**BRIEFING**

**Edetate Calcium Disodium, USP 29 page 779.** The Japanese Pharmacopoeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the *Edetate Calcium Disodium* monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph, which represents the **ADPTION STAGE 6** document, is based on the corresponding monograph for Edetate Calcium Disodium that was prepared by the Japanese Pharmacopoeia. The Japanese Pharmacopoeia draft was based in part on comments from the European Pharmacopoeia and the United States Pharmacopoeia in response to the Provisional Harmonized Text Stage 5A and 5B drafts prepared by the Japanese Pharmacopoeia.

Differences between the Japanese Pharmacopoeia **Adoption Stage 6** document and the current *USP* monograph for Edetate Calcium Disodium include the following:

1. **Definition**— Changed to reflect new purity specifications (not less than 98.0%).
2. **Storage**— Retained as a nonharmonized attribute.
3. **Identification**— *Identification* test A (IR absorption) is retained as a nonharmonized attribute. Tests B and C are replaced by more definitive tests for calcium and sodium, respectively. Test B was updated to include experimental detail consistent with JP standards. *Identification* test C replaced the existing procedure with a pyroantimonate test to be consistent with JP standards.
4. **pH**— No change.
5. **Chloride**— New test added to reflect sign-off draft.
6. **Magnesium-chelating substances**— Renamed as *Disodium edetate*. Changed to reflect decrease in sample concentration, and titrant changed to magnesium chloride to be consistent with JP.
7. **Water**— Updated specification to include lower limit of 5.0% to be consistent with JP.
8. **Heavy metals**— Retained as a nonharmonized attribute.
9. **Limit of nitritotriacetic acid**— Retained as a nonharmonized attribute.
10. **Assay**— Procedure changed to harmonize with JP and EP standards. Decreased sample size to 0.5 g and increased volume of water in test solution to 200 mL. Changed titrant to bismuth nitrate and indicator to xylenol orange to eliminate use of mercuric nitrate.

(MD-GRE: K. Moore) RTS—C44011

**Edetate Calcium Disodium**

*Add the following:*

<table>
<thead>
<tr>
<th><strong>Pharmacopeial Discussion Group Sign-Off Document</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Attributes</strong></td>
</tr>
<tr>
<td>Definition</td>
</tr>
<tr>
<td>Identification B</td>
</tr>
<tr>
<td>Identification C</td>
</tr>
</tbody>
</table>

**Attributes**

<table>
<thead>
<tr>
<th>Attributes</th>
<th>EP</th>
<th>JP</th>
<th>USP</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Purity (1) Chloride</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Purity (2) Disodium edetate</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Water</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Assay</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

**Legend:** + will adopt and implement; - will not stipulate.

**Nonharmonized attributes:** Clarity and/or color of solution, Heavy metals, Identification by IR absorption, Limit of nitrilotriacetic acid, Storage.

**Specific local attributes:** Description (JP), Iron (EP). ♦\(^{2S}\) (USP30)

![Chemical Structure](image)

\[C_{10}H_{12}CaNa_2O_8 \cdot xH_2O\] 374.27

Calcitate (2-), \([N,N'\text{-}1,2\text{-ethanediylbis}[N\text{-}(carboxymethyl)glycinato]](4-)\text{-}N,N',O,O'N,O'N\text{-},\] disodium, hydrate, (OC-6-21)-.

Disodium[(ethylenedinitrilo)tetraacetato]calciate(2-) hydrate \([23411-34-9]\).

Anhydrous [62-33-9].

**Delete the following:**

- Edetate Calcium Disodium is a mixture of the dihydrate and trihydrate of calcium disodium ethylenediaminetetraacetate (predominantly the dihydrate). It contains not less than 97.0 percent and not more than 102.0 percent of \(C_{10}H_{12}CaNa_2O_8\) calculated on the anhydrous basis.

**Add the following:**

Edetate Calcium Disodium contains not less than 98.0 percent and not more than 102.0 percent of \( \text{C}_{10}\text{H}_{12}\text{CaN}_{2}\text{Na}_{2}\text{O}_{8} \) (374.27), calculated on the anhydrous basis.

**Delete the following:**

- **Packaging and storage**—Preserve in tight containers.

**Add the following:**

- **Packaging and storage**—Preserve in tight containers. No storage requirements specified.

**USP Reference standards** (11) — *USP Edetate Calcium Disodium RS.*

**Delete the following:**

- **Identification**—

  A: *Infrared Absorption* (197M).

  B: A solution (1 in 20) responds to the oxalate test for *Calcium* (191) and to the flame test for *Sodium* (191).

  C: To 5 mL of water add 2 drops of ammonium thiocyanate TS and 2 drops of ferric chloride TS. To the deep red solution add about 50 mg of Edetate Calcium Disodium, and mix: the deep red color disappears.

**Add the following:**

- **Identification**—

  A: *Infrared Absorption* (197M).

  B: Dissolve 2 g in 10 mL of water, add 6 mL of lead (II) nitrate solution (33 in 1000), shake, and add 3 mL of potassium iodide TS: no yellow precipitate is formed. Make this solution alkaline by the addition of diluted ammonia solution (7 in 50), and add 3 mL of ammonium oxalate TS: a white precipitate is formed.

  C: Dissolve 0.5 g in 10 mL of water, and add 10 mL of potassium pyroantimonate TS: a white, crystalline precipitate is formed. The formation of the precipitate is accelerated by rubbing the inside wall of the test tube with a glass rod.

  **pH** (791): between 6.5 and 8.0, in a solution (1 in 5).

**Add the following:**

- **Chloride** (221) — To 0.70 g add 20 mL of water and 30 mL of diluted nitric acid, allow to stand for 30 minutes, and filter. To 10 mL of the filtrate add water to make 50 mL, and perform the test using this solution as the test solution. Prepare the control solution with 0.40 mL of 0.01 M hydrochloric acid VS (not more than 0.10%).
Delete the following:

**Magnesium-chelating substances**— Weigh accurately 1.0 g, transfer to a small beaker, and dissolve in 5 mL of water. Add 5 mL of ammonia-ammonium chloride buffer TS. Then to the buffered solution add 5 drops of eriochrome black TS, and titrate with 0.10 M magnesium acetate to the appearance of a deep wine-red color; not more than 2.0 mL is required. 2S (USP30)

Add the following:

**Disodium edetate**— Dissolve 1.00 g of Edetate Calcium Disodium in 50 mL of water, add 5 mL of ammonia-ammonium chloride buffer TS, and 40 mg of eriochrome black T–sodium chloride indicator. Titrate with 0.01 M magnesium chloride VS until the color of the solution changes from blue to red-violet: not more than 3.0 mL of 0.01 M magnesium chloride VS is consumed (not more than 1.0%). 2S (USP30)

Delete the following:

**Water, Method I (921)**: not more than 13.0%. 2S (USP30)

Add the following:

**Water, Method I (921)**: between 5.0% and 13.0%, determined on 0.2 g. 2S (USP30)

Heavy metals, Method II (231): 0.002%.

Limit of nitrilotriacetic acid—

Mobile phase, Cupric nitrate solution, Stock standard solution, and Chromatographic system — Prepare as directed in the test for Limit of nitrilotriacetic acid under Edetate Disodium.

Resolution solution— Using Edetate Calcium Disodium instead of Edetate Disodium, prepare as directed for Resolution solution in the test for Limit of nitrilotriacetic acid under Edetate Disodium.

Standard solution— Transfer 1.0 g of Edetate Calcium Disodium to a 100-mL volumetric flask, add 100 µL of Stock standard solution, dilute with Cupric nitrate solution to volume, and mix. Sonicate, if necessary, to achieve complete solution.

Test solution— Transfer 1.0 g of Edetate Calcium Disodium to a 100-mL volumetric flask, dilute with Cupric nitrate solution to volume, and mix. Sonicate, if necessary, to achieve complete solution.

Procedure— Proceed as directed for Procedure in the test for Limit of nitrilotriacetic acid under Edetate Disodium; the response of the nitrilotriacetic acid peak of the Test solution does not exceed the difference between the nitrilotriacetic acid peak responses obtained from the Standard solution and the Test solution (0.1%).

Delete the following:

**Residual solvents** (467): meets the requirements. (Official January 1, 2007) 2S (USP30)
Delete the following:

- **Assay**—Weigh accurately about 1.2 g of Edetate Calcium Disodium, transfer to a 250-mL beaker, and dissolve in 75 mL of water. Add 25 mL of 1 N acetic acid and 1 mL of diphenylcarbazone TS, and titrate slowly with 0.1 M mercuric nitrate VS to the appearance of the first purplish color. Perform a blank determination, and make any necessary correction. Each mL of 0.1 M mercuric nitrate is equivalent to 37.43 mg of \( \text{C}_{40}\text{H}_{42}\text{CaN}_{2}\text{Na}_{2}\text{O}_{8} \cdot 2\text{H}_{2}\text{O} \) (USP30).

Add the following:

- **Assay**—Transfer about 500 mg of Edetate Calcium Disodium, accurately weighed, into a 200-mL volumetric flask. Dissolve in and dilute with water to volume, and mix. Transfer exactly 20 mL of this solution to 80 mL of water, and adjust with dilute nitric acid to a pH of 2 to 3. Add two drops of xylenol orange TS, and titrate with 0.01 M bismuth nitrate VS until the color of the solution changes from yellow to red. Each mL of 0.01 M bismuth nitrate VS is equivalent to 3.743 mg of \( \text{C}_{10}\text{H}_{12}\text{CaN}_{2}\text{Na}_{2}\text{O}_{8} \cdot 2\text{H}_{2}\text{O} \) (USP30).

**Auxiliary Information**—Staff Liaison: Elena Gonikberg, Ph.D., Senior Scientist

*Expert Committee*: (MDGRE05) Monograph Development-Gastrointestinal Renal and Endocrine

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