary Supplements: Background

- Dietary Supplements are composed of dietary ingredients + other components (excipients)
  - Herbs and other botanicals, Vitamins, Minerals, Amino Acids, Probiotics, Proteins
  - Wide range of dosage forms: tablets, capsules, soft-gels, chewable gels, powders

- Ingredients from natural sources are subject to contamination from water, air pollution, soil, agricultural inputs and processing procedures
  - A survey of 109 herbal products
    - 4 of 109 had elevated lead
    - 20 out of 109 had elevated cadmium
  - Some Ayurvedic medicines mix metal ash with herbs – contamination with extremely high levels of lead identified

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1 Current Findings on the Heavy Metal Content in Herbal Drugs, U. Gasser, B. Klier, A.V. Kühn, B. Steinhoff, © Pharmeuropa Scientific Notes 2009-1
Dietary Supplements and the Need for Limits

Ginkgo biloba supplements found to be heavily contaminated with lead

https://ods.od.nih.gov/factsheets/list-all/BotanicalDietarySupplements/
FDA regulates both finished dietary supplement products and dietary ingredients under a different set of regulations than those covering "conventional" foods and drug products.

Dietary Supplement Health and Education Act of 1994 (DSHEA):
- Manufacturers and distributors of dietary supplements and dietary ingredients:
  - Are prohibited from marketing products that are adulterated or misbranded.
  - Firms responsible for evaluating safety and labeling of products before marketing to ensure compliance with all DSHEA requirements and FDA regulations.
- FDA is responsible for taking action against any adulterated or misbranded dietary supplement product after it reaches the market.

Unlike drugs, compliance with USP standards is voluntary in the US.

Compliance is enforceable only for supplements claiming to meet USP/NF standards through the misbranding provisions of the Act.
Chapter Objective

Limit amounts of elemental contaminants in finished dietary supplement dosage forms labeled as conforming to USP or NF standards

- Only covers finished dosage forms, not dietary ingredients
- Focused on the 4 major elements of toxicological concern
  - Arsenic (inorganic)
  - Cadmium
  - Lead
  - Mercury (total and methylmercury)
- Extent of testing - determined by risk-based approach that takes into account likelihood of contamination from source through manufacturing
Limits of elemental contaminants based on Permitted Daily Exposure (PDE)

PDE derived from the Provisional Tolerable Weekly Intake (PTWI) recommended by Food and Agricultural Organization of the United Nations and World Health Organization (FAO/WHO)
- Daily exposure (μg/day) derived for each elemental contaminant from air, food and water
- PDE calculated by subtracting daily exposure from other sources
  • Based on average 50 kg body weight
  • Additional safety factor

Other regulations (such as California Proposition 65) may require different limits
Manufacturers are responsible for compliance with applicable local requirements differing from PDE values
Limits of Elemental Contaminants

<table>
<thead>
<tr>
<th>Element</th>
<th>PDE (µg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic (Inorganic)</td>
<td>15</td>
</tr>
<tr>
<td>Cadmium</td>
<td>5</td>
</tr>
<tr>
<td>Lead</td>
<td>5</td>
</tr>
<tr>
<td>Mercury (total)</td>
<td>15</td>
</tr>
<tr>
<td>Methylmercury (as Hg)</td>
<td>2</td>
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</table>

- Arsenic – may be measured using nonspeciation procedure under assumption that all arsenic is inorganic – where limit is exceeded using nonspeciation procedure, compliance with the inorganic limit may be demonstrated using a speciation procedure.

- Methylmercury determination is not required when content for total mercury is less than the limit for methylmercury.
Options for Compliance

- Dietary Supplement Analysis Option
- Individual Component Option
- Summation Option
- [Speciation procedures for inorganic arsenic and methyl mercury are provided in this chapter]
Dietary Supplement Analysis Option

- This option is generally applicable

- The finished dietary supplement dosage form is analyzed based on the methods in Elemental Impurities – Procedures <233>

- Speciation procedures in <2232> should be used if necessary

- Analysis:
  - Calculate the measured amount of each elemental contaminant in μg/daily intake as:
    - Result = MVSS x N
    - Where
      - MVSS= measurement amount of each elemental contaminant (μg/serving size)
      - N = Maximum daily intake recommended in labeling (servings/day)
Individual Component Option

- Applicable to finished dietary supplement dosage forms with maximum daily intake of NMT 10g of dietary supplement finished product
  - If all components in a formulation meet the limits given for the Individual Component Limits, these components can be used in any proportion without further calculation

- Unless otherwise specified in the monograph, proceed with analysis of individual components

  **Elemental Limits for use with the Individual Component Option**

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<th>Element</th>
<th>Individual Component Limits (µg/g)</th>
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<tbody>
<tr>
<td>Arsenic (inorganic)*</td>
<td>1.5</td>
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<tr>
<td>Cadmium</td>
<td>0.5</td>
</tr>
<tr>
<td>Lead</td>
<td>0.5</td>
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*Speciation is not necessary when the total arsenic or mercury is less than the limit above
Option can be used

- For any finished dietary supplement dosage forms that are consumed in quantities greater than 10 g/day
- Where the acceptance limit for any contaminant in any component of the dietary supplement exceeds the applicable individual component limits

Proceed with the analysis of the components (unless otherwise specified in the monograph)
Summation Option: Calculation and Acceptance Criteria

- Calculate the amount of each elemental contaminant in μg/daily intake present in finished dietary supplement dosage form
  - Result = Σ(Cᵢ x Wᵢ) x N
    - Cᵢ – elemental contaminant concentration in the individual component (μg/g)
    - Wᵢ – weight of each individual component per serving of dietary supplement (g/serving)
    - N = maximum daily intake of supplement

- Acceptance Criteria
  - The calculated amount of each elemental contaminant/daily intake is NMT the PDE

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Questions

Empowering a healthy tomorrow
Thank You

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