Module 4

Considerations for Parenteral Products

ICH Q3D Elemental Impurities

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Content

• Wording in guideline
• Principles supporting the 2 L parenteral limit
• Examples
Q3D: Large Volume Parenteral Section

Parenteral drug products with maximum daily volumes up to 2 liters may use the maximum daily volume to calculate permissible concentrations from PDEs. For products whose daily volumes, as specified by labeling and/or established by clinical practice, may exceed 2 liters (e.g., saline, dextrose, total parenteral nutrition, solutions for irrigation), a 2-liter volume may be used to calculate permissible concentrations from PDEs. (Reference 4)

Maintenance Fluid Replacement

• In 1957, Holliday and Segar proposed a method for determining the average daily fluid replacement need for hospitalized patients. (Holliday, Segar [1957], ref. 1)
  o Summary, based on patient body weight
    - First 10 kg body weight: 100 ml/kg/day
    - Second 10 kg body weight: 50 ml/kg/day
    - Thereafter: 20 ml/kg/day

• This method is still considered the standard of care.
  o “The Holliday-Segar equation remains the standard method for calculating maintenance fluid requirements.” (Meyers, [2009], ref. 2)

Holliday-Segar nomogram

- Summary: 1 ml of replacement fluid is required for every 1 Calorie expended. Caloric expenditure is correlated with body weight.

- A 50 kg patient requires about 2000 ml of fluid per day parenterally.

- Q3D established 2 liters as the reference volume for determining elemental impurity levels in parenteral products that may be delivered in large volume.
  - Q3D PDEs are based on 50 kg body weight

- On the basis of body weight, the Holliday-Segar nomogram confers an additional safety factor when volumes exceeding 2 liters are delivered to patients whose body weight exceeds 50 kg.
Example 1: 10% Dextrose Injection, USP

• Product information
  o Supplied in 1L PVC bags
  o Dose1: daily dose set at 2L
  o USP water for injection is used to produce the drug product

• Risk assessment approach
  o Risk assessment conducted using the drug product approach
    - During a review of the components of the drug product no potential elemental impurities were identified as likely to be present
    - Manufacturer conducted testing on samples from 3 representative commercial batches of the drug product to support the risk assessment (testing included class 1, 2A and 3 elements)
  o Leachable studies demonstrate that there are no significant elemental impurity contributions from the container closure system over the shelf life of the product.

1. Package Insert Dosage: “As directed by a physician. Dosage is dependent upon the age, weight and clinical condition of the patient.”
### Example 1: 10% Dextrose Injection, USP

<table>
<thead>
<tr>
<th>Lot number</th>
<th>As, µg/L</th>
<th>Cd, µg/L</th>
<th>Hg, µg/L</th>
<th>Pb, µg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>20xx001</td>
<td>&lt;0.50</td>
<td>&lt;0.10</td>
<td>&lt;0.25</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>20xx002</td>
<td>&lt;0.50</td>
<td>&lt;0.10</td>
<td>&lt;0.25</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>20xx003</td>
<td>&lt;0.50</td>
<td>&lt;0.10</td>
<td>&lt;0.25</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Total daily level¹</td>
<td>&lt;1.0</td>
<td>&lt;0.20</td>
<td>&lt;0.50</td>
<td>&lt;0.20</td>
</tr>
<tr>
<td>PDE</td>
<td>15 µg/day</td>
<td>2 µg/day</td>
<td>3 µg/day</td>
<td>5 µg/day</td>
</tr>
<tr>
<td>Control threshold</td>
<td>4.5 µg/day</td>
<td>0.6 µg/day</td>
<td>0.9 µg/day</td>
<td>1.5 µg/day</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lot number</th>
<th>Co, µg/L</th>
<th>V, µg/L</th>
<th>Ni, µg/L</th>
<th>Li, µg/L</th>
<th>Sb, µg/L</th>
<th>Ba, µg/L</th>
<th>Mo, µg/L</th>
<th>Cu, µg/L</th>
<th>Sn, µg/L</th>
<th>Cr, µg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>20xx001</td>
<td>&lt;0.20</td>
<td>&lt;0.40</td>
<td>&lt;2.0</td>
<td>&lt;10.0</td>
<td>&lt;2.0</td>
<td>&lt;1.0</td>
<td>&lt;10.0</td>
<td>&lt;2.0</td>
<td>&lt;3.0</td>
<td>&lt;10.0</td>
</tr>
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<td>&lt;1.0</td>
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<td>&lt;2.0</td>
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</tr>
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<td>20xx003</td>
<td>&lt;0.20</td>
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<td>&lt;2.0</td>
<td>&lt;10.0</td>
<td>&lt;2.0</td>
<td>&lt;1.0</td>
<td>&lt;10.0</td>
<td>&lt;2.0</td>
<td>&lt;3.0</td>
<td>&lt;10.0</td>
</tr>
<tr>
<td>Total daily level¹</td>
<td>&lt;0.40</td>
<td>&lt;0.80</td>
<td>&lt;4.0</td>
<td>&lt;20.0</td>
<td>&lt;4.0</td>
<td>&lt;2.0</td>
<td>&lt;20.0</td>
<td>&lt;2.0</td>
<td>&lt;6.0</td>
<td>&lt;20.0</td>
</tr>
<tr>
<td>PDE</td>
<td>5 µg/day</td>
<td>10 µg/day</td>
<td>20 µg/day</td>
<td>250 µg/day</td>
<td>90 µg/day</td>
<td>700 µg/day</td>
<td>1500 µg/day</td>
<td>300 µg/day</td>
<td>600 µg/day</td>
<td>1100 µg/day</td>
</tr>
<tr>
<td>Control threshold</td>
<td>1.5 µg/day</td>
<td>3 µg/day</td>
<td>6 µg/day</td>
<td>75 µg/day</td>
<td>27 µg/day</td>
<td>210 µg/day</td>
<td>450 µg/day</td>
<td>90 µg/day</td>
<td>180 µg/day</td>
<td>330 µg/day</td>
</tr>
</tbody>
</table>

¹ (2L x observed level)
Example 1: 10% Dextrose Injection, USP

- **Conclusions**
  - All values for the potential elemental impurities of concern were observed to be less than the detection limit.
  - For each element, the limit of quantitation is less than the control threshold.
Example 2: 0.45% Sodium Chloride Injection, USP

**Product information**
- Supplied in 1L PVC bags
- Dose1: daily dose set at 2L
- USP water for injection is used to produce the drug product

**Risk assessment approach – component approach**
- An assessment of the water for injection revealed that the only potential elemental impurities to be considered were As, Cd, Hg, and Pb.
- Literature revealed mean results for three grades of salt using validated methods ([http://eusalt.com/salt-quality, As, Cd, Hg, Pb testing in salt](http://eusalt.com/salt-quality, As, Cd, Hg, Pb testing in salt))
- Manufacturing equipment does not contribute elemental impurities due to mild conditions employed in the manufacture of the drug product
- Leachable studies demonstrate that there are no significant elemental impurity contributions from the container closure system
- Monitoring of the WFI quality demonstrates that there are no significant elemental impurity contributions.

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1 Package Insert Dosage: “As directed by a physician. Dosage is dependent upon the age, weight and clinical condition of the patient.”
Example 2: 0.45% Sodium Chloride Injection, USP

<table>
<thead>
<tr>
<th></th>
<th>As, conc.</th>
<th>Cd, conc.</th>
<th>Hg, conc.</th>
<th>Pb, conc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum level in NaCl*</td>
<td>0.024 µg/g</td>
<td>0.011 µg/g</td>
<td>0.00062 µg/g</td>
<td>0.0808, µg/g</td>
</tr>
<tr>
<td>Water for injection</td>
<td>&lt;0.50 µg/L</td>
<td>&lt;0.10 µg/L</td>
<td>&lt;0.25 µg/L</td>
<td>&lt;0.10 µg/L</td>
</tr>
<tr>
<td>Impurity level per liter of drug product</td>
<td>&lt;0.5108</td>
<td>&lt;0.1495</td>
<td>&lt;0.25279</td>
<td>&lt;0.464</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>As, µg</th>
<th>Cd, µg</th>
<th>Hg, µg</th>
<th>Pb, µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total µg/day (based on total 2L/day)</td>
<td>&lt;1.0216 µg</td>
<td>&lt;0.299 µg</td>
<td>&lt;0.50558 µg</td>
<td>&lt;0.928 µg</td>
</tr>
<tr>
<td>PDE</td>
<td>15 µg/day</td>
<td>2 µg/day</td>
<td>3 µg/day</td>
<td>5 µg/day</td>
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<td>1.5 µg/day</td>
</tr>
</tbody>
</table>

* NaCl data reported represent the maximum levels reported in the literature (see references)

Conclusions:

- All potential elemental impurity levels are lower than the control threshold for each elemental impurity
References

• European Committee for the Study of Salt, ECSS/CN 287-1982, Statistical Study of Inter-Laboratory Analysis of Sodium Chloride (As, Cd, Hg, Pb)
  o As: EuSalt/AS 011-2005
  o Hg: EuSalt/AS 012-2005
  o Pb: EuSalt/AS 013-2005
  o Cd: EuSalt/AS 014-2005