⟨5⟩ INHALATION AND NASAL DRUG PRODUCTS—GENERAL INFORMATION AND PRODUCT QUALITY TESTS

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1. INTRODUCTION

Inhalation drug products deliver drugs into the lungs by oral inhalation and include inhalation aerosols, inhalation powders, inhalation sprays, inhalation solutions, inhalation suspensions, solutions for inhalation, and drugs for inhalation solutions dosage forms. Nasal drug products deliver drugs into the nasal cavity and include nasal sprays, nasal solutions, nasal aerosols, and nasal powder dosage forms. This chapter does not address nasal products in gel and ointment form. See *Table 1* for established names and definitions of these dosage forms. Definitions of these drug product dosage forms, brief information about their manufacture, and a glossary of dosage form names can be found in *Pharmaceutical Dosage Forms* ⟨1151⟩. [NOTE—All references to general information chapters are for informational purposes only, for use as a helpful resource. ▲See *General Notices, 3.10 Applicability of Standards* for further information on the applicability of USP standards pertaining to a specific monograph requirement.▲ (USP 1-Dec-2020)]

Table 1. Established Names and Definitions

Established Name	Definition
Inhalation Aerosol	A drug product for oral inhalation that is packaged under pressure, aerosolizes, and delivers a specified amount of active ingredient(s) upon activation of an accurate metering valve system in association with an actuator mechanism. Inhalation aerosol drug products are more commonly known as metered-dose inhalers or MDIs.
Inhalation Powder	Drug powder for oral inhalation with the use of a device that aerosolizes and delivers an accurately metered amount of active ingredient(s). Inhalation powder drug products are more commonly known as dry powder inhalers or DPIs.
Inhalation Spray	A nonpressurized liquid, sterile (if aqueous-based) drug dosage form for oral inhalation that is packaged in a container–closure system that upon activation aerosolizes and delivers in fine droplets of formulation an accurately metered amount of active ingredient(s).
Inhalation Solution	A sterile drug solution for oral inhalation with the use of a nebulization system.
Inhalation Suspension	A sterile drug suspension for oral inhalation with the use of a nebulization system.
Solution for Inhalation	A sterile drug solution for oral inhalation that must be diluted before it is administered with the use of a nebulization system.
[Drug] for Inhalation Solution	A sterile drug powder that, upon the addition of a suitable vehicle, yields a sterile solution conforming in all respects to an inhalation solution.
Nasal Spray	A nonpressurized, accurately metered, liquid drug dosage form for local application into the nasal passages that is packaged in a container–closure system that upon activation aerosolizes and delivers in droplets of formulation an accurately metered amount of active ingredient(s).
Nasal Aerosol	A drug product for local application into the nasal passages that is packaged under pressure, aerosolizes, and delivers a specified amount of active ingredient(s) upon activation of an accurate metering valve system in association with an actuator mechanism.
Nasal Solution	A nonpressurized, liquid drug dosage form for local application into the nasal passages.
Nasal Powder	Drug powder for local application into the nasal passages with the use of a device that aerosolizes and delivers an accurately metered amount of active ingredient(s).

This chapter provides lists of consolidated common product quality test requirements in a concise and coherent fashion. This general chapter applies, in part or in its entirety, when referenced in a drug product monograph (see *General Notices, 3.10 Applicability of Standards*) and includes the quality tests for the specific route of administration. The quality tests listed can be used, as appropriate, by manufacturers toward the development of new drug product monographs for submission to the *USP–NF*. If a validated performance test procedure is available for the specific drug product, it is identified in a general chapter below 1000. Additional information, or information on promising technologies that have not yet been fully validated, may be presented in general information chapters.

Drug Product General Quality Tests and Performance Quality Tests

A *USP* drug product monograph contains tests, analytical procedures, and acceptance criteria. Drug product tests are divided into two categories: 1) general quality tests; and 2) product performance tests, e.g., delivered dose uniformity and its physical characteristics such as aerodynamic particle size distribution and/or droplet size distribution. General quality tests assess the

integrity of the dosage form, whereas product performance quality tests assess delivery of the drug and other attributes that may relate to in vivo drug performance.

Taken together, general quality and product performance tests ensure the identity, strength, quality, and purity of inhalation and nasal drug products.

The next two sections of this chapter list product quality attributes for inhalation drug products and for nasal drug products, respectively. The final section describes in greater detail the quality tests for inhalation and nasal drug products. *Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders—Performance Quality Tests* ⟨601⟩ contains product performance tests for inhalation and nasal drug products and should be used in conjunction with this chapter.

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2. GENERAL QUALITY TESTS FOR INHALATION DRUG PRODUCTS

Inhalation Aerosol

DESCRIPTION

Aerosol in this context is a dosage form consisting of a liquid preparation packaged under pressure and intended for administration as a fine mist. The descriptive term "aerosol" also refers to the fine mist of small droplets and/or solid particles that are emitted from the product. Inhalation aerosols, also known as metered-dose inhalers (MDIs), are preparations characterized by dispersion of the active pharmaceutical ingredient into the airways during oral inspiration for either local or systemic effect, and nasal aerosols, also known as nasal MDIs, are characterized by deposition in the nasal cavity for either local or systemic effect.

An aerosol formulation typically contains a drug substance(s) dissolved or suspended in a propellant or a mixture of propellant(s) and co-solvent(s) and possibly other suitable excipients. An inhalation aerosol drug product delivers a specified amount and quality of therapeutically active ingredient(s) upon activation of an accurate metering valve system. General quality tests for inhalation aerosol drug products include the following attributes (see *4. Description of Product Quality Tests* for more detailed discussions of each test):

- *Assay (strength and content uniformity)*
- *Co-Solvent Content [(e.g., ethanol) if present]*
- *Elemental Impurities*
- *Foreign Particulate Matter*
- *Identification*
- *Impurities and Degradation Products*
- *Leachables*
- *Leak Rate*
- *Microbial Limits*
- *Net Fill Weight*
- ▲*Residual Solvents*▲ (USP 1-Dec-2020)
- *Spray Pattern*
- *Valve Delivery*
- *Water Content*
- For performance quality tests, refer to ⟨601⟩

Inhalation Solution

DESCRIPTION

Inhalation solution drug products typically are water-based sterile preparations. They are intended for delivery to the lungs by nebulization with a specified nebulizer. Such drug preparations typically are packaged in single-dose semipermeable containers within protective packaging to minimize ingress of volatile foreign contaminants, loss of solvent, and exposure to oxygen and light. Nebulization involves continuous generation and delivery to the patient of a fine mist of aqueous droplets containing a drug solution by means of ultrasonic energy, Venturi effect, or other appropriate mechanical/electrical means. General quality tests for inhalation solutions include the following attributes (see *4. Description of Product Quality Tests* for more detailed discussions of each test):

- *Assay (strength and content uniformity)*
- *Assay for Antimicrobial Preservative and Stabilizing Excipients (if present)*
- *Content Uniformity for Premetered Dosage Forms*
- *Elemental Impurities*
- *Foreign Particulate Matter*
- *Identification*
- *Impurities and Degradation Products*
- *Leachables*
- *Net Fill Weight*

- *Osmolality*, if relevant
- *pH*
- ▲*Residual Solvents*▲ (USP 1-Dec-2020)
- *Sterility*
- *Viscosity*, if relevant
- *Weight Loss*
- For information on performance quality tests, refer to *Products for Nebulization—Characterization Tests* ⟨1601⟩

Inhalation Suspension

DESCRIPTION

Inhalation suspension drug products typically are water-based sterile preparations. They are intended for delivery to the lungs by nebulization with a specified nebulizer. Such drug preparations typically are packaged in single-dose semipermeable containers within protective packaging to minimize ingress of volatile foreign contaminants, loss of solvent, and exposure to oxygen and light. Nebulization involves continuous generation and delivery to the patient of a fine mist of aqueous droplets containing the formulation components by means of ultrasonic energy, Venturi effect, or other appropriate mechanical means. General quality tests for inhalation suspensions include the following attributes (see *4. Description of Product Quality Tests* for more detailed discussions of each test):

- *Primary Particle Size Distribution*
- For all other general quality attributes, refer to the previous *Inhalation Solution* attributes

Solution for Inhalation

DESCRIPTION

Solution for inhalation drug products typically are water-based sterile preparations. Upon dilution, in accordance with labeling, including identity and amount of dilution vehicle, they are intended for delivery to the lungs by nebulization with a specified nebulizer. Such drug preparations typically are packaged in single-dose semipermeable containers within protective packaging to minimize ingress of volatile foreign contaminants, loss of solvent, and exposure to oxygen and light. Nebulization involves continuous generation and delivery to the patient of a fine mist of aqueous droplets containing the formulation components by means of ultrasonic energy, Venturi effect, or other appropriate mechanical/electrical means. General quality tests for solutions for inhalation include the following attributes (see *4. Description of Product Quality Tests* for more detailed discussions of each test):

- *Clarity and Color of Solution upon Dilution* in accordance with the labeling
- For all other general quality attributes, refer to the previous *Inhalation Solution* attributes

Drug for Inhalation Solution

DESCRIPTION (POWDER)

Drug for inhalation solution is a (specified color) sterile drug powder formulation that upon the addition of a suitable vehicle, in accordance with labeling, including identity and amount of dilution vehicle, yields a sterile solution conforming in all respects to the *Inhalation Solution* requirements. General quality tests for drug for inhalation solutions include the following attributes (see *4. Description of Product Quality Tests* for more detailed discussions of each test):

- *Reconstitution Time (powder)*
- *Water Content*
- Clarity, color, and completeness of solution within specified time, upon reconstitution
- For all other general quality attributes, refer to the previous *Inhalation Solution* attributes upon (re)constitution of the drug product

Inhalation Spray

DESCRIPTION

Inhalation spray drug products typically are water-based sterile formulations packaged in a compact container–closure system containing an integral spray pump unit that, upon activation, delivers an accurately metered amount of fine droplets of the formulation. The droplets can be generated by various means such as mechanical action, power assistance, or energy from the patient's inspiration. The mechanisms by which they generate droplets distinguish the various types of inhalation sprays. These drug products may be unit-dose or multidose presentations. Inhalation spray drug products may be designed as premetered or device-metered presentations. A premetered unit contains a previously measured amount of liquid formulation in an individual container (e.g., a blister) that is inserted in the device by the patient before use. A device-metered product contains a sufficient amount of liquid formulation for a prescribed number of doses in a reservoir, and each dose is delivered as an accurately metered spray by the device throughout the unit's life. General quality tests for inhalation sprays include the following attributes (see *4. Description of Product Quality Tests* for more detailed discussions of each test):

- *Plume Geometry*
- For all other general quality attributes, refer to the previous *Inhalation Solution* attributes
- For performance quality tests, refer to ⟨601⟩

Inhalation Powder

DESCRIPTION

Inhalation powder drug products, commonly known as dry powder inhalers (DPIs), dispense powders for inhalation with the use of a device that aerosolizes and delivers an accurately metered amount of active ingredient(s) with consistent physical characteristics alone or with a suitable excipient(s). Current designs include premetered and device-metered DPIs, all of which rely on various energy sources to create and disperse the aerosol during patient inspiration.

Premetered DPIs contain previously measured amounts of formulation in individual containers (e.g., capsules or blisters) that are inserted into the device before use. Premetered DPIs also may contain premetered dose units as ordered multidose assemblies in the delivery system. Device-metered DPIs have an internal reservoir that contains a sufficient quantity of formulation for multiple doses that are metered by the device itself during actuation by the patient. General quality tests for inhalation powders include the following attributes (see *4. Description of Product Quality Tests* for more detailed discussions of each test):

- *Assay (strength and content uniformity)*
- *Content Uniformity for Premetered Dosage Forms*
- *Elemental Impurities*
- *Foreign Particulate Matter*
- *Identification*
- *Impurities and Degradation Products*
- *Leachables*
- *Microbial Limits*
- Net Content (device-metered)
- *Residual Solvents*
- *Water Content*
- For performance quality tests, refer to ⟨601⟩

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3. GENERAL QUALITY TESTS FOR NASAL DRUG PRODUCTS

Nasal Aerosol

Refer to the above *Inhalation Aerosol* attributes.

Nasal Spray

DESCRIPTION

Nasal spray drug products typically are water-based formulations applied to the nasal cavity for local and/or systemic effects. They contain therapeutically active ingredient(s) dissolved or suspended in solution or mixtures of excipients in a nonpressurized compact container–closure system. The container–closure system includes an integral spray pump unit that upon activation delivers an accurately metered amount of the formulation as a mist. Dispersion of the formulation as a spray typically is accomplished by forcing the formulation through the nasal actuator and its orifice. Often, such drug products are multidose device-metered (see *Inhalation Spray*) presentations in which the dose is metered by the spray pump. Nasal spray drug products also may be designed as premetered presentations. General quality tests for nasal sprays include the following attributes (see *4. Description of Product Quality Tests* for more detailed discussions of each test):

- *Assay (strength and content uniformity)*
- *Assay for Antimicrobial Preservative and Stabilizing Excipients (if present)*
- *Content Uniformity for Premetered Dosage Forms*
- *Elemental Impurities*
- *Foreign Particulate Matter*
- *Identification*
- *Impurities and Degradation Products*
- *Leachables*
- *Microbial Limits*
- *Net Fill Weight*
- *Osmolality*
- *pH*

- *Primary Particle Size Distribution* (for suspensions)
- *Pump Delivery*
- ▲*Residual Solvents*▲ (USP 1-Dec-2020)
- *Spray Pattern*
- *Viscosity*
- For performance quality tests, refer to ⟨601⟩

Nasal Powder

Refer to the previous *Inhalation Powder* quality attributes as applicable.

Nasal Solution

DESCRIPTION

Nasal solutions are drug products that typically are water-based formulations applied to the nasal cavity for local effect. They may contain drug substance(s) dissolved in solution or mixtures of excipients in a nonpressurized compact container–closure system. The container–closure system includes a delivery system that administers nonmetered amounts of drops or a fine mist of droplets of the formulation. Typically, such drug products are multidose presentations. General quality tests for nasal solution drug products include the following attributes (see *4. Description of Product Quality Tests* for more detailed discussions of each test):

- *Assay (strength and content uniformity)*
- *Assay for Antimicrobial Preservative and Stabilizing Excipients (if present)*
- *Elemental Impurities*
- *Foreign Particulate Matter*
- *Identification*
- *Impurities and Degradation Products*
- *Leachables*
- *Microbial Limits*
- *Net Fill Weight*
- *Osmolality*
- *pH*
- ▲*Residual Solvents*▲ (USP 1-Dec-2020)
- *Viscosity*

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4. DESCRIPTION OF PRODUCT QUALITY TESTS

Product quality tests are listed as follows and should be applied to inhalation and nasal drug products and to products for nebulization. Product-specific quality tests are addressed in product monographs.

Assay (strength and content uniformity)

The USP assay test of a drug substance in the drug product container is determined by means of a validated stability-indicating procedure following *Validation of Compendial Procedures* ⟨1225⟩. The USP assay test should measure the amount of drug substance(s) in the unit and its stability throughout the expiration dating period, including adherence of the drug substance to the container–closure components. Appropriate acceptance criteria can provide added assurance of manufacturing reproducibility and may ensure better conformance in performance attributes (e.g., delivered dose uniformity).

If a drug product is labeled to contain a single enantiomer of a chiral drug substance, analysts can use a chiral assay or a combination of an achiral assay and a validated procedure to control the presence of the undesired enantiomer as an impurity.

Assay for Antimicrobial Preservative and Stabilizing Excipients (if present)

The assay of any preservative (e.g., an antimicrobial) in a multidose container or stabilizing excipient (e.g., an antioxidant, an agent specifically added to minimize or prevent degradation) in a formulation should be determined analytically, typically with a validated stability-indicating procedure following the current International Council for Harmonisation ICH Q2 guidance. The assay acceptance criteria for antimicrobial preservatives normally are based on appropriate preservative effectiveness demonstrated by a microbial challenge test.

Clarity and Color of Solution upon Dilution

Solution for inhalation and drug for inhalation solution dosage forms must be diluted and reconstituted in accordance with labeling before administration by nebulization. The type and amount of the vehicle used for dilution and reconstitution must

be specified on the labeling. Appropriate studies must be undertaken to fully assess quantitatively the clarity and color of the solution upon dilution and reconstitution. The studies also should include appropriate physical and chemical stability studies as well as studies of performance characteristics.

Content Uniformity for Premetered Dosage Forms

See *Uniformity of Dosage Units* ⟨905⟩.

Co-Solvent Content [(e.g., ethanol) if present]

If a co-solvent is used in a drug product formulation, a specific assay with appropriate acceptance criteria should be included.

Description

See the previous descriptions corresponding to applicable dosage forms, outlined in *2. General Quality Tests for Inhalation Drug Products* and *3. General Quality Tests for Nasal Drug Products* of this chapter, in association with their container–closure delivery systems and the respective labeling statement of the monograph of a drug product. This test should address the appearance of the contents of the container (i.e., dosage form) and the appearance and integrity of the components of the container–closure system for conformance to their respective descriptions.

Elemental Impurities

Drug products should be evaluated for elemental impurities (see *Elemental Impurities—Limits* ⟨232⟩). Validated analytical procedures should be used as described in *Elemental Impurities—Procedures* ⟨233⟩.

Foreign Particulate Matter

Foreign particulate matter in these drug products should be controlled adequately. Particulate matter in inhalation and nasal drug products may originate during manufacturing and from formulation and container–closure components. Following a detailed toxicological assessment of the type, origin, amount, and size of any foreign particulates, including fine particulates (e.g., less than 10 µm), appropriate specifications should be established throughout the stability storage period to confirm overall quality.

Identification

A specific identification test or tests are used to verify the identity of the drug substance in the drug product. If a nonspecific method is used for identification, then it should be combined with a second independent and complementary method. A specific identification test for polymorphic forms should be carried out, if applicable. Moreover, if the drug substance is a salt, an appropriate identification test also should be included for the counterion.

Impurities and Degradation Products

Validated stability-indicating analytical procedure(s) following ⟨1225⟩ should be used to determine the levels of impurities and degradation products in a drug product. Typically, the acceptance criteria are set for individual, unspecified, and total impurities and degradation products following current ICH Q3B guidance. For reporting, identification, and qualification thresholds and other relevant information, follow current ICH Q3B and ICH M7 guidelines.

Leachables

Inhalation and nasal drug products should be evaluated for compounds that may leach from elastomeric and plastic components and from coatings of components of the container–closure system in direct contact with the formulation. Additionally, the drug product inadvertently may contain other residual contaminants from manufacturing and processing. Leachables may include polynuclear aromatics, nitrosamines, monomers, plasticizers, accelerators, antioxidants, and vulcanizing agents. Processing contaminants may include surface treatment or processing agents that may dissolve, chemically associate, or become suspended in the formulation.

Thus, throughout the expiration-dating period, the drug product should be evaluated for compounds that can migrate into the formulation from a variety of sources. The type of testing that should be performed depends on whether the formulation is a powder or a liquid and the composition of the container–closure system, e.g., a drug product packaged in a semipermeable container should be evaluated for ingress of volatile leachables. Appropriate specifications using validated analytical procedures should be applied to identify, monitor, and quantify the compounds in the drug product with appropriate minimum levels of quantification. Corresponding acceptance criteria should be established and justified from toxicological and safety perspectives.

Leak Rate

Leak rate studies of inhalation and nasal aerosol drug products can be used during drug product development and characterization to support the selection of appropriate container–closure components (e.g., valve and canister) and drug

product manufacturing parameters, including the crimping process and 100% heat stress test prior to the equilibration/quarantine period. Release and stability specifications for the USP leak rate test can include multiple units from each batch based on weight difference determination with time at a specified temperature. See *Leak Rate* ⟨604⟩ for additional information.

Microbial Limits

The microbial quality of dosage forms where indicated in *2. General Quality Tests for Inhalation Drug Products* and *3. General Quality Tests for Nasal Drug Products* normally is controlled by appropriate validated test(s) and acceptance criteria for total aerobic count, total yeasts and molds count, and freedom from designated indicator pathogens. Acceptance criteria can be expressed on a per-container basis. Refer to *Microbial Enumeration Tests* ⟨61⟩, *Alternative Microbiological Sampling Methods for Nonsterile Inhaled and Nasal Products* ⟨610⟩, and *Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use* ⟨1111⟩ for additional information.

Net Fill Weight

The total net weight of the formulation in the container should be assessed and controlled with a test and acceptance criteria. See *Minimum Fill* ⟨755⟩ for additional information.

Osmolality

To control the tonicity of the formulation of dosage forms where indicated in *2. General Quality Tests for Inhalation Drug Products*, the product should be tested for osmolality with appropriate specifications as described in *Osmolality and Osmolarity* ⟨785⟩.

pH

Appropriate specification for the pH of the formulation of dosage forms where indicated in *2. General Quality Tests for Inhalation Drug Products* and *3. General Quality Tests for Nasal Drug Products* should be established as described in *pH* ⟨791⟩.

Primary Particle Size Distribution

For suspension preparation drug products, appropriate method(s) and corresponding acceptance criteria should be used for the determination of the particle size distribution of the drug substance particles in the formulation within the container. Microscopic examination of the product formulation provides information and changes over product stability on the presence of large particles, morphology of the drug substance and carrier particles, extent of agglomerates, crystal growth, and foreign particulate matters. Additionally, where the crystalline form of the drug substance can affect the bioavailability, performance, stability, or other properties of the drug product, microscopic evaluation or other appropriate methods are recommended to control and monitor the crystalline and amorphous forms if changes are observed on stability. See *Optical Microscopy* ⟨776⟩ for additional information. For aerodynamic particle size distribution and droplet size distribution tests of inhalation and nasal drug products, as applicable, refer to ⟨601⟩.

Plume Geometry

Because various factors can affect the plume characteristics of the spray of an inhalation aerosol, inhalation spray, nasal aerosol, nasal spray▲, or nasal powder (if device is pump-dependent)▲ (USP 1-Dec-2020) drug product, its full characterization is important for assessing the performance of the delivery system. Plume geometry can be determined by a variety of procedures using appropriately validated methods. Plume geometry also can be controlled by appropriate acceptance criteria that measure spray pattern characteristics, including shape and size of the evolving spray plume under defined experimental and instrumental test conditions.

Pump Delivery

▲A shot weight test (amount of formulation released per actuation) delivered from the individual pump of the drug product▲ (USP 1-Dec-2020) should be performed to better ensure reproducible performance of nasal spray drug products. Appropriate specifications for the pump delivery should be set.

Reconstitution Time (powder)

Drug for inhalation solution dosage forms must be (re)constituted before administration with the use of a specified nebulization system. Hence, appropriate compatibility studies should be undertaken to fully assess the type and amount of the solvent(s), as well as (re)constitution time for preparation of the final solution for patient administration. The compatibility studies also should include appropriate physical and chemical stability studies on the reconstituted solution, including its performance characterization.

Residual Solvents

Suitable and validated tests should be used to determine the levels of any solvent(s) in the drug product. Refer to *Residual Solvents* ⟨467⟩ for additional information.

Spray Pattern

Because various factors can affect the spray pattern of an inhalation aerosol, nasal aerosol, or nasal spray drug product, full spray pattern characterization is important for assessing the performance of the specific valve and the actuator or the pump. The spray pattern can be determined using appropriately validated methods and corresponding acceptance criteria that measure the shape, density, and size of the pattern. The test procedure for spray patterns normally is specific to the drug product and may include, among others, the distance between the mouthpiece and the measurement plane or collection surface, minimum number of actuations per spray pattern to enable discrimination, orientation of the collection surface relative to the mouthpiece, and visualization procedure(s).

Sterility

All aqueous-based inhalation dosage forms are sterile preparations and should meet the requirements of *Sterility Tests* ⟨71⟩.

▲Valve Delivery

A shot weight test (amount of formulation released per actuation) delivered from the individual valve of the drug product should be performed to better ensure reproducible performance of inhalation and nasal aerosol drug products. Appropriate specifications for the valve delivery should be set.▲ (USP 1-Dec-2020)

Viscosity

A test for viscosity with appropriate acceptance criteria should be included for dosage forms where indicated in *2. General Quality Tests for Inhalation Drug Products* and *3. General Quality Tests for Nasal Drug Products* as appropriate (see *Viscosity—Capillary Methods* ⟨911⟩, *Viscosity—Rotational Methods* ⟨912⟩, and *Viscosity—Rolling Ball Method* ⟨913⟩).

Water Content

Appropriate specification for water content of dosage forms where indicated in *2. General Quality Tests for Inhalation Drug Products* and *3. General Quality Tests for Nasal Drug Products* should be established to ensure the drug product's continued stability and acceptable performance. Validated analytical procedures should be used as described in *Water Determination* ⟨921⟩. Proceed as directed in ⟨921⟩ with the following modification: provide the closed-system titrating vessel with an opening through which passes a coarse-porosity gas dispersion tube connected to a sampling cylinder.

Weight Loss

Drug products should be evaluated for weight loss where applicable, e.g., drug products packaged in semipermeable containers, to assess the moisture-loss protective properties of the overall container–closure system.