BRIEFING

Anhydrous Lactose, NF 25 page 3357. The United States Pharmacopeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the Anhydrous Lactose 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 ADOPTION STAGE 6 document, is based on the corresponding monograph for Anhydrous Lactose that was prepared by USP. The USP draft was based in part on comments from EP and JP in response to the Provisional Harmonized Text Stage 5A and 5B drafts prepared by USP.

Differences between the USP Adoption Stage 6 document and the current NF monograph for Anhydrous Lactose include the following:

1. **Definition** — Provided additional detail to maintain consistency with harmonized text.
2. **Packaging and storage** — Removed from Other requirements section. Added detail to maintain consistency with the harmonized text.
   - No storage requirements specified.
3. **Labeling** — Removed from Other requirements section. Added detail to maintain consistency with the harmonized text.
4. **USP Reference standards** — No change.
5. **Clarity and color of solution** — Removed from Other requirements section. Added detail to maintain consistency with the harmonized text.
6. **Identification** — Test A is retained as a nonharmonized attribute. Tests B and C are retained as specific local attributes.
7. **Specific rotation** — Removed from Other requirements section. Added detail to maintain consistency with the harmonized text.
8. **Microbial limits** — Removed from Other requirements section. Added detail to maintain consistency with the harmonized text.
9. **Acidity or alkalinity** — Removed from Other requirements section. Added detail to maintain consistency with the harmonized text.
10. **Loss on drying** — No change.
11. **Water** — No change.
12. **Residue on ignition** — Removed from Other requirements section. Added detail to maintain consistency with the harmonized text.
13. **Heavy metals** — Retained as a nonharmonized attribute.
14. **Protein and light-absorbing impurities** — Removed from Other requirements section. Added detail to maintain consistency with the harmonized text.
15. **Content of alpha and beta anomers** — No change.

(ASN: K. Moore) RTS—C43927

**No change:**

**Anhydrous Lactose**

**Add the following:**

<table>
<thead>
<tr>
<th>Attribute</th>
<th>JP</th>
<th>EP</th>
<th>USP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>+</td>
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</table>

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</tr>
</tbody>
</table>

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

**Nonharmonized attributes:** Characters, Labeling, Microbial limits, Heavy metals, Packaging and storage, Identification (IR).

**Specific local attributes:** Identification B and C (USP), Particle size distribution (USP), Particle size distribution EP (FRC).

**No change:**

![Chemical structure of alpha-Lactose](http://www.usppf.com/pf/pub/index.html)
Change to read:

» Anhydrous Lactose is primarily beta lactose or a mixture of alpha and beta lactose.

▲ Anhydrous Lactose is O-β-D-galactopyranosyl-(1→4)-β-D-glucopyranose (β-lactose) or a mixture of O-β-D-galactopyranosyl-(1→4)-β-D-glucopyranose and O-β-D-galactopyranosyl-(1→4)-α-D-glucopyranose (α-lactose). ▲ NF26

Add the following:

▲ Packaging and storage— Preserve in tight containers. ▲ NF26

Change to read:

Labeling— Where the labeling indicates the relative quantities of alpha and beta lactose, determine compliance using Content of alpha and beta anomers.

▲ Where the labeling states the particle size distribution, it also indicates the d_{10}, d_{50}, and d_{90} values and the range for each. ▲ NF26

No change:

USP Reference standards (11) — USP Dextrose RS. USP Fructose RS. USP Anhydrous Lactose RS. USP Sucrose RS.

Add the following:

▲ Clarity and color of solution— A solution of 1 g in 10 mL of boiling water is clear and nearly colorless. Determine the absorbance of this solution at a wavelength of 400 nm. The absorbance divided by the path length, in cm, is not more than 0.04. ▲ NF26

No change:

Identification—

A: Infrared Absorption (197K).

B: Proceed as directed in Identification test B under Lactose Monohydrate, except to use USP Anhydrous Lactose RS instead of USP Lactose Monohydrate RS in Standard solution A and B and to use Anhydrous Lactose in the Test solution.

C: Proceed as directed in Identification test C under Lactose Monohydrate.

Add the following:

▲ Specific rotation (781) — Dissolve 10 g by heating in 80 mL of water to 50°. Allow to cool, and add 0.2 mL of 6 N ammonium hydroxide. Allow to stand for 30 minutes, and dilute with water to 100 mL: the specific rotation, calculated on the anhydrous basis, determined at 20°, is between +54.4° and +55.9°. ▲ NF26

Add the following:
**Microbial limits** (61) — The total aerobic microbial count does not exceed 100 cfu per g, the total combined molds and yeasts count does not exceed 50 cfu per g, and it meets the requirements of the test for absence of *Escherichia coli*. ▲ NF26

**Add the following:**

**Acidity or alkalinity**— Dissolve 6 g by heating in 25 mL of carbon dioxide-free water, cool, and add 0.3 mL of phenolphthalein TS: the solution is colorless, and not more than 0.4 mL of 0.1 N sodium hydroxide is required to produce a red color. ▲ NF26

**No change:**

**Loss on drying** (731) — Dry it at 80° for 2 hours: it loses not more than 0.5% of its weight.

**No change:**

**Water, Method I** (921) : not more than 1.0%, determined on a preparation containing anhydrous lactose in a mixture of methanol and formamide (2:1).

**Add the following:**

**Residue on ignition** (281) : not more than 0.1%, determined on a specimen ignited at a temperature of 600 ± 50°. ▲ NF26

**No change:**

**Heavy metals, Method II** (231) : 5 µg per g.

**Add the following:**

**Protein and light-absorbing impurities** (851) — Measure the light absorption of a 1% (w/v) solution in the range of 210 nm to 300 nm. The absorbance divided by the path length, in cm, is not more than 0.25 in the range of 210 nm to 220 nm and is not more than 0.07 in the range of 270 nm to 300 nm. ▲ NF26

**No change:**

**Content of alpha and beta anomers**—

*Silylation reagent*— Prepare a mixture of pyridine and trimethylsilylimidazole (72:28).

*Resolution mixture*— Prepare a mixture of alpha lactose monohydrate and beta lactose having an anomeric ratio of about 1:1 based on the labeled anomeric contents of the alpha lactose monohydrate and the beta lactose.

*Chromatographic system* (see *Chromatography* (621) )—The gas chromatograph is equipped with a flame-ionization detector and a 4-mm × 0.9-m glass column packed with 3% liquid phase G19 on support S1A. The column temperature is maintained at about 215°, and the injection port and the detector temperatures are maintained at about 275°. The carrier gas is helium, flowing at a rate of about 40 mL per minute.
**Derivatization procedure**—Transfer about 1 mg of Anhydrous Lactose to a 5-mL reaction vial equipped with a screw cap, add 0.45 mL of dimethyl sulfoxide, seal the vial tightly with a screw cap, and mix on a vortex mixer to dissolve. Add 1.8 mL of Silylation reagent, seal the vial tightly with a screw cap, and mix gently. Transfer about 1 mg of Resolution mixture to a second 5-mL reaction vial equipped with a screw cap, add 0.45 mL of dimethyl sulfoxide, seal the vial tightly with a screw cap, and mix on a vortex mixer to dissolve. Add 1.8 mL of Silylation reagent, seal the vial tightly with a screw cap, and mix gently. Maintain both vials at room temperature for 20 minutes before using.

**Procedure**—Inject a 2.0-µL portion of the derivatized Resolution mixture into the chromatograph, and record the areas for the major peaks: the relative retention times are about 0.7 for the silyl derivative of alpha lactose and 1.0 for the silyl derivative of beta lactose; and the resolution, $R$, between the two peaks is not less than 3.0. Similarly inject a 2.0-µL portion of the derivatized Anhydrous Lactose into the chromatograph, and record the areas for the major peaks. Determine the percentage of alpha anomer in the portion of Anhydrous Lactose taken by the formula:

$$100 \frac{r_a}{(r_a + r_b)}$$

in which $r_a$ is the response of the alpha anomer silyl derivative peak, and $r_b$ is the response of the beta anomer silyl derivative peak. Determine the percentage of beta anomer in the portion of Anhydrous Lactose taken by the formula:

$$100 \frac{r_b}{(r_a + r_b)}$$

in which the terms are as defined above.

**Delete the following:**

▲ Other requirements—It meets the requirements for Packaging and storage, Labeling, Clarity and color of solution, Specific rotation, Microbial limits, Acidity or alkalinity, Residue on ignition, and Protein and light-absorbing impurities under Lactose Monohydrate.

**Auxiliary Information**—Staff Liaison: Kevin T. Moore, Ph.D., Scientist

Expert Committee: (EM105) Excipient Monographs 1

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