Fluticasone Propionate and Salmeterol Inhalation Powder

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 4 Expert Committee has revised the Fluticasone Propionate and Salmeterol Inhalation Powder monograph. The purpose for the revision is to add Aerodynamic Size Distribution Test 2 to accommodate the use of a different apparatus and different specifications.

- The liquid chromatographic procedure is based on analyses performed with the Acquity BEH C18 brand of column with L1 packing. The typical retention times for fluticasone propionate and salmeterol are 0.5 min and 1.9 min, respectively.

Existing references to reagents have been updated for consistency with the reagent entry names. For additional information about reagent cross references, please see the related Compendial Notice. The revision also necessitates the following revisions:
  - Add a statement under Aerodynamic Size Distribution to identify the existing test as Test 1
  - Clarify the units in Table 1
  - Add a Labeling section to support articles that use Aerodynamic Size Distribution tests other than Test 1
  - Renumber the tables and references to tables, as needed, throughout the monograph
  - Update the chemical information in USP Reference Standards.

The Fluticasone Propionate and Salmeterol Inhalation Powder Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Heather Joyce, Senior Scientific Liaison–Team Leader (301-998-6792 or hrj@usp.org).
Fluticasone Propionate and Salmeterol Inhalation Powder

**DEFINITION**
Fluticasone Propionate and Salmeterol Inhalation Powder is a mixture of fluticasone propionate and salmeterol xinafoate for use in dry powder inhalers. The Inhalation Powder contains NLT 90% and NMT 110% of the labeled amount of fluticasone propionate (C_{23}H_{21}F_{2}O_{5}S) and NLT 90% and NMT 110% of the labeled amount of salmeterol (C_{25}H_{17}NO_{3}) as salmeterol xinafoate.

**IDENTIFICATION**

- **A. ULTRAVIOLET ABSORPTION (197U)**

  **Diluent:** Methanol and water (70:30)

  **Standard solution:** A mixture of USP Fluticasone Propionate RS and USP Salmeterol Xinafoate RS according to the individual product strengths in the Inhalation Powder under test in Diluent

  **Sample solution:** Dissolve a suitable number of unit doses of the Inhalation Powder under test in a suitable volume of Diluent.

  **Acceptance criteria:** Meets the requirements

- **B.** The retention time of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in the test for Delivered-Dose Uniformity.

**ASSAY**

**Change to read:**

- **PROcedure**

  **Buffer:** To each liter of 2.9 g/L of sodium dodecyl sulfate in water, add 1 mL of glacial acetic acid. ▲ (RB 8-Feb-2019)

  **Solution A:** Methanol and Buffer (20:80)

  **Mobile phase:** Acetonitrile and Solution A (50:50)

  **Diluent:** Methanol and water (70:30)

  **Standard solution:** 10 µg/mL of USP Fluticasone Propionate RS and 3 µg/mL of USP Salmeterol Xinafoate RS in Diluent

  **Sample solution:** Nominally 5–25 µg/mL of fluticasone propionate and 2.4 µg/mL of salmeterol from NLT 12 unit doses in Diluent

  **Chromatographic system**

  (See Chromatography (621), System Suitability.)

  **Mode:** LC

  **Detectors**

  - Fluticasone propionate: UV 239 nm
  - Salmeterol: Fluorescence with excitation at 225 nm and emission at 305 nm. Use emission response for quantification.

  **Column:** 4.6-mm × 5-cm; 3.5-µm packing L1

  **Flow rate:** 2 mL/min

  **Column temperature:** 40°

  **Injection volume:** 10 µL

  **Run time:** NLT 1.5 times the retention time of salmeterol

  **System suitability**

  **Sample:** Standard solution

  [Note—The relative retention times for fluticasone propionate and salmeterol are 0.6 and 1.0, respectively.]

  **Suitability requirements**

  - **Resolution:** NLT 3.5 between salmeterol and fluticasone propionate
  - **Tailing factor:** NMT 1.5 for salmeterol and fluticasone propionate
  - **Relative standard deviation:** NMT 2.0% for salmeterol and fluticasone propionate

  **Analysis**

  **Samples:** Standard solution and Sample solution

  Calculate the percentage of the labeled amount of fluticasone propionate (C_{23}H_{21}F_{2}O_{5}S) in the portion of Inhalation Powder taken:

  \[ \text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_U}{C_S} \right) \times 100 \]

  \[ r_U = \text{peak response of fluticasone propionate from the Sample solution} \]

  \[ r_S = \text{peak response of fluticasone propionate from the Standard solution} \]

  \[ C_U = \text{concentration of USP Fluticasone Propionate RS in the Standard solution (µg/mL)} \]

  \[ C_S = \text{nominal concentration of fluticasone propionate in the Sample solution (µg/mL)} \]

  Calculate the percentage of the labeled amount of salmeterol (C_{25}H_{17}NO_{3}) in the portion of sample taken:

  \[ \text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_U}{C_S} \right) \times \left( \frac{M_U}{M_S} \right) \times 100 \]

  \[ r_U = \text{peak response of salmeterol from the Sample solution} \]

  \[ r_S = \text{peak response of salmeterol from the Standard solution} \]

  \[ C_U = \text{concentration of USP Salmeterol Xinafoate RS in the Standard solution (µg/mL)} \]

  \[ C_S = \text{nominal concentration of salmeterol free base in the Sample solution (µg/mL)} \]

  \[ M_U = \text{molecular weight of salmeterol free base, 415.57} \]

  \[ M_S = \text{molecular weight of salmeterol xinafoate, 603.75} \]

  **Acceptance criteria:** 90%–110% each for fluticasone propionate and salmeterol

**PERFORMANCE TESTS**

**Change to read:**

- **AERODYNAMIC SIZE DISTRIBUTION**


**Test 1** ▲ (RB 8-Feb-2019)

**Sampling apparatus:** Modified Apparatus 3 (Figure 1) in (601) with a modified induction port (Figure 2), and preseparator lid (Figure 3) are to be used.
Buffer, Solution A, and Mobile phase: Proceed as directed in the Assay.

Diluent: Methanol and water (70:30)

Standard solution: 2.5 µg/mL of USP Fluticasone Propionate RS and 0.75 µg/mL of USP Salmeterol Xinafoate RS in Diluent

Sample solutions: Discharge 10 unit doses given into the cascade impaction sampling apparatus described in Figure 1. Operate the pump for 3 s at an airflow rate of 60 L/min for each dose discharged. Detach the inhaler, and rinse each piece of the apparatus with methanol into a separate suitable volumetric flask containing 30% of the flask volume of water. The final expected amount of fluticasone propionate should be in the concentration range of 0.1–5 µg/mL. Allow the solutions to equilibrate, and dilute with methanol to volume. Repeat these steps for three additional sample preparations, for a total of four Sample solutions.

Chromatographic system and System suitability: Proceed as directed in the Assay, except for Injection volume.

Injection volume: 50 µL

Analysis

Samples: Standard solution and Sample solutions

Calculate the quantity, in µg/actuation, of fluticasone propionate (C_{25}H_{31}F_{3}O_{5}S) in the Sample solutions:

Result = \left( \frac{r_{U}}{r_{S}} \times C_{S} \right) \times \left( \frac{V}{N} \right)

\begin{align*}
r_{U} &= \text{peak response from the Sample solution} \\
r_{S} &= \text{peak response from the Standard solution} \\
C_{S} &= \text{concentration of USP Fluticasone Propionate RS in the Standard solution (µg/mL)} \\
V &= \text{total volume of the Sample solution (mL)} \\
N &= \text{number of unit doses discharged into the apparatus}
\end{align*}

Calculate the quantity, in µg/actuation, of salmeterol (C_{25}H_{37}NO_{4}) in the Sample solutions:

Result = \left( \frac{r_{U}}{r_{S}} \times C_{S} \right) \times \left( \frac{V}{N} \right) \times \left( \frac{M_{1}}{M_{2}} \right)

\begin{align*}
r_{U} &= \text{peak response of salmeterol from the Sample solution} \\
r_{S} &= \text{peak response of salmeterol from the Standard solution} \\
C_{S} &= \text{concentration of USP Salmeterol Xinafoate RS in the Standard solution (µg/mL)} \\
V &= \text{total volume of the Sample solution (mL)} \\
N &= \text{number of unit doses discharged into the apparatus}
\end{align*}
If the product complies with this test, the labeling indicates that it meets USP Aerodynamic Size Distribution Test 2.

**Sampling apparatus:** Apparatus S

**Buffer:** To each liter of 3.1 g/L of sodium phosphate and 5 g/L of sodium dodecyl sulfate in water, add 4 mL of 1 M phosphoric acid TS.

**Solution A:** 1% silicone prepared as follows. To an appropriate volumetric flask, transfer 1% of the flask volume of silicone oil and dilute with cyclohexane. [Note—Silicone oil (poly(dimethylsiloxane-co-methylphenylsiloxane); 63148-52-7) with a viscosity of 125 centistokes may be suitable.]

**Mobile phase:** Methanol and Buffer (60:40)

**Standard stock solution A:** 20 µg/mL of USP Fluticasone Propionate Propionate RS prepared as follows. Transfer a suitable quantity of USP Fluticasone Propionate RS to an appropriate volumetric flask and dissolve in 2% of the flask volume of methanol. Dilute with Mobile phase to volume.

**Standard stock solution B:** 29 µg/mL of USP Salmeterol Xinafoate RS (20 µg/mL of salmeterol) prepared as follows. Transfer a suitable quantity of USP Salmeterol Xinafoate RS to an appropriate volumetric flask and dissolve in 2% of the flask volume of methanol. Dilute with Mobile phase to volume.

**Standard solution:** 2 µg/mL of USP Fluticasone Propionate RS from Standard stock solution A and 0.58 µg/mL of USP Salmeterol Xinafoate RS (0.4 µg/mL of salmeterol) from Standard stock solution B in Mobile phase

**Sensitivity solution:** 0.2 µg/mL of USP Fluticasone Propionate Propionate RS from Standard stock solution A and 0.15 µg/mL of USP Salmeterol Xinafoate RS (0.1 µg/mL of salmeterol) from Standard stock solution B in Mobile phase

**Sample solutions:** Proceed as directed in the chapter using Solution A to coat the particle collection surface. Discard waste solution and then allow Solution A to evaporate. Add 15 mL of Mobile phase to the central cup of the preseparator insert as the solvent used for sample recovery. Discharge a single actuation of an inhaler by operating the pump for 4 s at a flow rate of 60 L/min. Dismantle the apparatus and prepare the Sample solutions. Repeat these steps for 5 additional inhalers for a total of 6 sets of Sample solutions. See Table 2.

---

**Table 2**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Final Volume (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouthpiece adapter and induction port</td>
<td>Add 80 mL of Buffer to a volumetric flask. Transfer any powder from the mouthpiece adapter and induction port to the volumetric flask using methanol. Dilute with methanol to volume.</td>
<td>200</td>
</tr>
<tr>
<td>Preparator</td>
<td>Stopper the preparator and add 85 mL of Mobile phase.</td>
<td>100</td>
</tr>
<tr>
<td>Stages 1–5 and MOC*</td>
<td>Transfer 10 mL of Mobile phase to each cup.</td>
<td>10</td>
</tr>
<tr>
<td>Stages 6 and 7*</td>
<td>Transfer 5 mL of Mobile phase to each cup.</td>
<td>5</td>
</tr>
</tbody>
</table>

*Agitation using a gentle rocker may be used to promote dissolution.

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Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Amount of Fluticasone Propionate Deposited (µg/actuation)</th>
<th>Amount of Salmeterol Deposited (µg/actuation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Label claim of fluticasone propionate/salmeterol (µg/actuation)</td>
<td>∆ ▲ ▲ (RB 8-Feb-2019)</td>
<td>∆ ▲ ▲ (RB 8-Feb-2019)</td>
</tr>
<tr>
<td>Sum of Stages 3 and 4</td>
<td>6–18</td>
<td>19–45</td>
</tr>
<tr>
<td>Sum of Stages 6, 7, and filter</td>
<td>NMT 1</td>
<td>NMT 2</td>
</tr>
</tbody>
</table>

\[ F_0 = \text{peak response of salmeterol from the Sample solution} \]
\[ F_3 = \text{peak response of salmeterol from the Standard solution} \]
\[ C_s = \text{concentration of USP Salmeterol Xinafoate RS in the Standard solution (µg/mL)} \]
\[ V = \text{total volume of the Sample solution (mL)} \]
\[ N = \text{number of unit doses discharged into the apparatus, 1} \]
\[ M_{12} = \text{molecular weight of salmeterol xinafoate, 603.75} \]

Acceptance criteria: The requirements for the masses of fluticasone propionate and salmeterol deposited in each grouping of the Sampling apparatus for each inhaler are given in Table 3. The article meets the requirements if NMT 1 of the 6 inhalers fails to meet the requirements in Table 3 but meets the requirements in Table 4.

Table 3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Amount of Fluticasone Propionate Deposited (µg/actuation)</th>
<th>Amount of Salmeterol Deposited (µg/actuation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Label claim of fluticasone propionate/salmeterol (µg/actuation)</td>
<td>100/50</td>
<td>250/50</td>
</tr>
<tr>
<td>Sum of Stages 3–7 and MOC</td>
<td>12–27</td>
<td>27–64</td>
</tr>
<tr>
<td>Sum of Stages 4 and 5</td>
<td>6–15</td>
<td>13–38</td>
</tr>
<tr>
<td>Sum of Stage 6, Stage 7, and MOC</td>
<td>NMT 2</td>
<td>NMT 3</td>
</tr>
</tbody>
</table>

Table 4

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Amount of Fluticasone Propionate Deposited (µg/actuation)</th>
<th>Amount of Salmeterol Deposited (µg/actuation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Label claim of fluticasone propionate/salmeterol (µg/actuation)</td>
<td>100/50</td>
<td>250/50</td>
</tr>
<tr>
<td>Sum of mouthpiece adapter, induction port, preseparator, Stage 1 and Stage 2</td>
<td>57–100</td>
<td>142–255</td>
</tr>
<tr>
<td>Sum of Stages 3–7 and MOC</td>
<td>11–30</td>
<td>24–70</td>
</tr>
<tr>
<td>Sum of Stages 4 and 5</td>
<td>5–17</td>
<td>12–42</td>
</tr>
</tbody>
</table>
| Sum of Stage 6, Stage 7, and MOC                  | NMT 2 | NMT 3 | NMT 8 | NMT 1 | NMT 0.6 | NMT

Change to read:

**Delivered-Dose Uniformity**
(See Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders—Performance Quality Tests (601), Delivered-Dose Uniformity, Inhalation Powders.)

**Sampling apparatus:** Use the apparatus in Figure 4A with modified glass sampling device (Figure 4B).
Buffer, Solution A, Mobile phase, and Diluent: Proceed as directed in the Assay.

Standard solution: 2.5 µg/mL of USP Fluticasone Propionate RS and 0.75 µg/mL of USP Salmeterol Xinafoate RS in Diluent

Sample solutions: Discharge a single unit dose into the apparatus shown in Figure 4A. Operate the pump for 2 s at an airflow of 60 L/min to collect the dose. Detach the inhaler. Rinse the mouthpiece adapter and each piece of the sample collection chamber with methanol. Place the filter and washings into a container. Sonicate for 5 min. Quantitatively transfer the contents to a 200-mL volumetric flask containing 60 mL of water. Allow the solution to equilibrate, and dilute with methanol to volume. Prepare nine additional Sample solutions from nine additional unit doses. For multi-dose inhalers, collect one dose from each of 10 inhalers with the 10 doses collected across the minimum number of recommended doses on the label of the inhaler.

Chromatographic system and System suitability: Proceed as directed in the Assay, except for the Injection volume.

Injection volume: 50 µL

Analysis

Samples: Standard solution and Sample solutions

Calculate the percentage of the labeled amount of fluticasone propionate (C_{25}H_{31}F_{3}O_{5}) and salmeterol (C_{25}H_{37}NO_{4}) delivered by the inhaler in each Sample solution:

\[
\text{Result} = \frac{r_u}{r_s} \times \frac{C_s}{C_{0s}} \times 100
\]

\(r_u\) = peak response from the Sample solution

\(r_s\) = peak response from the Standard solution

\(C_s\) = concentration of USP Fluticasone Propionate RS in the Standard solution (µg/mL)

\(C_{0s}\) = nominal concentration of fluticasone propionate in the Sample solution (µg/mL), based on target emitted dose from Table 5

\(M_{s1}\) = molecular weight of fluticasone propionate, 415.57

\(M_{s2}\) = molecular weight of salmeterol xinafoate, 603.75

Calculate the percentage of the labeled amount of salmeterol delivered by the inhaler in each Sample solution:

\[
\text{Result} = \frac{r_u}{r_s} \times \frac{C_s}{C_{0s}} \times \frac{M_{s1}}{M_{s2}} \times 100
\]

\(r_u\) = peak response of salmeterol from the Sample solution

\(r_s\) = peak response of salmeterol from the Standard solution

\(C_s\) = concentration of USP Salmeterol Xinafoate RS in the Standard solution (µg/mL)

\(C_{0s}\) = nominal concentration of salmeterol free base in the Sample solution (µg/mL), based on target emitted dose from Table 5

\(M_{s1}\) = molecular weight of salmeterol free base, 415.57

\(M_{s2}\) = molecular weight of salmeterol xinafoate, 603.75

Acceptance criteria

1. The mean content of fluticasone propionate and salmeterol from 10 doses is NLT 85% and NMT 115% of the target emitted dose.

2. NMT 1 emitted dose is outside 80%–120% of the target emitted dose.

3. No dose is outside 75%–125% of the target emitted dose.

If requirements 1 and 2 described above are not met, test an additional 20 unit doses. The mean dose of fluticasone propionate and salmeterol from 30 doses is:

- NLT 85% and NMT 115% of the target emitted dose.
- NMT 3 doses are outside 80%–120% of the target emitted dose.
- No dose is outside 75%–125% of the target emitted dose.

IMPURITIES

Change to read:

- **Organic Impurities**
  [Note—Protect all solutions containing fluticasone propionate or salmeterol from light.]

Solution A: 5.7 g/L of monobasic ammonium phosphate in water adjusted with 10% phosphoric acid to a pH of 2.9

Solution B: Acetonitrile

Mobile phase: See Table 6.
Diluent: Methanol, water, and phosphoric acid (70:30: 0.05)

Acidified methanol: To each liter of methanol, add 0.5 mL of phosphoric acid.

System suitability solution: 0.15 mg/mL of USP Salmeterol Xinafoate RS, 0.05 mg/mL of USP Fluticasone Propionate RS, and 0.4 µg/mL each of USP Salmeterol Related Compound D RS, USP Fluticasone Propionate Related Compound H RS, and USP Fluticasone Propionate Related Compound J RS in Diluent.

Standard solution: 2 µg/mL of USP Salmeterol Related Compound D RS and 4 µg/mL of USP Fluticasone Propionate RS in Diluent.

Sensitivity solution: 0.05 µg/mL of USP Fluticasone Propionate RS in Diluent.

Sample solution: Nominally 200–500 µg/mL of fluticasone propionate prepared as follows. Transfer the contents of NLT 10 unit doses to a 10-mL volumetric flask. Add 6 mL of acidified methanol and sonicate for 10 min. Add 3 mL of water, mix, and allow the solution to equilibrate. Dilute with acidified methanol to volume.

Chromatographic system
(See Chromatography (621), System Suitability.)

Mode: LC

Detector: UV 228 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Flow rate: 1 mL/min

Column temperature: 35°

Injection volume: 50 µL

System suitability

Samples: System suitability solution, Standard solution, and Sensitivity solution

Suitability requirements

Resolution: NLT 1.5 between fluticasone propionate related compound J and salmeterol; NLT 1.5 between fluticasone propionate related compound D and fluticasone propionate, System suitability solution

Tailing factor: NMT 2.0 for salmeterol related compound H and fluticasone propionate, Standard solution

Relative standard deviation: NMT 5.0% for salmeterol related compound H and fluticasone propionate, Standard solution

Signal-to-noise ratio: NLT 10 for both fluticasone propionate and salmeterol related compound H, Sensitivity solution

Analysis

Samples: Standard solution, Sensitivity solution, and Sample solution

Calculate the percentage of each fluticasone propionate related degradation product in the portion of Inhalation Powder taken:

\[ \text{Result} = \left( \frac{r_i}{r_s} \right) \times C_i \times V \times \left( \frac{W_1}{W_2} \right) \times (1/L) \times 100 \]

Where:
- \( r_i \) = peak response of each fluticasone propionate related degradation product from the Sample solution
- \( r_s \) = peak response of fluticasone propionate from the Standard solution
- \( C_i \) = concentration of USP Fluticasone Propionate RS in the Standard solution (µg/mL)
- \( V \) = volume of the Sample solution (mL)
- \( W_N \) = nominal weight of each unit dose (mg)
- \( W_U \) = weight of the unit doses in the Sample solution (mg)
- \( L \) = label claim of fluticasone propionate (µg/unit dose)

Disregard any fluticasone propionate related degradation product peak less than the area of fluticasone propionate in the Sensitivity solution.

Calculate the percentage of each salmeterol related degradation product in the portion of Inhalation Powder taken:

\[ \text{Result} = \left( \frac{r_i}{r_s} \right) \times C_i \times V \times \left( \frac{W_1}{W_2} \right) \times (1/L) \times 100 \]

Where:
- \( r_i \) = response of each salmeterol related degradation product from the Sample solution
- \( r_s \) = response of salmeterol related compound H from the Standard solution
- \( C_i \) = concentration of USP Salmeterol Related Compound H RS in the Standard solution (µg/mL)
- \( V \) = volume of the Sample solution (mL)
- \( W_N \) = nominal weight of each unit dose (mg)
- \( W_U \) = weight of the unit doses in the Sample solution (mg)
- \( L \) = label claim of salmeterol free base (µg/unit dose)

Acceptance criteria: See Table 7 for relative retention times.

Disregard any salmeterol related degradation product peak less than the area of salmeterol related compound H in the Sensitivity solution. [Note—Any unspecified degradation product eluting before salmeterol is related to salmeterol. Any unspecified degradation product eluting after salmeterol is related to fluticasone propionate.]

![Table 7](RB 8-Feb-2019)

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria (NMT %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmeterol-N-phenylbutyl aminoisobutyroxy-&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.14</td>
<td>—</td>
</tr>
<tr>
<td>Salmeterol-phenylethoxy-&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.25</td>
<td>—</td>
</tr>
<tr>
<td>Salmeterol-propoxy-&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.32</td>
<td>—</td>
</tr>
<tr>
<td>Salmeterol-phenyl-2-butoxy-&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.37</td>
<td>—</td>
</tr>
<tr>
<td>Fluticasone propionate related compound J&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.38</td>
<td>—</td>
</tr>
<tr>
<td>Salmeterol-&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.41</td>
<td>N/A</td>
</tr>
<tr>
<td>Hydroxynaphthoic acid&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.5</td>
<td>—</td>
</tr>
<tr>
<td>Salmeterol-dideoxy-&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.55</td>
<td>—</td>
</tr>
<tr>
<td>Fluticasone propionate dithioacetate&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.67</td>
<td>—</td>
</tr>
<tr>
<td>Salmeterol-N-alkyl&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.71</td>
<td>0.2</td>
</tr>
<tr>
<td>Salmeterol related compound H</td>
<td>0.74</td>
<td>0.9</td>
</tr>
<tr>
<td>Fluticasone propionate related compound D&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.97</td>
<td>—</td>
</tr>
</tbody>
</table>

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Change to read:

**Table 7** (RB 8-Feb-2019) (continued)

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria (NMT %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluticasone propionate</td>
<td>1.0</td>
<td>N/A</td>
</tr>
<tr>
<td>Fluticasone dimer</td>
<td>1.09</td>
<td>—</td>
</tr>
<tr>
<td>Any fluticasone propionate related unspecified degradation product</td>
<td>—</td>
<td>0.1</td>
</tr>
<tr>
<td>Any salmeterol related unspecified degradation product</td>
<td>—</td>
<td>0.1</td>
</tr>
<tr>
<td>Total degradation products</td>
<td>—</td>
<td>1.3</td>
</tr>
</tbody>
</table>

This is a process impurity that is included in this table for identification only. This impurity is controlled in the drug substance. This impurity is not to be reported for the drug product or to be included in the total degradation products.

4-1-[1-Hydroxy-2-(4-phenylbutylamino)ethyl]-2-(hydroxymethyl)phenol.

4-1-[1-Hydroxy-2-(6-phenethoxyhexylamino)ethyl]-2-(hydroxymethyl)phenol.

4-1-[1-Hydroxy-2-(6-[3-phenylpropoxy]hexylamino)ethyl]-2-(hydroxymethyl)phenol.

4-1-[1-Hydroxy-2-[6-(4-phenylbutan-2-yloxy)hexylamino]ethyl]-2-(hydroxymethyl)phenol.

4-1-[1-Hydroxy-2-(6-[4-phenylbutan-2-yloxy]hexylamino)ethyl]-2-(hydroxymethyl)phenol.

6a,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionylxandrosta-1,4-diene-17β-carbodithioic acid.

6a,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionylxandrosta-1,4-diene-17β-carboxylic acid

1-Hydroxy-4-[2-hydroxy-5-[1-hydroxy-2-[6-(4-phenethoxy)hexylamino]ethyl]benzyl]-2-naphthoic acid.

1-Hydroxy-4-[1-hydroxy-2-(4-phenylbutoxy)hexylamino]ethyl]-2-(hydroxymethyl)phenol.

1-Hydroxy-4-[1-hydroxy-2-(6-phenethoxyhexylamino)ethyl]-2-methylphenol.

1-Hydroxy-4-[1-hydroxy-2-[6-(4-phenylbutan-2-yloxy)hexylamino]ethyl]-2-methylphenol.

1-Hydroxy-4-[1-hydroxy-2-(6-[4-phenylbutan-2-yloxy]hexylamino)ethyl]-2-(hydroxymethyl)phenol.

6a,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionylxandrosta-1,4-diene-17β-carbodithioic acid

1-Hydroxy-4-[1-hydroxy-2-(6-[3-phenylpropoxy]hexylamino)ethyl]-2-(hydroxymethyl)phenol.

1-Hydroxy-4-[1-hydroxy-2-[6-(4-phenylbutan-2-yloxy)hexylamino]ethyl]-2-(hydroxymethyl)phenol.

1-Hydroxy-4-[1-hydroxy-2-(6-[4-phenylbutan-2-yloxy]hexylamino)ethyl]-2-(hydroxymethyl)phenol.

6a,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionylxandrosta-1,4-diene-17β-carboxylic acid

6a,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionylxandrosta-1,4-diene-17β-carboxylic acid

1-Hydroxy-4-[1-hydroxy-2-(6-[3-phenylpropoxy]hexylamino)ethyl]-2-methylphenol.

1-Hydroxy-4-[1-hydroxy-2-(6-[4-phenylbutan-2-yloxy]hexylamino)ethyl]-2-(hydroxymethyl)phenol.

1-Hydroxy-4-[1-hydroxy-2-(6-[3-phenylpropoxy]hexylamino)ethyl]-2-methylphenol.

**SPECIFIC TESTS**

- **Microbial Enumeration Tests** (61) and **Tests for Specified Microorganisms** (62): The total aerobic microbial count does not exceed 10³ cfu/g of powder. The total aerobic yeasts and molds count does not exceed 10¹ cfu/g of formulation. It meets the requirements of the tests for absence of Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, and Salmonella species.

- **Foreign Particulate Matter**

  Particulate Matter in Injections (788) describes details of the test apparatus to be used for the determination of particulate matter using a microscopic particle count test methodology. Samples should be carefully prepared to avoid environmental contamination, and testing should be performed with suitable controls, including the appropriate use of blank determinations.

  **Diluent**: Methanol and water (65:35) passed through a filter of 0.45-µm pore size

  **Filter**: Mixed cellulose and ester filter; 25-mm diameter and 0.45-µm pore size

  **Sample solution**: Transfer contents of NLT 8 unit doses to a suitable container. Dissolve in 75 mL of Diluent.

  **Analysis Sample**: Sample solution

  Pass the Sample solution through the filter and allow the filter to dry under conditions that will limit particulate contamination. Using a microscopic particle count test method, enumerate the number of particles present in the Sample solution.

  Calculate the total number of particles per actuation by the formula:

  \[ \text{Result} = \frac{N_{<10} + N_{10-100} + N_{>100}}{8} \]

  \[ N_{<10} = \text{total number of particles <10 µm present in the Sample solution} \]

  \[ N_{10-100} = \text{total number of particles between 10 and 100 µm present in the Sample solution} \]

  \[ N_{>100} = \text{total number of particles >100 µm present in the Sample solution} \]

  **Acceptance criteria**: See **Table 8**.

  **Table 8** (RB 8-Feb-2019)

<table>
<thead>
<tr>
<th>Particle Size Range (µm)</th>
<th>Number of Particles/Dose (NMT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>200</td>
</tr>
<tr>
<td>10–100</td>
<td>100</td>
</tr>
<tr>
<td>&gt;100</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>300</td>
</tr>
</tbody>
</table>

  **ADDITIONAL REQUIREMENTS**

  - **Packaging and Storage**: Preserve in tight, light-resistant containers. Store at controlled room temperature, in a dry place away from direct heat or sunlight.

  **Add the following**:

  - **LABELING**: The labeling states the Aerodynamic Size Distribution test used only if Test 1 is not used.

  **Change to read**:

  - **USP Reference Standards** (11)

    USP Fluticasone Propionate RS
    USP Fluticasone Propionate Related Compound D RS
    S-Methyl 6a,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionylxandrosta-1,4-diene-17β-carbodithioic acid.
    C<sub>27</sub>H<sub>24</sub>F<sub>2</sub>O<sub>4</sub> 373.38
    USP Fluticasone Propionate Related Compound J RS
    6a,9α-Difluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandros-1,4-diene-17β-carboxylic acid
    C<sub>27</sub>H<sub>24</sub>F<sub>2</sub>O<sub>4</sub> 396.42
    USP Salmeterol Related Compound H RS
    1-Hydroxy-4-[2-hydroxy-5-(1-hydroxy-2-[6-(4-phenylbutoxy)hexylamino]ethyl]benzyl]-2-naphthoic acid, monohydrate.
    C<sub>28</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>·H<sub>2</sub>O 603.76
    USP Salmeterol Xinafoate RS

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