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).

[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 ($C_{25}H_{31}F_3O_5S$) and NLT 90% and NMT 110% of the labeled amount of salmeterol ($C_{25}H_{37}NO_4$) 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.▲ (TBD)
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 ($C_{25}H_{31}F_3O_5S$) in the portion of Inhalation Powder taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of fluticasone propionate from the *Sample solution*
r_S = peak response of fluticasone propionate from the *Standard solution*
C_S = concentration of USP Fluticasone Propionate RS in the *Standard solution* (µg/mL)
C_U = nominal concentration of fluticasone propionate in the *Sample solution* (µg/mL)

Calculate the percentage of the labeled amount of salmeterol ($C_{25}H_{37}NO_4$) in the portion of sample taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

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_U = nominal concentration of salmeterol free base in the *Sample solution* (µg/mL)
M_{r1} = molecular weight of salmeterol free base, 415.57
M_{r2} = 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**
(See *Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders—Performance Quality Tests* ⟨601⟩, *Aerodynamic Size Distribution—Inhalation Aerosols, Sprays, and Powders*.)
▲**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.

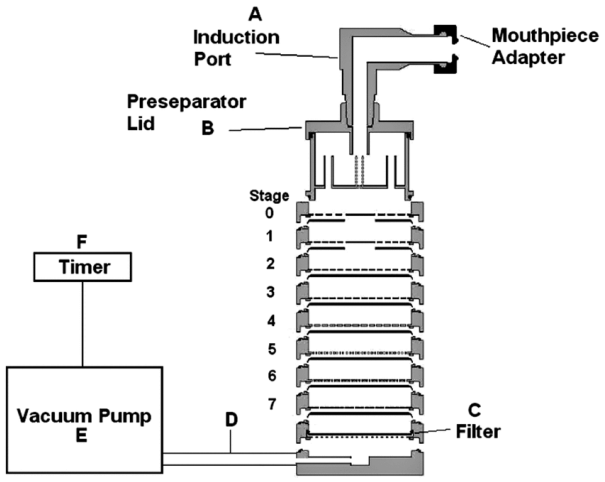

Figure 1. Cascade impaction sampling apparatus (modified *Apparatus 3* in ⟨601⟩) including *Induction Port* and *Preseparator Lid*.

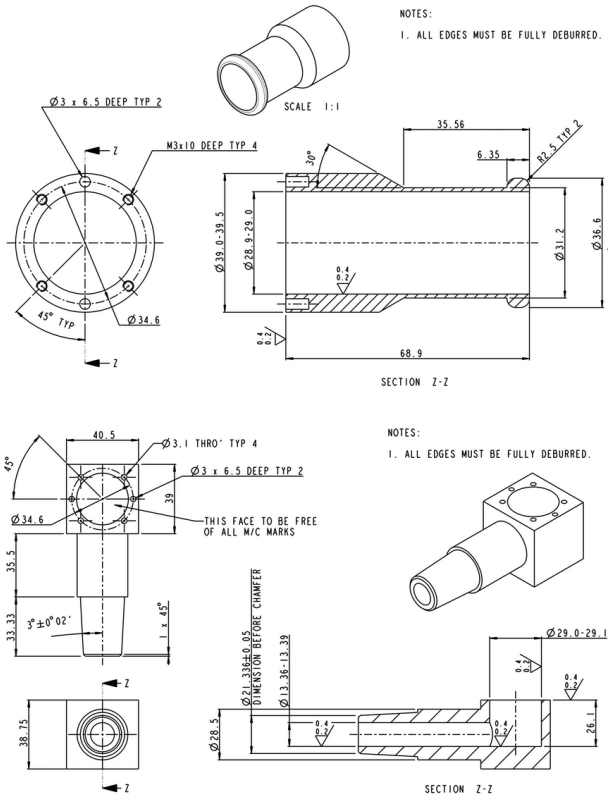

Figure 2. Expanded view of the modified induction port.

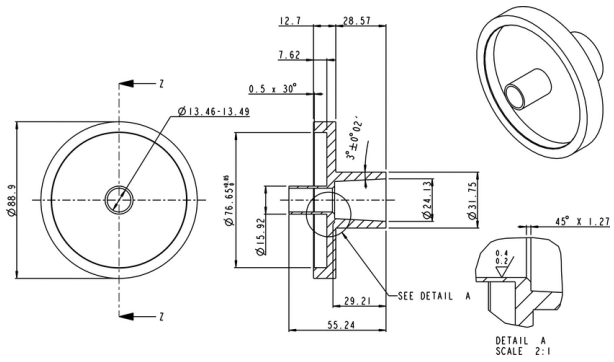

Figure 3. Expanded view of the preseparator lid.

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 ($C_{25}H_{31}F_3O_5S$) in the *Sample solutions*:

$$\text{Result} = [(r_U/r_S) \times C_S] \times (V/N)$$

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*:

$$\text{Result} = [(r_U/r_S) \times C_S] \times (V/N) \times (M_{r1}/M_{r2})$$

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

M_{r1} = molecular weight of salmeterol free base, 415.57
M_{r2} = molecular weight of salmeterol xinafoate, 603.75

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 (poly[dimethylsiloxane-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

Parameter	Description	Final Volume (mL)
Mouthpiece adapter and induction port	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.	200
Preseparator	Stopper the preseparator and add 85 mL of *Mobile phase*.	100
Stages 1–5 and MOC[a]	Transfer 10 mL of *Mobile phase* to each cup.	10
Stages 6 and 7[a]	Transfer 5 mL of *Mobile phase* to each cup.	5

[a] 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 ($C_{25}H_{31}F_3O_5S$) in each of the *Sample solutions*:

$$\text{Result} = [(r_U/r_S) \times C_S] \times (V/N)$$

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, 1

Calculate the quantity, in µg/actuation, of salmeterol ($C_{25}H_{37}NO_4$) in each of the *Sample solutions*:

$$\text{Result} = [(r_U/r_S) \times C_S] \times (V/N) \times (M_{r1}/M_{r2})$$

[1] A suitable grade is available as catalog #378488 from www.sigmaaldrich.com.

Table 1

Parameter	Amount of Fluticasone Propionate Deposited (µg▲/actuation)▲ (TBD)			Amount of Salmeterol Deposited (µg▲/actuation)▲ (TBD)		
Label claim of fluticasone propionate/salmeterol (µg/actuation)	100/50 ▲▲ (TBD)	250/50 ▲▲ (TBD)	500/50 ▲▲ (TBD)	100/50 ▲▲ (TBD)	250/50 ▲▲ (TBD)	500/50 ▲▲ (TBD)
Mass of mouthpiece adapter, induction port, pre-separator, and Stage 0	55–80	140–200	290–400	28–42	28–42	28–42
Sum of Stages 1–5	15–30	42–73	96–150	7–13	7–13	7–13
Sum of Stages 3 and 4	6–18	19–45	43–92	3–8	3–8	4–8
Sum of Stages 6, 7, and filter	NMT 1	NMT 2	NMT 2	NMT 0.5	NMT 0.5	NMT 0.5

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, 1
M_{r1} = molecular weight of salmeterol free base, 415.57
M_{r2} = 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

Parameter	Amount of Fluticasone Propionate Deposited (µg/actuation)			Amount of Salmeterol Deposited (µg/actuation)		
Label claim of fluticasone propionate/salmeterol (µg/actuation)	100/50	250/50	500/50	100/50	250/50	500/50
Sum of mouthpiece adapter, induction port, preseparator, Stage 1 and Stage 2	63–91	158–232	285–454	34–47	36–48	32–46
Sum of Stages 3–7 and MOC	12–27	27–64	64–140	5–11	4–10	6–11
Sum of Stages 4 and 5	6–15	13–38	30–78	2–6	2–6	2–6
Sum of Stage 6, Stage 7, and MOC	NMT 2	NMT 3	NMT 7	NMT 1	NMT 0.5	NMT 0.5

Table 4

Parameter	Amount of Fluticasone Propionate Deposited (µg/actuation)			Amount of Salmeterol Deposited (µg/actuation)		
Label claim of fluticasone propionate/salmeterol (µg/actuation)	100/50	250/50	500/50	100/50	250/50	500/50
Sum of mouthpiece adapter, induction port, preseparator, Stage 1 and Stage 2	57–100	142–255	256–499	31–52	32–53	29–51
Sum of Stages 3–7 and MOC	11–30	24–70	58–154	4–12	4–11	5–12
Sum of Stages 4 and 5	5–17	12–42	27–86	2–7	2–7	2–7
Sum of Stage 6, Stage 7, and MOC	NMT 2	NMT 3	NMT 8	NMT 1	NMT 0.6	NMT 0.6▲ (TBD)

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*).

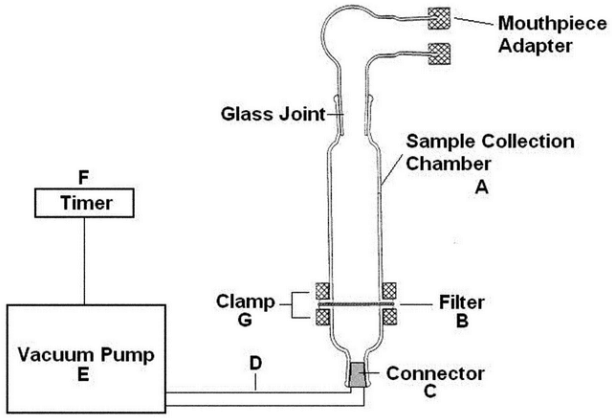

Figure 4A. Sampling apparatus.

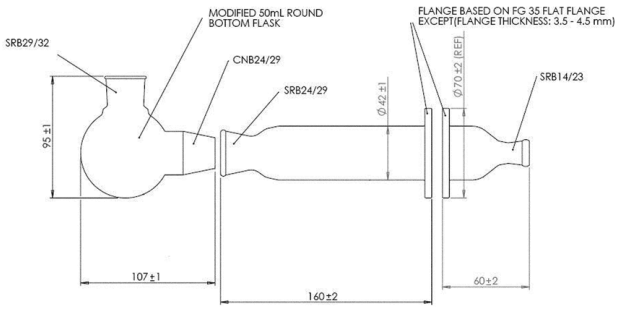

Figure 4B. Expanded view of the modified glass sample collection apparatus.

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 ($C_{25}H_{31}F_3O_5S$) delivered by the inhaler in each *Sample solution*:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

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_U = nominal concentration of fluticasone propionate in the *Sample solution* (µg/mL), based on target emitted dose from ▲*Table 5*▲ (TBD)

Calculate the percentage of the labeled amount of salmeterol ($C_{25}H_{37}NO_4$) delivered by the inhaler in each *Sample solution*:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

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_U = nominal concentration of salmeterol free base in the *Sample solution* (µg/mL), based on target emitted dose from ▲*Table 5*▲ (TBD)
M_{r1} = molecular weight of salmeterol free base, 415.57
M_{r2} = molecular weight of salmeterol xinafoate, 603.75

▲Table 5▲ (TBD) Target Emitted Dose

Label Claim of Fluticasone Propionate/ Salmeterol (µg/unit dose)	Fluticasone Propionate Target Emitted Dose (µg/unit dose)	Salmeterol Target Emitted Dose (µg/unit dose)
100/50	93	45
250/50	233	45
500/50	465	45

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▲ (TBD) to a pH of 2.9

Solution B: Acetonitrile

Mobile phase: See ▲*Table 6*.

Table 6▲ (TBD)

Time (min)	Solution A (%)	Solution B (%)
0	70	30
60	22	78
61	70	30
70	70	30

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

Acidified methanol: ▲To each liter of methanol, add 0.5 mL of phosphoric acid.▲ (TBD)

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 Fluticasone Propionate 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 × 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*
[NOTE—See ▲*Table 7*▲ (TBD) for relative retention times.]
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:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (W_N/W_U) \times (1/L) \times 100$$

r_U = 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_S = 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:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (W_N/W_U) \times (1/L) \times 100$$

r_U = response of each salmeterol related degradation product from the *Sample solution*
r_S = response of salmeterol related compound H from the *Standard solution*
C_S = 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*.▲ (TBD) 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▲ (TBD)

Name	Relative Retention Time	Acceptance Criteria (NMT %)
Salmeterol-*N*-phenylbutyl aminoalcohol[a, b]	0.14	—
Salmeterol-phenylethoxy[a, c]	0.25	—
Salmeterol-phenylpropoxy[a, d]	0.32	—
Salmeterol-phenyl-2-butoxy[a, e]	0.37	—
Fluticasone propionate related compound J[a]	0.38	—
Salmeterol[a]	0.41	N/A
Hydroxynapthoic acid[f]	0.5	—
Salmeterol-deoxy[a, g]	0.55	—
Fluticasone propionate dithioacid[a, h]	0.67	—
Salmeterol-*N*-alkyl[i]	0.71	0.2
Salmeterol related compound H	0.74	0.9
Fluticasone propionate related compound D[a]	0.97	—

▲Table 7▲ (TBD) *(continued)*

Name	Relative Retention Time	Acceptance Criteria (NMT %)
Fluticasone propionate	1.0	N/A
Fluticasone dimer[a, j]	1.09	—
Any fluticasone propionate related unspecified degradation product	—	0.1
Any salmeterol related unspecified degradation product	—	0.1
Total degradation products	—	1.3

[a] 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.
[b] 4-[1-Hydroxy-2-(4-phenylbutylamino)ethyl]-2-(hydroxymethyl)phenol.
[c] 4-[1-Hydroxy-2-(6-phenethoxyhexylamino)ethyl]-2-(hydroxymethyl)phenol.
[d] 4-{1-Hydroxy-2-[6-(3-phenylpropoxy)hexylamino]ethyl}-2-(hydroxymethyl) phenol.
[e] 4-{1-Hydroxy-2-[6-(4-phenylbutan-2-yloxy)hexylamino]ethyl}-2-(hydroxymethyl)phenol.
[f] 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.
[g] 4-{1-Hydroxy-2-[6-(4-phenylbutoxy)hexylamino]ethyl}-2-methylphenol.
[h] 6α,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbodithioic acid.
[i] 4-{1-Hydroxy-2-[(2-hydroxy-5-{1-hydroxy-2-[6-(4-phenylbutoxy)hexylamino] ethyl}benzyl)[6-(4-phenylbutoxy)hexyl]amino]ethyl}-2-(hydroxymethyl) phenol.
[j] 6α,9α-Difluoro-11β,17α-dihydroxy-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-yl ester.

SPECIFIC TESTS

- **MICROBIAL ENUMERATION TESTS** ⟨61⟩ and **TESTS FOR SPECIFIED MICROORGANISMS** ⟨62⟩**:** The total aerobic microbial count does not exceed 10^1 cfu/g of powder. The total aerobic yeasts and molds count does not exceed 10^1 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:

$$\text{Result} = (N_{<10} + N_{10–100} + N_{>100})/8$$

$N_{<10}$ = total number of particles <10 µm present in the *Sample solution*
$N_{10–100}$ = total number of particles between 10 and 100 µm present in the *Sample solution*
$N_{>100}$ = total number of particles >100 µm present in the *Sample solution*

Acceptance criteria: See *▲Table 8*.

Table 8▲ (TBD)

Particle Size Range (µm)	Number of Particles/Dose (NMT)
<10	200
10–100	100
>100	10
Total	300

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** ⟨11⟩

USP Fluticasone Propionate RS
USP Fluticasone Propionate Related Compound D RS
S-Methyl 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17▲α▲ (TBD)-propionyloxyandrosta-1,4-diene-17▲β▲ (TBD)-carbothioate.
$C_{25}H_{32}F_2O_5S$ 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.
$C_{21}H_{26}F_2O_5$ 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.
$C_{36}H_{43}NO_6 \cdot H_2O$ 603.76
USP Salmeterol Xinafoate RS