**MONOGRAPHS (USP)**

**BRIEFING**

Saccharin Sodium, USP 28 page 1745 and page 612 of PF 31(2) [Mar.–Apr. 2005]. The United States Pharmacopeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the Saccharin Sodium monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopoeias. The following monograph, which represents the ADOPTION STAGE 6 document, is based in part on comments from the Japanese Pharmacopoeia and the European Pharmacopoeia in response to the Provisional Harmonized Text Stage 5A and 5B drafts prepared by the United States Pharmacopeia.

Pharmacopeial Discussion Group Sign-Off Document

<table>
<thead>
<tr>
<th>Attributes</th>
<th>EP</th>
<th>JP</th>
<th>USP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Identification B</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Identification C</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Acidity or alkalinity</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Water</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Readily carbonizable substances</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Limit of benzoate and salicylate</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:**
- Packaging and storage.
- Heavy metals.
- Labeling.
- Clarity of solution.
- Color of solution.
- Limit of toluenesulfonamides.
- Identification A (IR).

**Specific local attributes:**
- USP: Organic volatile impurities;
- JP: Description.

**Reagents and reference materials:** Each pharmacopeia will adapt the text to take account of local reference materials and reagent specifications.

Differences between the ADOPTION STAGE 6 document and the current NF monograph include the following:
1. In the opening paragraph (the Definition) — The lower limit is changed from not less than 98.0 percent to not less than 99.0 percent.
2. Packaging and storage — Storage conditions at room temperature are added.
3. Labeling — No change.
4. USP Reference standards — A reference for Saccharin Sodium is added for use in the Identification test A.
5. Clarity of solution — This test is added to comply with EP standards.
6. Color of solution — This test is added to comply with EP standards.
7. Identification — Identification tests A, B, and D are replaced with a more definitive IR absorption test. Identification test C is retained, but separated into two tests (B and C). Because the preparation of potassium pyroantimonate TS has changed, the preparation of the potassium pyroantimonate solution for this test is added to comply with the harmonization draft.
8. Water — No change.
9. Readily carbonizable substances — No change.
10. Selenium — This test is deleted because it is unnecessary for this compound.
11. Limit of toluenesulfonamides — The test method and limits are changed to those of the European Pharmacopoeia, which include a more modern test method. The Test solution is corrected to that of the EP. Editorial changes are made.
12. Heavy metals — No change.
13. Limit of benzoate and salicylate — No change.
14. Organic volatile impurities — No change.
15. Assay — No change.

(EMC: J. Lane) RTS — 42529-1

**Change to read:**

**Saccharin Sodium**

![Chemical structure of Saccharin Sodium](image)

C$_7$H$_7$NNaO$_5$S·2H$_2$O 244.20
1,2-Benzisothiazol-3-(2H)-one, 1,1-dioxide, sodium salt, dihydrate.
1,2-Benzisothiazolin-3-one, 1,1-dioxide, sodium salt dihydrate
[6155-52-2].

Anhydrous 205.17 [428-14-0].

Saccharin Sodium contains not less than 98.0 percent and not more than 101.0 percent of C$_7$H$_7$NNaO$_5$S calculated on the anhydrous basis.

**Packaging and storage** — Preserve in well-closed containers.

**Labeling** — Where the quantity of saccharin sodium is indicated in the labeling of any preparation containing Saccharin Sodium, this shall be expressed in terms of saccharin (C$_7$H$_7$NO$_5$S).

**USP Reference standards**
- USP o-Toluenesulfonamide RS
- USP Toluenesulfonamide RS

**Identification**

A: The residue obtained by igniting it responds to the tests for

B: To 10 mL of a solution (1 in 10) add 1 mL of hydrochloric acid: a crystalline precipitate of saccharin is formed. Wash the precipitate with cold water until the last washing is free from chloride, and dry at 105° for 2 hours: it melts between 226° and 230° C. The procedure for Class I being used (see Melting Range or Temperature: 241).

**Alkalinity** — A solution (1 in 10) is neutral or alkaline to litmus, but no red color is produced with phenolphthalein TS.
Toluenesulfonamides—


Test preparation—Prepare as directed under Column Partition Chromatography (see Chromatography (621)), employing a chromatographic tube fitted with a porous glass disk in its base, a plastic stopcock on the delivery tube, and a reservoir on the top. Add a mixture consisting of 10 g of Solid Support and a solution of 2.0 g, accurately weighed, of Saccharin Sodium in 8.0 mL of sodium carbonate solution (1 in 20), and proceed as directed under Test preparation in the test for Toluenesulfonamides under Saccharin (see NF monograph), beginning with “Pack the contents.”

Chromatographic system and Procedure—Proceed as directed for Chromatographic system and Procedure in the test for Toluenesulfonamide under Saccharin (see NF monograph).

Heavy metals, Method I (231)—Dissolve 4 g in 46 mL of water, add 1 mL of 1 N hydrochloric acid, mix, and rub the inner wall of the vessel with a glass rod until crystallization begins. Allow the solution to stand for 1 hour, and then filter through a dry filter, discarding the first 10 mL of the filtrate: the limit, determined on 25 mL of the subsequent filtrate, is 0.001%.

Organic volatile impurities, Method IV (467) meets the requirements.

Other requirements—It responds to Identification tests A and B, and meets the requirements of the tests for Water, Benzoate and salicylate, Selenium, and Readily carbonizable substances under Saccharin Calcium.

Assay—Proceed with Saccharin Sodium as directed in the Assay under Saccharin Calcium. Each mL of 0.1 N sodium hydroxide is equivalent to 20.52 mg of C₇H₄NNaO₃S.

Saccharin Sodium

\[ \text{C}_7\text{H}_4\text{NNaO}_3\text{S} \cdot 2\text{H}_2\text{O} \quad 241.20 \]

1,2-Benzisothiazol-3(2H)-one, 1,1-dioxide, sodium salt, dihydrate.

1,2-Benzisothiazolin-3-one 1,1-dioxide sodium salt dihydrate \[ 6155-57-3 \].

Anhydrous 205.17 \[ 128-44-9 \].

> Saccharin Sodium contains not less than 99.0 percent and not more than 101.0 percent of C₇H₅NNaO₃S · 2H₂O, calculated on the anhydrous basis.

Packaging and storage—Preserve in well-closed containers. Store at room temperature.

Labeling—Where the quantity of saccharin sodium is indicated in the labeling of any preparation containing Saccharin Sodium, this shall be expressed in terms of saccharin (C₇H₅NO₃S).

USP Reference standards (11)—USP Saccharin Sodium RS. USP o-Toluenesulfonamide RS. USP p-Toluenesulfonamide RS.

Clarity of solution—[NOTE—The Test solution is to be compared to Reference suspension A and to water in diffused daylight 5 minutes after preparation of Reference suspension A.]

Hydrazine solution—Transfer 1.0 g of hydrazine sulfate to a 100-mL volumetric flask, dissolve in and dilute with water to volume, and mix. Allow to stand for 4 to 6 hours.

Methenamine solution—Transfer 2.5 g of methenamine to a 100-mL glass-stoppered flask, add 25.0 mL of water, insert the glass stopper, and mix to dissolve.

Primary opalescent suspension—[NOTE—This suspension is stable for 2 months, provided it is stored in a glass container free from surface defects. The suspension must not adhere to the glass and must be well mixed before use.] Transfer 25.0 mL of Hydrazine solution to the Methenamine solution in the 100-mL glass-stoppered flask. Mix, and allow to stand for 24 hours.
Opalescence standard—[NOTE—This suspension should not be used beyond 24 hours after preparation.] Transfer 15.0 mL of the Primary opalescent suspension to a 1000-mL volumetric flask, dilute with water to volume, and mix.

Reference suspensions—Transfer 5.0 mL of the Opalescence standard to a 100-mL volumetric flask, dilute with water to volume, and mix to obtain Reference suspension A. Transfer 10.0 mL of the Opalescence standard to a second 100-mL volumetric flask, dilute with water to volume, and mix to obtain Reference suspension B.

Test solution—Dissolve 5.0 g of test material in about 20 mL of a 200 g per L solution of sodium acetate, dilute with water the same solution to 25 mL, and mix.

Procedure—Transfer a sufficient portion of the Test solution to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 mm to 25 mm to obtain a depth of 40 mm. Similarly transfer portions of Reference suspension A, Reference suspension B, water, and a 200 g per L solution of sodium acetate to separate matching test tubes. Compare the Test solution, Reference suspension A, Reference suspension B, water, and a 200 g per L solution of sodium acetate in diffused daylight, viewing vertically against a black background (see Visual Comparison under Spectrophotometry and Light-Scattering (851)). [NOTE—The diffusion of light must be such that Reference suspension A can readily be distinguished from water, and that Reference suspension B can readily be distinguished from Reference suspension A.] The Test solution shows the same clarity as that of water, or of the 200 g per L solution of sodium acetate, or its opalescence is not more pronounced than that of Reference suspension A.

Color of solution—

Standard stock solution—Combine 3.0 mL of ferric chloride CS, 3.0 mL of cobaltous chloride CS, 2.4 mL of cupric sulfate CS, and 1.6 mL of dilute hydrochloric acid (10 g per L).

Standard solution—[NOTE—Prepare the Standard solution immediately before use.] Transfer 1.0 mL of Standard stock solution to a 100-mL volumetric flask, dilute with dilute hydrochloric acid (10 g per L) to volume, and mix.

Test solution—Use the Test solution from the test for Clarity of solution.

Procedure—Transfer a sufficient portion of the Test solution to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 mm to 25 mm to obtain a depth of 40 mm. Similarly transfer portions of Standard solution, a 200 g per L solution of sodium acetate, and water to separate matching test tubes. Compare the Test solution, the Standard solution, a 200 g per L solution of sodium acetate, and water in diffused daylight, viewing vertically against a white background (see Visual Comparison under Spectrophotometry and Light-Scattering (851)). The Test solution has the appearance of water or of the 200 g per L solution of sodium acetate, or is not more intensely colored than the Standard solution.

Identification—

A: Infrared Absorption (197K)—Dry the specimen at 105° for 2 hours before use.

B: To a solution (1 in 10) add 2 mL of 15% potassium carbonate, and heat to boiling. No precipitate is formed. Add 4 mL of potassium pyroantimonate TS Potassium pyroantimonate solution, and heat to boiling. Allow to cool in ice water and, if necessary, rub the inside of the test tube with a glass rod. A dense precipitate is formed.
Potassium pyroantimonate solution—Dissolve 2 g of potassium pyroantimonate in 95 mL of hot water. Cool quickly, and add a solution containing 2.5 g of potassium hydroxide in 50 mL of water and 1 mL of sodium hydroxide solution (8.5 in 100). Allow to stand for 24 hours, filter, and dilute with water to 150 mL.

C: Sodium salts impart an intense yellow color to a non-luminous flame.

Acidity or alkalinity—To a solution of 1.0 g in 10 mL of carbon dioxide-free water add 1 drop of phenolphthalein TS: no pink color is produced. Then add 1 drop of 0.1 N sodium hydroxide: a pink color is produced.

Water, Method I (291): not more than 15.0%.

Readily carbonizable substances (271)—Dissolve 200 mg in 5 mL of sulfuric acid (between 94.5% and 95.5% [w/w] of H₂SO₄), and keep at a temperature of 48° to 50° for 10 minutes: the solution has no more color than Matching Fluid A, when viewed against a white background.

Heavy metals, Method I (231)—Dissolve 4 g in 46 mL of water, add 4 mL of dilute hydrochloric acid (1 in 12), mix, and rub the inner wall of the vessel with a glass rod until crystallization begins. Allow the solution to stand for 1 hour, then pass through a dry filter, discarding the first 10 mL of the filtrate, and use 25 mL of the subsequent filtrate for the Test Preparation: the limit is 0.001%.

Limit of toluenesulfonamides—

Internal standard solution—Dissolve 25 mg of caffeine in methylene chloride, and dilute with the same solvent to 100 mL.

Reference solution—Dissolve 20.0 mg of USP o-Toluene- sulfonamide RS and 20.0 mg of USP p-Toluene sulfonamide RS in methylene chloride, and dilute with the same solvent to 100.0 mL. Dilute 5.0 mL of the solution with methylene chloride to 50.0 mL. Evaporate 5.0 mL of the final solution to dryness in a stream of nitrogen. Dissolve the residue in 1.0 mL of the Internal standard solution.

Test solution—Suspend 10.0 g of the substance to be examined in 20 mL of water, and dissolve using 5 mL to 6 mL of 1 N sodium hydroxide. Dissolve 10.0 g of the substance to be examined in about 45 mL of water. If necessary, adjust the solution with 1 N sodium hydroxide or 1 N hydrochloric acid to a pH of 7 to 8, and dilute with water to 50 mL. Shake the solution with four quantities each of 50 mL of methylene chloride. Combine the lower layers, dry over anhydrous sodium sulfate, and filter. Wash the filter and the sodium sulfate with 10 mL of methylene chloride. Combine the solution and the washings, and evaporate almost to dryness in a water bath at a temperature not exceeding 40°. Using a small quantity of methylene chloride, quantitatively transfer the residue into a suitable 10-mL tube, evaporate to dryness in a stream of nitrogen, and dissolve the residue in 1.0 mL of the Internal standard solution.

Blank solution—Evaporate 200 mL of methylene chloride to dryness in a water bath at a temperature not exceeding 40°. Dissolve the residue in 1 mL of methylene chloride.

Chromatographic system (see Chromatography (621))—The instrument gas chromatograph is equipped with a flame-ionization detector and contains a 0.53-mm × 10-m fused silica column, coated with G3 phase (film thickness 2 μm). The injector port, column, and detector temperatures are maintained at about 250°, 180°, and 250°, respectively; and nitrogen is used as the carrier gas at a flow rate of about 10 mL per minute. The injector employs a split ratio of 1:2.

Procedure—Inject about 1 μL of the Reference solution. Adjust the sensitivity of the detector so that the height of the peak due to caffeine is not less than 50% of the full scale of
the recorder. The substances are eluted in the following order: \( o \)-toluenesulfonamide, \( p \)-toluenesulfonamide, and caffeine. The test is not valid unless the resolution between the peaks due to \( o \)-toluenesulfonamide and \( p \)-toluenesulfonamide is at least 1.5. Inject about 1 \( \mu \)L of the Blank solution. In the chromatogram obtained, verify that there are no peaks with the same retention times as the internal standard, \( o \)-toluenesulfonamide, and \( p \)-toluenesulfonamide. Inject about 1 \( \mu \)L of the Test solution and 1 \( \mu \)L of the Reference solution. If any peaks due to \( o \)-toluenesulfonamide and \( p \)-toluenesulfonamide appear in the chromatogram obtained with the Test solution, the ratio of their areas to that of the internal standard is not greater than the corresponding ratio in the chromatogram obtained with the Reference solution (10 ppm of \( o \)-toluenesulfonamide and 10 ppm of \( p \)-toluenesulfonamide).

**Limit of benzoate and salicylate**—To 10 mL of a solution (1 in 20), previously acidified with 5 drops of 6 N acetic acid, add 3 drops of ferric chloride TS: no precipitate or violet color appears.

**Organic volatile impurities, Method I (467):** meets the requirements.

**Assay**—Dissolve, with the aid of slight heating if necessary, about 150 mg of Saccharin Sodium, accurately weighed, in 50 mL of glacial acetic acid. Titrate with 0.1 N perchloric acid, determining the endpoint potentiometrically. Perform a blank titration, if necessary, and make the appropriate correction. Each mL of 0.1 N perchloric acid is equivalent to 20.52 mg of \( C_7H_4NNaO_3S \) (USP29).

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**MONOGRAPHS (NF)**

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**Briefing**

**Silicon Dioxide, NF 23 page 3073 and page 7187 of PF 24(6) [Nov.–Dec. 1998].** The Japanese Pharmacopoeia is the coordinating pharmacopoeia for the international harmonization of the compendial standards for the Silicon Dioxide monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopoeias. The following monograph, which represents the Revised OFFICIAL INQUIRY STAGE 4 document, is based in part on comments from the Japanese Pharmacopoeia and the European Pharmacopoeia in response to the Provisional Harmonized Text Stage 4 draft prepared by the Japanese Pharmacopoeia.

Differences between the Revised OFFICIAL INQUIRY STAGE 4 document and the current NF monograph include the following:

1. In the opening paragraph (the Definition)—The Definition is modified to include the term, "separating," to allow for the two processes of manufacturing, gel and precipitate. An upper limit for Assay is added. The current EP lower limit of 98.0% is adopted.
2. Packaging and storage—No change. The USP text is retained as a nonharmonized attribute.
3. Labeling—The requirement to label the different types of silica are omitted, because the Definition is changed. A requirement to label with the bulk density is added.
4. Identification—Two additional identification procedures are added to strengthen the monograph.
5. pH—The limit is unchanged, but the slurry concentration is slightly less.
6. Loss on drying—The drying time and temperature are changed to 2 hours and 105\( ^\circ \), respectively, and the limit is increased to 7.0%, as related to the time and temperature change.
7. Loss on ignition—The ignition time is increased from 1 hour to 2 hours.
8. Heavy metals—The USP test is retained as a nonharmonized attribute.
9. Chloride—The test is omitted, because it is not necessary.
10. Hydrochloric acid soluble substances—This test is added to indirectly control levels of aluminum and calcium.
11. Sulfate—The JP test is adopted and the limit is increased to 1.0%.
12. Organic volatile impurities—This test is retained as a specific local attribute for USP.
13. Arsenic—This test is retained as a nonharmonized attribute.
14. Iron—This test is added to limit iron impurities.

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