**Fluticasone Propionate and Salmeterol Inhalation Powder**

**Type of Posting**
Notice of Intent to Revise

**Posting Date**
13–Dec–2018

**Targeted Official Date**
To Be Determined, Revision Bulletin

**Expert Committee**
Chemical Medicines Monographs 4

In accordance with section 7.04 (c) of the 2015–2020 Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Chemical Medicines Monographs 4 Expert Committee intends to revise the Fluticasone Propionate and Salmeterol Inhalation Powder monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add *Aerodynamic Size Distribution Test 2* to accommodate the use of a different apparatus and different specifications.

*Aerodynamic Size Distribution Test 2* was validated using an Acquity BEH C18 brand of L1 column. The typical retention times for fluticasone propionate and salmeterol are 0.5 and 1.9 min, respectively.

Additionally, it is proposed to revise the following:

- Add a statement under *Aerodynamic Size Distribution* to identify the existing test as *Test 1*.
- Clarify the units listed in *Table 1*.
- Add a *Labeling* section to support articles that use *Aerodynamic Size Distribution* tests other than *Test 1*.
- Update solution descriptions for consistency with current USP style throughout the monograph.
- Renumber the tables and references to tables, as needed, throughout the monograph.
- Update the chemical information in *USP Reference Standards*.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.¹

Should you have any questions, please contact Ravi Ravichandran, Principal Scientific Liaison (301-816-8330 or rr@usp.org).

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¹ This text is not the official version of a USP–NF monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the USP–NF for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product’s final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the Pharmacopeial Forum must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the USP–NF.
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_{22}H_{31}F_{2}O_{5}S) and NLT 90% and NMT 110% of the labeled amount of salmeterol (C_{25}H_{31}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:

**PERFORMANCE TESTS**

**Aerodynamic Size Distribution**

**Test 1** (TBD)

**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.

Analysis
**Samples:** *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of fluticasone propionate (C_{22}H_{31}F_{2}O_{5}S) in the portion of Inhalation Powder taken:

\[
\text{Result} = \left( \frac{r_u}{r_s} \right) \times \left( \frac{C_u}{C_s} \right) \times 100
\]

- \( r_u \) = peak response of fluticasone propionate from the Sample solution
- \( r_s \) = peak response of fluticasone propionate from the Standard solution
- \( C_u \) = concentration of USP Fluticasone Propionate RS in the Standard solution (µg/mL)
- \( C_s \) = concentration of USP Salmeterol Xinafoate RS in the Standard solution (µg/mL)

Calculate the percentage of the labeled amount of salmeterol (C_{25}H_{31}NO_{3}) in the portion of sample taken:

\[
\text{Result} = \left( \frac{r_u}{r_s} \right) \times \left( \frac{C_u}{C_s} \right) \times \left( \frac{M_{u1}}{M_{s1}} \right) \times 100
\]

- \( r_u \) = peak response of salmeterol from the Sample solution
- \( r_s \) = peak response of salmeterol from the Standard solution
- \( C_u \) = concentration of USP Salmeterol Xinafoate RS in the Standard solution (µg/mL)
- \( C_s \) = concentration of USP Salmeterol Xinafoate RS in the Standard solution (µg/mL)
- \( M_{u1} \) = molecular weight of salmeterol free base, 415.57
- \( M_{s1} \) = molecular weight of salmeterol xinafoate, 603.75

Acceptance criteria: 90%–110% each for fluticasone propionate and salmeterol.
Figure 1. Cascade impaction sampling apparatus (modified Apparatus 3 in (601)) including Induction Port and Preseparator Lid.

Figure 2. Expanded view of the modified induction port.

Figure 3. Expanded view of the preseparator lid.

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:

\[
\text{Result} = \left( \frac{r_u}{r_s} \right) \times C_s \times \frac{V}{N}
\]

\(r_u\) = 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)
\(V\) = total volume of the Sample solution (mL)
\(N\) = number of unit doses discharged into the apparatus

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

\[
\text{Result} = \left( \frac{r_u}{r_s} \right) \times C_s \times \frac{V}{N} \times \frac{M_1}{M_2}
\]

\(r_u\) = 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)
\(V\) = total volume of the Sample solution (mL)
\(N\) = number of unit doses discharged into the apparatus
If the product complies with this test, the labeling  
To each liter of 3.1 g/L of Methanol and Apparatus 5  
Proceed as directed in the chapter www.sigmaaldrich.com.  

Acceptance criteria  
The mass of fluticasone propionate and salmeterol deposited in each grouping of the Sampling apparatus for each inhaler is given in Table 1.  
All the groupings for each sample preparation must meet the criteria in Table 1.  
If NMT one of the four sample preparations fails to meet the requirements in Table 1, but is within 25% of either the lower or upper specification limit being tested, analyze two additional samples. The batch meets the requirements if five of the six sample preparations meet the limits in Table 1 for the individual sample preparations.  

Test 2: If the product complies with this test, the labeling indicates that it meets USP Aerodynamic Size Distribution Test 2.  
Sampling apparatus: Apparatus 5  
Buffer: To each liter of 3.1 g/L of dihydrate monobasic 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 (polymethylsiloxane-co-methylphenylsiloxane); 63148-52-7) with a viscosity of 125 centistokes may be suitable 1]  
Mobile phase: Methanol and Buffer (60:40)  
Standard stock solution A: 20 µg/mL of USP Fluticasone 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 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>Preseparator</td>
<td>Stopper the preseparator and add 85 mL of Mobile phase.</td>
<td>100</td>
</tr>
<tr>
<td>Stages 1–5 and MOC&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Transfer 10 mL of Mobile phase to each cup.</td>
<td>10</td>
</tr>
<tr>
<td>Stages 6 and 7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Transfer 5 mL of Mobile phase to each cup.</td>
<td>5</td>
</tr>
</tbody>
</table>

<sup>a</sup> Agitation using a gentle rocker may be used to promote dissolution. [Note—The use of a gentle rocker for 10–15 min may be suitable.]

Chromatographic system  
(See Chromatography (621), System Suitability.)  
Mode: LC  
Detectors: The wavelength may be switched from 240 to 220 nm after the elution of fluticasone propionate and before the elution of salmeterol.  
Fluticasone propionate: UV 240 nm  
Salmeterol: UV 220 nm  
Column: 2.1-mm × 5-cm; 1.7-µm packing L1  
Flow rate: 1 mL/min  
Temperatures  
Autosampler temperature: 5°  
Column temperature: 75°  
Injection volume: 20 µL  
Run time: NLT 1.5 times the retention time of salmeterol  

System suitability  
Samples: Standard solution and Sensitivity solution  
[Note—The relative retention times for fluticasone propionate and salmeterol are 0.28 and 1.0, respectively.]  
Suitability requirements  
Tailing factor: NMT 2.0 for fluticasone propionate; NMT 1.7 for salmeterol, Standard solution  
Relative standard deviation: NMT 1.0% for fluticasone propionate and salmeterol, Standard solution; NMT 10.0% for fluticasone propionate and salmeterol, Sensitivity solution  

Analysis  
Samples: Standard solution and Sample solutions  
Calculate the quantity, in µg/actuation, of fluticasone propionate (C<sub>22</sub>H<sub>24</sub>F<sub>25</sub>O<sub>3</sub>S) in each of the Sample solutions:

\[
\text{Result} = \left( \frac{r_0}{r_C} \times C_J \right) \times \left( \frac{V}{N} \right)
\]

\[r_0\] = peak response from the Sample solution  
\[r_C\] = peak response from the Standard solution  
\[C_J\] = concentration of USP Fluticasone Propionate RS in the Standard solution (µg/mL)  
\[V\] = total volume of the Sample solution (mL)  
\[N\] = number of unit doses discharged into the apparatus, 1

Calculate the quantity, in µg/actuation, of salmeterol (C<sub>32</sub>H<sub>37</sub>NO<sub>6</sub>) in each of the Sample solutions:

\[
\text{Result} = \left( \frac{r_0/r_C \times C_J \times (V/N)}{M_{32}/M_{21}} \right)
\]

\[M_{32}\] = molecular weight of salmeterol free base, 415.57  
\[M_{21}\] = molecular weight of salmeterol xinafoate, 603.75

1 A suitable grade is available as catalog #378488 from www.sigmaaldrich.com.
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></td>
<td>(µg/actuation)</td>
<td>(µg/actuation)</td>
</tr>
<tr>
<td>Label claim of fluticasone propionate/salmeterol (µg/actuation)</td>
<td>100/50 ▲ (TBD) 250/50 ▲ (TBD) 500/50 ▲ (TBD)</td>
<td>100/50 ▲ (TBD) 250/50 ▲ (TBD) 500/50 ▲ (TBD)</td>
</tr>
<tr>
<td>Sum of Stages 3 and 4</td>
<td>6–18 19–45 43–92</td>
<td>3–8 3–8 4–8</td>
</tr>
<tr>
<td>Sum of Stages 6, 7, and filter</td>
<td>NMT 1 NMT 2 NMT 2</td>
<td>NMT 0.5 NMT 0.5 NMT 0.5</td>
</tr>
</tbody>
</table>

\[ R_{p0} = \text{peak response of salmeterol from the Sample solution} \]
\[ R_{p3} = \text{peak response of salmeterol from the Standard solution} \]
\[ C_{S} = \text{concentration of USP Salmeterol Xinafoate RS in the Standard solution (µg/mL)} \]
\[ V = \text{total volume of the Sample solution (mL)} \]
\[ N = \text{number of unit doses discharged into the apparatus, 1} \]
\[ M_{r1} = \text{molecular weight of salmeterol free base, 415.57} \]
\[ M_{r2} = \text{molecular weight of salmeterol xinafoate, 603.75} \]

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></td>
<td>(µg/actuation)</td>
<td>(µg/actuation)</td>
</tr>
<tr>
<td></td>
<td>(µg/actuation)</td>
<td>(µg/actuation)</td>
</tr>
<tr>
<td>Label claim of fluticasone propionate/salmeterol (µg/actuation)</td>
<td>100/50 250/50 500/50</td>
<td>100/50 250/50 500/50</td>
</tr>
<tr>
<td>Sum of Stages 3–7 and MOC</td>
<td>12–27 27–64 64–140</td>
<td>5–11 4–10 6–11</td>
</tr>
<tr>
<td>Sum of Stages 4 and 5</td>
<td>6–15 13–38 30–78</td>
<td>2–6 2–6 2–6</td>
</tr>
<tr>
<td>Sum of Stage 6, Stage 7, and MOC</td>
<td>NMT 2 NMT 3 NMT 7</td>
<td>NMT 1 NMT 0.5 NMT 0.5</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></td>
<td>(µg/actuation)</td>
<td>(µg/actuation)</td>
</tr>
<tr>
<td></td>
<td>(µg/actuation)</td>
<td>(µg/actuation)</td>
</tr>
<tr>
<td>Label claim of fluticasone propionate/salmeterol (µg/actuation)</td>
<td>100/50 250/50 500/50</td>
<td>100/50 250/50 500/50</td>
</tr>
<tr>
<td>Sum of mouthpiece adapter, induction port, preseparor, Stage 1 and Stage 2</td>
<td>57–100 142–255 256–499</td>
<td>31–52 32–53 29–51</td>
</tr>
<tr>
<td>Sum of Stages 3–7 and MOC</td>
<td>11–30 24–70 58–154</td>
<td>4–12 4–11 5–12</td>
</tr>
<tr>
<td>Sum of Stages 4 and 5</td>
<td>5–17 12–42 27–86</td>
<td>2–7 2–7 2–7</td>
</tr>
<tr>
<td>Sum of Stage 6, Stage 7, and MOC</td>
<td>NMT 2 NMT 3 NMT 8</td>
<td>NMT 1 NMT 0.6 NMT 0.6</td>
</tr>
</tbody>
</table>

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\textsubscript{25}H\textsubscript{31}F\textsubscript{3}O\textsubscript{5}S) delivered by the inhaler in each Sample solution:

$$\text{Result} = \left( \frac{r_u}{r_s} \right) \times \left( \frac{C_s}{C_u} \right) \times 100$$

$r_u = \text{peak response from the Sample solution}$

$r_s = \text{peak response from the Standard solution}$

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

$$C_u = \text{nominal concentration of fluticasone propionate in the Sample solution (µg/mL), based on target emitted dose from Table 5 (TBD)}$$

$$M_{r1} = \text{molecular weight of salmeterol free base, 415.57}$$

$$M_{r2} = \text{molecular weight of salmeterol xinafoate, 603.75}$$

**Table 5 (TBD) Target Emittted Dose**

<table>
<thead>
<tr>
<th>Label Claim of Fluticasone Propionate/Salmeterol (µg/unit dose)</th>
<th>Fluticasone Propionate Target Emitted Dose (µg/unit dose)</th>
<th>Salmeterol Target Emitted Dose (µg/unit dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100/50</td>
<td>93</td>
<td>45</td>
</tr>
<tr>
<td>250/50</td>
<td>233</td>
<td>45</td>
</tr>
<tr>
<td>500/50</td>
<td>465</td>
<td>45</td>
</tr>
</tbody>
</table>

**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 TS\textsubscript{(TBD)} to a pH of 2.9

**Solution B:** Acetonitrile

**Mobile phase:** See Table 6.
6 Fluticasone

Table 6

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>60</td>
<td>22</td>
<td>78</td>
</tr>
<tr>
<td>61</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>70</td>
<td>70</td>
<td>30</td>
</tr>
</tbody>
</table>

**Diluent:** Methanol, water, and phosphoric acid (70:30:0.05)

**Acidified methanol:** Add 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 and USP Fluticasone Propionate Related Compound J RS in Diluent

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

**Sensitivity solution:** 0.05 µg/mL of USP Salmeterol Related Compound H RS and 0.1 µg/mL of USP Fluticasone Propionate RS from Standard solution 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 x 25-cm; 5-µm packing L1

**Flow rate:** 1 mL/min

**Column temperature:** 35°C

**Injection volume:** 50 µL

**System suitability**

**Samples:** Standard solution, Sensitivity solution, and Sample 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:

\[
\text{Result} = (r_i/r_j) \times C_i \times V \times (W_N/W_U) \times (1/L) \times 100
\]

**Acceptance criteria:** See Table 7. Disregard any fluticasone propionate related degradation product peak less than the area of fluticasone propionate in the Sensitivity solution.

**Acceptance criteria:** See Table 7. 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.]
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. This is a counter ion of salmeterol that is included in this table for identification only. It is not to be reported for the drug product or to be included in the total degradation products.

### Table 7 (TBD) (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&lt;sup&gt;1&lt;/sup&gt;</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>

<sup>a</sup> 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.

<sup>b</sup> 4-{1-Hydroxy-2-(4-phenylethoxy)-5-{1-hydroxy-2-(6-(4-phenylbutoxy)hexylamino)ethyl}benzyl} [6-(4-phenylbutoxy)hexyl] amino]ethyl]-2-(hydroxymethyl)phenol.

<sup>c</sup> 6α,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosa-1,4-diene-17β-carbodihioc acid.

<sup>d</sup> 4-{1-Hydroxy-2-[6-(3-phenylpropoxy)hexylamino]ethyl}-2-(hydroxymethyl)phenol.

<sup>e</sup> 4-{1-Hydroxy-2-[6-(4-phenylbutoxy)-2-yloxy]hexylamino}ethyl]-2-(hydroxymethyl)phenol.

<sup>f</sup> 6α,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carboxylic acid 6α,9α-difluoro-17β-(fluoromethylthio)carbonyl-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-y] ester.

<sup>g</sup> 4-{1-Hydroxy-2-[6-(4-phenylbutoxy)hexylamino]ethyl]-2-methylphenol.

<sup>h</sup> 6α,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosa-1,4-diene-17β-carboxylic acid 6α,9α-difluoro-17β-(fluoromethylthio)carbonyl-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-y] ester.

<sup>i</sup> 6α,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid 6α,9α-difluoro-17β-(fluoromethylthio)carbonyl-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-y] ester.

<sup>j</sup> 6α,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid 6α,9α-difluoro-17β-(fluoromethylthio)carbonyl-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-y] ester.

### Specific Tests

#### Microbial Enumeration Tests (61) and Tests for Specified Microorganisms (62)

The total aerobic microbial count does not exceed 10<sup>3</sup> cfu/g of powder. The total aerobic yeasts and molds count does not exceed 10<sup>3</sup> cfu/g of formulation. It meets the requirements of the tests for absence of Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, and Salmonella species.

### Change to read:

#### 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:

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

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

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

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

**Acceptance criteria:** See Table 8.

### Table 8 (TBD)

<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. *(TBD)*

### Change to read:

- **USP Reference Standards** *(1)*
  - USP Fluticasone Propionate RS
  - USP Fluticasone Propionate Related Compound D RS
  - S-Methyl 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-g17α-carboxyloxyandrosa-1,4-diene-17β-carboxylic acid.
  - C<sub>21</sub>H<sub>34</sub>F<sub>5</sub>OS 482.58
  - USP Fluticasone Propionate Related Compound J RS
  - 6α,9α-Difluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid.
  - C<sub>21</sub>H<sub>34</sub>NO<sub>3</sub> 396.42
  - USP Salmeterol Related Compound H RS
  - 1-Hydroxy-4-[2-hydroxy-5-(1-hydroxy-2-[6-(4-phenylbutoxy)hexyl]amino)ethyl]benzyl]-2-naphthoic acid, monohydrate.
  - C<sub>21</sub>H<sub>36</sub>NO<sub>3</sub>·H<sub>2</sub>O 603.76
  - USP Salmeterol Xinafoate RS