Guidance for Industry

Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

July 2002

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GUIDANCE FOR INDUSTRY[1]

Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation

I. INTRODUCTION

This document provides guidance for industry on the chemistry, manufacturing, and controls (CMC) documentation that should be submitted in new drug applications (NDAs) and abbreviated new drug applications (ANDAs) for nasal spray and inhalation solution, suspension, and spray drug products intended for local and/or systemic effect. This guidance covers CMC information recommended for inclusion in the application regarding the drug product components, manufacturing process, and associated controls for each of these areas, but does not address the manufacture of drug substances. The guidance also provides recommendations on labeling. This guidance does not address propellant-based inhalation and nasal aerosols (also known as oral and nasal metered-dose inhalers, MDIs), inhalation powders (also known as dry powder inhalers, DPIs), and nasal powders.[2]

This guidance sets forth information that should be provided to ensure continuing quality and performance characteristics for these drug products. The guidance does not impose mandatory requirements but does suggest approaches that are appropriate for submitting CMC-related regulatory information. The guidance provides recommendations for drug

[1] This guidance has been prepared by the Inhalation Drug Products Working Group of the Chemistry, Manufacturing, and Controls Coordinating Committee (CMCCC) in the Center for Drug Evaluation and Research (CDER) at the FDA.

[2] In November 1998 (63 FR 64270), the Agency made available a draft guidance document on *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation*. When finalized, this guidance will provide CMC recommendations for MDIs and DPIs.

products that are used to treat a variety of diseases and patient populations. Therefore, CMC recommendations may vary depending on the specific drug product and stage of development. For example, the recommendations in this guidance should be considered during the investigational stages and phased in by the initiation of critical clinical studies (phase 2 and phase 3 studies) to provide supporting documentation for an NDA. Applicants are encouraged to discuss significant departures from the approaches outlined in this guidance (including decisions to provide less CMC documentation than recommended) with the appropriate Agency review division before implementation to avoid expending resources on development avenues that may later be deemed inappropriate.

Reference to information in Drug Master Files (DMFs) for particular portions of the CMC section of the application is appropriate if the DMF holder provides written authorization that includes specific reference (e.g., submission date, page number, item name and unique identifier) to the pertinent and up-to-date information (21 CFR 314.420(d)). Refer to FDA=s *Guideline for Drug Master Files* (September 1989) for more information about DMFs.

II. BACKGROUND

A. Nasal Sprays

Nasal spray drug products contain therapeutically active ingredients (drug substances) dissolved or suspended in solutions or mixtures of excipients (e.g., preservatives, viscosity modifiers, emulsifiers, buffering agents) in nonpressurized dispensers that deliver a spray containing a metered dose of the active ingredient. The dose can be metered by the spray pump or could have been premetered during manufacture. A nasal spray unit can be designed for unit dosing or can discharge up to several hundred metered sprays of formulation containing the drug substance. Nasal sprays are applied to the nasal cavity for local and/or systemic effects.

Although similar in many features to other drug products, some aspects of nasal sprays may be unique (e.g., formulation, container closure system, manufacturing, stability, controls of critical steps, intermediates, and drug product). These aspects should be considered carefully during the development program because changes can affect the ability of the product to deliver reproducible doses to patients throughout the product=s shelf life. Some of the unique features of nasal sprays are listed below:

- Metering and spray producing (e.g., orifice, nozzle, jet) pump mechanisms and components are used for reproducible delivery of drug formulation, and these can be constructed of many parts of different design that are precisely controlled in terms of dimensions and composition.

- Energy is required for dispersion of the formulation as a spray. This is typically accomplished by forcing the formulation through the nasal actuator and its orifice.

- The formulation and the container closure system (container, closure, pump, and any protective packaging) collectively constitute the drug product. The design of the container closure system affects the dosing performance of the drug product.

- The concept of classical bioequivalence and bioavailability may not be applicable for all nasal sprays, depending on the intended site of action. The doses administered are typically so small that blood or serum concentrations are generally undetectable by routine analytical procedures. Additional information will be provided in a future guidance for industry on *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action.*[3]

B. Inhalation Solutions and Suspensions

Inhalation solution and suspension drug products are typically aqueous-based formulations that contain therapeutically active ingredients and can also contain additional excipients. Aqueous-based oral inhalation solutions and suspension must be sterile (21 CFR 200.51). Inhalation solutions and suspensions are intended for delivery to the lungs by oral inhalation for local and/or systemic effects and are to be used with a specified nebulizer. Unit-dose presentation is recommended for these drug products to prevent microbial contamination during use. The container closure system for these drug products consists of the container and closure, and can include protective packaging such as foil overwrap. Recommendations on overwrapping of inhalation drug products packaged in semipermeable container closure systems are provided in section III.G.5.

C. Inhalation Sprays

An inhalation spray drug product consists of the formulation and the container closure system. The formulations are typically aqueous based and, by definition, do not contain any propellant. Aqueous-based oral inhalation sprays must be sterile (21 CFR 200.51). Inhalation sprays are intended for delivery to the lungs by oral inhalation for local and/or systemic effects. The products contain therapeutically active ingredients and can also contain additional excipients. The formulation can be in unit-dose or multidose presentations. The use of preservatives or stablilizing agents in inhalation spray formulations is

[3] A notice of availability for the June 1999 draft guidance Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action published in the Federal Register on June 24, 1999 (64 FR 33869).

discouraged. If these excipients are included in a formulation, their use should be justified by assessment in a clinical setting to ensure the safety and tolerability of the drug product. The dose is delivered by the integral pump components of the container closure system to the lungs by oral inhalation for local and/or systemic effects. The container closure system of these drug products consists of the container, closure, and pump, and can also include protective packaging.

Current container closure system designs for inhalation spray drug products include both **premetered** and **device-metered** presentations using mechanical or power assistance and/or energy from patient inspiration for production of the spray plume. Premetered presentations contain previously measured doses or a dose fraction in some type of units (e.g., single or multiple blisters or other cavities) that are subsequently inserted into the device during manufacture or by the patient before use. Typical device-metered units have a reservoir containing formulation sufficient for multiple doses that are delivered as metered sprays by the device itself when activated by the patient.

Inhalation spray and nasal spray drug products have many similarities. Therefore, many of the unique features listed in section II.A for nasal sprays are also characteristic of inhalation spray drug products. Moreover, the potential wide array of inhalation spray drug product designs with unique characteristics will present a variety of development challenges. Regardless of the design, the most crucial attributes are the reproducibility of the dose, the spray plume, and the particle/droplet[4] size distribution, since these parameters can affect the delivery of the drug substance to the intended biological target. Maintaining the reproducibility of these parameters through the expiration dating period and ensuring the sterility of the content and the functionality of the device (e.g., spray mechanism, electronic features, sensors) through its lifetime under patient-use conditions will probably present the most formidable challenges. Therefore, changes in components of the drug product or changes in the manufacturer or manufacturing process that can affect these parameters should be carefully evaluated for their effect on the safety, clinical effectiveness and stability of the product. If such changes are made subsequent to the preparation of the batches used in critical clinical, bioequivalence, or primary stability studies, adequate supportive comparative data should be provided to demonstrate equivalency in terms of safety, clinical effectiveness, and stability of the product.

The remaining portion of this guidance will focus on specific chemistry, manufacturing, and controls information recommended for inclusion in the drug product section of applications for nasal spray and inhalation solution, suspension, and spray drug products.

[4] The term *particle/droplet* refers to a combination of droplets and particles or droplets alone, depending on the formulation and conditions of measurement.

III. DRUG PRODUCT

A. Formulation Components

A list of all components (i.e., ingredients) used in the manufacture of the drug product formulation, regardless of whether they undergo chemical change or are removed during manufacture, should be included in the application. Each component should be identified by its established name, if any, and by its complete chemical name, using structural formulas when warranted for specific identification. If any proprietary preparations or other mixtures are used as components, their identity should be fully described including a complete statement of their composition and other information that will properly identify the material.

B. Formulation Composition

The application should include a statement of the quantitative composition of the unit formula of the drug product, specifying the name and amount of each active ingredient and excipient contained in a stated quantity of the formulation. For components in the final formulation, the amounts should be expressed in concentration (i.e., amount per unit volume or weight), as well as amount per container and per spray, where applicable. The target container net content should also be indicated. Similarly, a production batch formula representative of the one to be employed in the manufacture of the drug product should be included. Any calculated overage for an ingredient should be designated as such and the percentage shown. The overage should be scientifically justified and documented in both the unit formula and batch formula. For these products, overages can be included only for justified reproducible manufacturing losses and/or for an ANDA product to match the overage present in the Reference Listed Drug. Any intended change in the formulation of the commercial product from that used in the submitted batches (e.g., critical clinical, biobatch, primary stability, production) should be clearly indicated by providing the composition of each formulation.

The composition of suspension formulations may be crucial in defining the physical stability and the performance characteristics of the drug product. The density and suspension properties of the solid materials of the formulation and the potential for agglomeration should be considered. Moreover, interaction of the suspended drug substance with the various internal container closure system components can also contribute to a nonhomogeneous distribution of drug substance. The above mentioned phenomena, which may be exacerbated with time, can contribute to inconsistent particle size distribution and medication dose delivery. See also the discussions in sections III.F.1.c and III.F.2.c.

C. Specifications for the Formulation Components

1. Active Ingredients

Information regarding the comprehensive characterization of the physical and chemical properties of the drug substance should be included in the application. Important properties of the drug substance used in suspension formulations can include, but are not necessarily limited to, density, particle size distribution, particle morphology, solvates and hydrates, polymorphs, amorphous forms, solubility profile, moisture and/or residual solvent content, microbial quality, dissociation constants (pKa), and specific rotation.

Appropriate acceptance criteria and tests for routine control (i.e., release, stability, and retest) should be instituted for those drug substance parameters considered key to ensuring reproducibility of the physicochemical properties of the drug substance. Specification parameters can include, as applicable, color, appearance (visual and microscopic), specific identification, moisture, residue on ignition, specific rotation, assay, impurities, microbial limits (U.S. Pharmacopeia (USP) <61>)[5], melting range, particle size distribution, crystalline forms, amorphous content, residual solvents, and heavy metals. Some of these parameters may not be pertinent for drug substances used in solution formulations.

The purity of the drug substance and its impurity profile should be characterized and controlled with appropriate specifications. Important impurity-related parameters can include organic volatile impurities and/or residual solvents, organic impurities (synthesis-related and degradation products), and inorganic impurities (e.g., heavy metals, reagents, catalysts). Any impurity found in the drug substance at a concentration of 0.10 percent or 1.0 milligram (mg) per day intake (whichever is lower), relative to the parent drug substance, should be identified. Moreover, the drug substance impurities should be appropriately qualified. Justification of acceptance criteria for the drug substance impurities should be based on toxicological considerations and levels of impurities found in the submitted batches (e.g., critical clinical, biobatch, primary stability, production). For guidance on toxicological qualification, the applicant is encouraged to refer to the following guidance documents: (1) ICH *Q3A Impurities in New Drug Substances* (January 1996),[6] (2) *NDAs: Impurities in Drug Substances* (February 2000), and (3) *ANDAs: Impurities in Drug Substances* (November 1999). The applicant can also contact the responsible review division for guidance on toxicological qualification.

For suspension formulations, the specification for drug substance should include controls for particle size distribution and physical properties (e.g., shape, crystal

[5] Sample size for microbial limits testing should be 10 grams unless otherwise justified.

[6] The guidance, *Q3A Impurities in New Drug Substances*, will be superseded by FDA's guidance for industry, *Q3A(R) Impurities in New Drug Substances*, once it is issued in final form. We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance page at http://www.fda.gov/cder/guidance/index.htm.

habit, morphology, surface texture) of the drug substance, parameters that are often critical for reproducible drug product performance. If laser diffraction methodology is used for testing the particle size distribution, it is crucial that test procedure instrumental parameters (e.g., apparatus and accessories, calculation theory, correction principles, software version, sample placement, laser trigger condition, measurement range, beam width) be defined accurately and with sufficient detail for Agency laboratories to validate the adequacy of the methodology. In addition, the potential effect of micronization processes on the levels of amorphous content and foreign particulates in the drug substance should be considered.

In general, acceptance criteria for all parameters defining the physicochemical properties should be based on historical data, thereby providing continuity of quality and reproducible performance of future batches of the drug substance. For additional information on various aspects of drug substance chemistry, manufacturing, and controls documentation, see the FDA *Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances* (February 1987).

2. Excipients

Because of the route of administration and the sensitive nature of various patient populations using oral inhalation (solution, suspension, spray) drug products, more thorough characterization with additional comprehensive controls (e.g., strength, quality, purity), as compared to drug products for other routes of administration, should be considered for excipients used in these drug products. Moreover, for nasal and inhalation suspension formulations, additional controls should be applied to critical excipients to ensure safety and effectiveness of the drug product. Critical excipients for suspension formulations (e.g., microcrystalline cellulose for nasal sprays) are those that can affect the suspension and/or particle characteristics and, therefore, the quality, stability, or performance of the drug product. The suitability of the physicochemical properties of these critical excipients should be thoroughly investigated and documented.

Unless otherwise indicated, the comments below regarding excipients pertain to nasal spray and inhalation solution, suspension, and spray drug products.

The source of each excipient should be assessed, and the material supplied should meet appropriate acceptance criteria that are based on test results from a minimum of one batch used to prepare the submitted batches of drug product (e.g., critical clinical, biobatch, primary stability, production). However, for critical excipients of suspension formulations, the sources should be identified and test results from multiple batches should be provided. Likewise, when the supplier of an excipient is changed prior to submission of the application, the new supplier's ability to

provide material of comparative quality should be assessed and supporting data should be provided.

For noncompendial excipients, appropriate authorization to a DMF that provides information on the noncompendial excipient or an equivalent package of information prepared by the excipient manufacturer should be provided in the application. The information should include analytical procedures, acceptance criteria, and a brief description of the manufacture and controls.

When a USP or *National Formulary* (NF) monograph material is used, the associated specifications may not always provide adequate assurance with regard to the assay, quality, or purity of the material or its performance in the drug product. In these cases, monograph specifications should be supplemented with appropriate controls (e.g., particle size distribution, crystal forms, amorphous content, foreign particulates) to ensure batch-to-batch reproducibility of these components. This can be particularly relevant for compendial excipients that have an impact on the purity of inhalation drug products or performance properties (e.g., droplet and particle size distribution, spray content uniformity) of suspension drug products. The additional test procedures should be included, and the acceptance criteria should reflect the data for the excipients used in the submitted batches (e.g., critical clinical, biobatch, primary stability, production). Acceptance criteria for physicochemical parameters of a qualified polymeric excipient (e.g., molecular weight distribution, viscosity) that are wider than what is reflective of the data on the submitted batches can be justified by demonstrating that the proposed ranges of the excipient attributes do not adversely affect the quality of the drug product. Justification should be based on adequate release and stability data that is specific to the drug product prepared with the excipient attributes near the limits of the allowable range.

The suitability of the toxicological properties of the excipients for these drug products should be thoroughly investigated and documented. Toxicological qualification of these excipients may be appropriate under various circumstances, including (1) increased concentration of an excipient above that previously used in inhalation and nasal drug products, (2) excipients that have been used previously in humans but not by the inhalation or nasal route, and (3) novel excipients not previously used in humans in the United States. The extent of toxicological investigation to qualify the use of an excipient under such circumstances will vary, and the applicant is encouraged to contact the responsible review division to discuss an appropriate strategy for toxicological qualification.

If excipients are accepted based on certificates of analysis from the manufacturers with the applicant performing a specific identification test upon receipt, the applicant should also develop validated procedures, have access to all of the manufacturer=s analytical and other test procedures, or use contract laboratories to allow them to establish the reliability of the test results at appropriate intervals, as required under 21 CFR 211.84. The applicant should confirm the supplier=s

results by (1) testing an adequate number of batches of each excipient used in preparing the submitted drug product batches (e.g., critical clinical, primary stability, biobatch, production batches) and (2) providing a commitment to test a predetermined number of batches of each excipient used in preparing postapproval drug product batches.

D. Manufacturers

The name, street address, and, if available, registration number[7] of each facility involved in the manufacture of the drug substance should be listed along with a statement of each manufacturer's specific operations and responsibilities. The same information should be provided for each facility involved in the manufacturing, processing, packaging, controls, stability testing, or labeling of the drug product, including all contractors (e.g., test laboratories, packagers, labelers). For sterile drug products, building numbers, filling rooms, and filling lines should also be identified. Manufacturers of critical and novel excipients should be identified by name and address.

E. Method of Manufacture and Packaging

A detailed description of the manufacturing, processing, and packaging procedures for the drug product should be included.

All aqueous-based oral inhalation drug products must be manufactured as sterile products (21 CFR 200.51), and their sterility should be ensured through the expiration dating period.

If micronization is used for the drug substance and/or excipients, the process should be fully validated and the equipment, operating conditions, and process controls should be described in detail. For example, the description of the controls for a milling operation could include the rate of feed, air pressure, air flow rate, particle size being fed, number of times a lot is micronized, re-use of carryovers from previous micronized lots. Potential contamination of the material during the micronization process should be controlled with appropriate tests and acceptance criteria. See the discussion of testing attributes specific for micronized material (e.g., particle size distribution, crystal forms, amorphous content, foreign particulates) discussed in section III.C.1.

A copy of the actual (executed) batch record, including process controls, and controls for critical steps and intermediates should be submitted, as appropriate, for representative batches (e.g., critical clinical, biobatch, primary stability). A schematic diagram of the proposed production process, a list of process controls, and a master batch production and controls record should be submitted. A brief

[7] Information on when registration is required and how to register is available in 21 CFR 207.

description of the packaging operations and associated process controls for these operations should also be included.

The manufacturing directions should include control procedures and specific information on processing variables (such as times, mixing speeds, and temperatures) to decrease controllable process variability and increase consistency in the quality of the drug product. Any formulation overfill per container to achieve a labeled deliverable volume should be appropriately justified.

A description of the controls for critical steps and intermediates, a description of the associated analytical procedures, and appropriate data to support the acceptance criteria should be provided. These controls should be performed at specified production steps and can include, for example, assay, osmolality, pH, viscosity, consistency of filling, and quality of sealing.

If protective packaging (such as a foil overwrap) is used for the drug product, the application should include a brief description of the primary and protective packaging operations and relevant process controls. In these cases, proper sealing, in terms of adhesion (e.g., heat seal, adhesive) or mechanical seal of the protective packaging, should be ensured. Appropriate integrity testing and acceptance criteria for seal completeness and for seal strength should be established to ensure acceptable sealing properties within a batch and among batches.

See section III.G.5 for recommendations on the use of protective packaging and labeling by embossing or debossing for inhalation drug products packaged in semipermeable containers.

F. Specifications for the Drug Product

A complete description of the acceptance criteria and analytical procedures with analytical sampling plans (i.e., number of samples tested, individual or composite samples specified, number of replicate analyses per sample) should be provided to ensure the identity, strength, quality, purity, and performance of the drug product throughout its shelf life and during the period of patient use. The proposed validated test procedures should be documented in sufficient detail to permit validation by Agency laboratories.[8]

Comprehensive and well-defined in vitro performance characteristics should be established before initiating critical clinical or bioequivalence studies.

[8] Guidance relating to validation of analytical procedures is available in the ICH guidances (Q2A) *Text on Validation of Analytical Procedures* (March 1995) and *Q2B Validation of Analytical Procedures: Methodology* (November 1996) and CDER s guidance on *Submitting Samples and Analytical Data for Methods Validation* (February 1987). CDER s 1987 guidance will be superseded by the guidance on *Analytical Procedures and Methods Validation*, when finalized. A notice of availability for a draft version of this guidance published in the *Federal Register* on August 30, 2000 (65 FR 52776).

Appropriate, validated test procedures and corresponding acceptance criteria that are reflective of the test results for submitted batches (e.g., critical clinical, biobatch, primary stability, production) are crucial to defining and controlling these characteristics.

1. Nasal Sprays

The following test parameters are recommended for nasal spray drug products. Appropriate acceptance criteria and validated test procedures should be established for each test parameter. In general, the acceptance criteria should be reflective of the data obtained from the submitted batches (e.g., critical clinical, biobatch, primary stability, production). Certain tests performed during the manufacturing process (e.g., pH, osmolality, viscosity, net content) can substitute for the release testing, if justified. However, the acceptance criteria should remain a part of the drug product specification.

a. Description

The appearance of the content of the container (i.e., formulation) and the container closure system (e.g., pump, container components) should conform to their respective descriptions (e.g., color and clarity of formulation, size and shape of pump components, texture of inside of the container) as an indication of the drug product integrity.

If any color is associated with the formulation (either present initially or from degradative processes occurring during shelf life), then a quantitative test with appropriate acceptance criteria should be established for the drug product.

b. Identification

A specific identification test or tests should be used to verify the identity of the drug substance in the drug product. Identification using a single chromatographic procedure is not considered to be specific. A second independent and complementary procedure (e.g., UV-spectroscopy, IR), two chromatographic procedures where the separation is based on different principles, or a combination of tests into a single procedure (e.g., HPLC/MS) should be used. If the drug substance is a salt, an identification test should be included for the counterion.

c. Assay

The assay of the drug substance in the container should be determined analytically with a stability indicating procedure unless the use of a nonstability indicating method is justified. Assay can be performed indirectly by determining concentration and actual net content, if justified. A suitable assay procedure should be designed to address potential

stability issues such as degradation of the drug substance, adherence of the drug substance to the container and closure components, and the potential effect of solvent evaporation and/or leakage.

For a drug product that contains a chiral drug substance, an achiral assay can be used when studies have demonstrated that racemization is insignificant during manufacture of the drug product and on storage. Otherwise, a chiral assay or a combination of an achiral assay and a validated procedure to control the presence of the opposite enantiomer should be used.

d. Impurities and Degradation Products

The levels of impurities and degradation products should be determined by a validated analytical procedure or procedures. Acceptance criteria should be set for individual and total impurities and degradation products**.** All related impurities appearing at levels of 0.1 percent or greater should be specified. Specified impurities and degradation products are those, either identified or unidentified, that are individually listed and limited in the drug product specification. For identification and qualification thresholds and other relevant information, refer to ICH guidance *Q3B Impurities in New Drug Products* (November 1996) and, when finalized, the guidance for industry *ANDAs: Impurities in Drug Products* (December 1998).[9]

e. Preservatives and Stabilizing Excipients Assay

If preservatives, antioxidants, chelating agents, or other stabilizing excipients (e.g., benzalkonium chloride, phenylethyl alcohol, edetate) are used in the formulation, there should be a specific assay for these components with associated acceptance criteria. Acceptance criteria for the chemical content of preservatives at the time of product release and through the product shelf life should be included in the drug product specification. For information on preservative effectiveness testing, refer to section IV.L below.

f. Pump Delivery

A test to assess pump-to-pump reproducibility in terms of drug product performance and to evaluate the delivery from the pump should be performed. The proper performance of the pump should be ensured primarily by the pump manufacturer, who should assemble the pump with parts of precise dimensions. Pump spray weight delivery should be verified by the applicant for the drug product. In general, pump spray weight delivery acceptance criteria should control the weight of the

[9] A notice of availability for this draft guidance published in the *Federal Register* on January 5, 1999 (64 FR 516).

individual sprays to within "15 percent of the target weight and their mean weight to within "10 percent of the target weight. However, for small dosage pumps (e.g., 20 µL) other acceptance criteria may be justified. Acceptance testing for pump delivery on incoming pump lots can substitute for the release testing of pump delivery for the drug product, if justified. However, the acceptance criteria for pump delivery should be included in the drug product specification.

g. Spray Content Uniformity (SCU)

The spray discharged from the nasal actuator should be thoroughly analyzed for the drug substance content of multiple sprays from beginning to the end of an individual container, among containers, and among batches of drug product. This test should provide an overall performance evaluation of a batch, assessing the formulation, the manufacturing process, and the pump. At most, two sprays per determination should be used except in the case where the number of sprays per minimum dose specified in the product labeling is one. Then the number of sprays per determination should be one spray. To ensure reproducible in vitro dose collection, the procedure should have controls for actuation parameters (e.g., stroke length, actuation force). The test can be performed with units primed following the instructions in the labeling. The amount of drug substance delivered from the nasal actuator should be expressed both as the actual amount and as a percentage of label claim.

This test is designed to demonstrate the uniformity of medication per spray (or minimum dose), consistent with the label claim, discharged from the nasal actuator, of an appropriate number (n = 10 from beginning and n = 10 from end) of containers from a batch. The primary purpose is to ensure SCU within the same container and among multiple containers of a batch.

The following acceptance criteria are recommended. However, alternative approaches (e.g., statistical) can be proposed and used if they are demonstrated to provide equal or greater assurance of SCU.

$ For acceptance of a batch (1) the amount of active ingredient per determination is not outside of 80 to 120 percent of label claim for more than 2 of 20 determinations (10 from beginning and 10 from end) from 10 containers, (2) none of the determinations is outside of 75 to 125 percent of the label claim, and (3) the mean for each of the beginning and end determinations are not outside of 85 to 115 percent of label claim.

If the above acceptance criteria are not met because 3 to 6 of the 20 determinations are outside of 80 to 120 percent of the label claim,

but none are outside of 75 to 125 percent of label claim and the means for each of the beginning and end determinations are not outside of 85 to 115 percent of label claim, an additional 20 containers should be sampled for second-tier testing.

- For the second tier of testing of a batch, the acceptance criteria are met if (1) the amount of active ingredient per determination is not outside of 80 to 120 percent of the label claim for more than 6 of all 60 determinations, (2) none of the 60 determinations is outside of 75 to 125 percent of label claim, and (3) the means for each of the beginning and end determinations are not outside of 85 to 115 percent of label claim.

h. Spray Pattern and Plume Geometry

Characterization of spray pattern and plume geometry are important for evaluating the performance of the pump. Various factors can affect the spray pattern and plume geometry, including the size and shape of the nozzle, the design of the pump, the size of the metering chamber, and the characteristics of the formulation. Spray pattern testing should be performed on a routine basis as a quality control for release of the drug product. However, the characterization of plume geometry typically should be established during the characterization of the product and is not necessarily tested routinely thereafter. (See discussion of plume geometry testing for inhalation spray drug products in section III.F.2.p and for nasal spray drug products in section IV.K.)

The proposed test procedure for spray pattern should be provided in detail to allow duplication by Agency laboratories. For example, in the evaluation of the spray pattern, the spray distance between the nozzle and the collection surface, number of sprays per spray pattern, position and orientation of the collection surface relative to the nozzle, and visualization procedure should be specified. The acceptance criteria for spray pattern should include the **shape** (e.g., ellipsoid of relative uniform density) as well as the **size** of the pattern (e.g., no axis is greater than x millimeters and the ratio of the longest to the shortest axes should lie in a specified range, for example, 1.00**B**1.30). Data should be provided to demonstrate that the collection distance selected for the spray pattern test will provide the optimal discriminatory capability. Variability in the test can be reduced by the development of a sensitive detection procedure and by providing procedure-specific training to the analyst.

Acceptance testing for spray pattern on incoming pump lots can substitute for the release testing of spray pattern for the drug product, if justified (e.g., spray patterns from pumps with drug product formulation and with the proposed simulating media are the same). However, the acceptance

criteria for spray pattern should be included in the drug product specification.

i. Droplet Size Distribution

For both suspension and solution nasal sprays, the specifications should include an appropriate control for the droplet size distribution (e.g., 3 to 4 cut-off values) of the delivered plume subsequent to spraying under specified experimental and instrumental conditions. If a laser diffraction method is used, droplet size distribution can be controlled in terms of ranges for the D_{10}, D_{50}, D_{90}, span $[(D_{90}-D_{10})/D_{50}]$, and percentage of droplets less than 10 µm. Appropriate and validated and/or calibrated droplet size analytical procedures should be described in sufficient detail to allow accurate assessment by Agency laboratories (e.g., apparatus and accessories, calculation theory, correction principles, software version, sample placement, laser trigger condition, measurement range, beam width).

For solution nasal sprays, acceptance testing for droplet size distribution on incoming pump lots with placebo formulation can substitute for the release testing of droplet size distribution for the drug product, if justified (i.e., droplet size distributions from pumps with drug product formulation and with the placebo are the same). However, the acceptance criteria for droplet size distribution should be included in the drug product specification.

j. Particle Size Distribution (Suspensions)

For suspension nasal sprays, the specification should include tests and acceptance criteria for the particle size distribution of the drug substance particles in the formulation. The quantitative procedure should be appropriately validated, if feasible, in terms of its sensitivity and ability to detect shifts that may occur in the distribution.

When examining formulations containing suspending agents in the presence of suspended drug substance, and it is demonstrated that the currently available technology cannot be acceptably validated, a qualitative and semiquantitative method for examination of drug and aggregated drug particle size distribution can be used. Supportive data, along with available validation information, should be submitted. For example, microscopic evaluation can be used and such an examination can provide information and data on the presence of large particles, changes in morphology of the drug substance particles, extent of agglomerates, and crystal growth.

k. Particulate Matter

For both solution and suspension nasal sprays, there should be validated tests and associated acceptance criteria for particulate matter. Particulate matter can originate during manufacturing, from formulation components, and from the container and closure components. Levels of particulate matter in the drug product can increase with time, temperature, and stress. If stability data generated in support of the application demonstrate that levels of particulate matter do not increase with time, this can be sufficient to justify testing of this attribute only on batch release.

l. Microbial Limits

The microbial quality should be controlled by appropriate tests and acceptance criteria for total aerobic count, total yeast and mold count, and freedom from designated indicator organisms. For a description of this test, refer to the procedure in USP <61>. Furthermore, appropriate testing should show that the drug product does not support the growth of microorganisms and that microbiological quality is maintained throughout the expiration dating period.

m. Net Content

Nasal spray drug products should include acceptance criteria for net content of the formulation in the container. The net content of each test container should be in accordance with the release specification. For a description of this type of testing, refer to the procedure in USP Chapter <755> Minimum Fill.

n. Weight Loss (Stability)

Nasal spray drug products should include acceptance criteria for weight loss on stability. Since storage orientation plays a role in assessment of the sealing characteristics of the container closure system, weight loss for the drug product stored in upright and inverted or upright and horizontal positions should be evaluated.

o. Leachables (Stability)

The drug product should be evaluated for compounds that leach from elastomeric or plastic components of the container closure system. Examples of leachables are nitrosamines, monomers, plasticizers, accelerators, antioxidants, and vulcanizing agents. Refer to Glossary for definition of leachables and extractables. The development of validated analytical procedures to identify, monitor, and quantify leached components in the drug product should be done during investigational

and/or development studies. These procedures can, in turn, be used for testing of the drug product throughout the expiration dating period. Appropriate acceptance criteria for the levels of leached compounds in the formulation should be established. For additional discussion, see the container closure system section of this guidance (section III.G). As stated in section III.G, if a correlation is established between levels of leachables in the drug product (through the shelf life or until an equilibrium is demonstrated) and the extractables of a drug product container and closure components, evaluation of leachables in future routine stability studies may not be needed. In general, the levels of extractables should be greater than the levels of leachables for the correlation to be considered valid.

p. pH

For both solution and suspension nasal sprays, the pH or apparent pH, as appropriate, of the formulation should be tested and an appropriate acceptance criterion established.

q. Osmolality

For formulations containing an agent to control the tonicity or for products having a label claim regarding tonicity, the osmolality of the formulation should be tested and controlled at release with an appropriate procedure and acceptance criterion.

r. Viscosity

For formulations containing an agent contributing to the viscosity, this parameter should be tested and controlled at release and on stability with an appropriate procedure and acceptance criterion.

2. Inhalation Solutions, Suspensions, and Sprays

The following test parameters are recommended for inhalation solution, suspension, and spray drug products. Appropriate acceptance criteria and validated test procedures should be established for each test parameter. In general, the acceptance criteria should be reflective of the data obtained from the submitted batches (e.g., critical clinical, biobatch, primary stability, production). Certain tests performed during the manufacturing process (e.g., pH, osmolality, viscosity, net content) can substitute for the release testing if justified. However, the acceptance criteria should remain a part of the drug product specification.

a. Description

See nasal sprays, section III.F.1.a.

b. Identification

See nasal sprays, section III.F.1.b.

c. Assay

See nasal sprays, section III.F.1.c. For a semipermeable container closure system, the potential for off-setting assay loss from degradation with apparent assay gain from evaporative effects should be considered. For unit dose inhalation solutions and suspensions, test results for content uniformity can be substituted for assay.

d. Impurities and Degradation Products

See nasal sprays, section III.F.1.d.

e. Preservatives and Stabilizing Excipients Assay

If the use of preservatives or stabilizing excipients is justified (refer to section II.C), see nasal sprays, section III.F.1.e and section IV.L.

f. Sterility

All aqueous-based oral inhalation solutions, suspensions, and spray drug products must be sterile (21 CFR 200.51), i.e., labeled as sterile and confirmed by testing. For test methodology, refer to USP <71> Sterility Tests.

g. Particulate Matter

See nasal sprays, section III.F.1.k. The acceptance criteria should include limits for foreign particulate matter less than 10 micrometers (µm), greater than 10 µm, and greater than 25 µm.

h. pH

See nasal sprays, section III.F.1.p.

i. Osmolality

See nasal sprays, section III.F.1.q.

j. Net Content

See nasal sprays, section III.F.1.m.

k. Weight Loss (Stability)

Acceptance criteria for the weight loss of individual units on stability should be included for inhalation drug products packaged in semipermeable container closure systems. The test is used to assess the moisture transmission properties of the container closure system and protective properties of a secondary packaging, when used.

l. Leachables (Stability)

See nasal sprays, section III.F.1.o. Additionally, for inhalation solutions and suspensions packaged in semipermeable containers (e.g., low density polyethylene) with protective packaging or if the immediate containers are indirectly exposed to components of the packaging that include paper labels (for example, inks, paper, adhesives components), the levels of the leachables originating from the packaging, labels, or related materials should be determined. Refer to section III.G. Procedures used for these determinations should be validated and have suitable detection and quantitation limits for the potential leachables. The associated acceptance criteria for the leached compounds should be toxicologically qualified and documented. Refer to section III.G .

m. Particle Size Distribution (Suspensions)

See nasal sprays, section III.F.1.j.

n. Pump Delivery for Inhalation Sprays

See nasal sprays, section III.F.1.f.

o. Spray Content Uniformity (SCU) for Inhalation Sprays

The recommendations for acceptance criteria and tests for SCU from the actuator/mouthpiece of inhalation sprays under defined optimum test conditions are the same as for nasal sprays (refer to section III.F.1.g). Acceptance criteria and tests would apply to both device-metered (e.g., reservoir) and premetered (e.g., blisters) inhalation spray drug products. For device-metered inhalation spray drug products, the SCU should be established and monitored at the beginning and end of the labeled number of sprays.

In addition, the content uniformity of the premetered dose units should be controlled by separate test and acceptance criteria.

p. Plume Geometry for Inhalation Sprays

Characterization of plume geometry is important for evaluating the performance of inhalation sprays. The design of the device and the nature of the formulation are two characteristics that can affect the plume geometry.

Plume geometry can be evaluated by a variety of procedures (e.g., the time sequence sound-triggered high speed flash photography method, videotape recording and taking pictures of different frames). Photographs should be of high quality. The approaches used should allow monitoring the plume development to define the shape (e.g., two side views, at 90° to each other and relative to the axis of the plume) of the individual spray plume over time.

The proposed test procedure for analysis of the geometry of a single spray plume should be provided in detail to allow its validation by Agency laboratories. For example, the procedure should indicate the visualization technique, the specified times (in microseconds) for visualization after spraying, and the examination orientations. The acceptance criteria for plume geometry should include limits that control the shape and size of the evolving spray plume (e.g., measurement after the specified elapsed times of the length, width, spray cone angle from two orientations). Variability in tests involving manual manipulations can be reduced by providing procedure-specific training to the analyst.

q. Particle/Droplet[10] Size Distribution for Inhalation Sprays

The particle/droplet size distribution is a critical parameter, and its control is crucial for maintaining the quality of both solution and suspension formulated inhalation spray drug products. This parameter is dependent on both the formulation and the container closure system. The optimum aerodynamic particle/droplet size distribution for most oral inhalation products has generally been recognized as being in the range of 1 to 5 μm.

From a pharmaceutical viewpoint, the aerodynamic particle/droplet size distribution of the outgoing spray is one of the most important parameters for an inhalation product. The measurement of the aerodynamic size distribution is influenced by the characteristics of the spray (e.g., shape, velocity) and is not solely determined by the size of the individual droplets/particles initially present in the spray plume.

[10] The term *particle/droplet* refers to a combination of droplets and particles or droplets alone, depending on the formulation and conditions of measurement.

A multistage cascade impactor fractionates and collects droplets/particles of the formulation by aerodynamic diameter through serial multistage impactions. Such a device with all associated accessories should allow determination of a size distribution throughout the whole dose including, in particular, the small particle/droplet size fraction of the dose. It also provides information that allows the complete mass balance of the total labeled dose to be determined. However, to minimize distortions and to ensure reproducibility, it is important to specify certain conditions such as information on the calibration of the equipment, flow rate, duration, size and shape of the expansion chamber or inlet stem, and the procedure, accessories, and adapter that introduce the inhalation spray into a specified impactor. These important parameters should be selected to obtain a complete profile of the dose. The rationale and documentation for selection of the above parameters should be presented. When multiple cascade impactors of the same design are used, data should be provided to demonstrate comparability between impactor units.

The number of sprays used to determine particle/droplet size distribution by multistage cascade impactor should be kept to the minimum justified by the sensitivity of the analytical procedure used to quantitate the deposited drug substance. The amount of drug substance deposited on the critical stages of the cascade impactor should be sufficient for reliable assay, but not so excessive as to bias the results by masking individual spray variation.

The aerodynamic particle/droplet size distribution analysis and the mass balance obtained (drug substance deposited on surfaces from the mouthpiece to the cascade impactor filter) should be reported. The total mass of drug collected on all stages and accessories is recommended to be between 85 and 115 percent of label claim on a per spray basis. If the procedure is based on a single actuation determination, then the range can be broadened to reflect the limits allowed for an individual actuation. At the time of application submission, data for the mass amount of drug substance found on each accessory and each of the various stages of the cascade impactor should be reported. In addition, data can also be presented in terms of the percentage of the mass found on the various stages and accessories relative to the label claim.

Acceptance criteria expressed in terms of mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) alone, as well as in terms of *respirable fraction* or *respirable dose* are not considered adequate to characterize the particle/droplet size distribution of the whole dose. Acceptance criteria can be proposed in terms of mass amount of drug substance found on appropriate groupings of stages and/or accessories. However, if this approach is used, at a minimum there should

be three to four groupings to ensure future batch-to-batch consistency of the particle/droplet size distribution.

Inhalation spray drug products can vary widely in design and mode of operation. These differences can lead to particle/droplet size distribution properties that are unique for the drug product and that cannot be characterized by cascade impaction alone. Under such conditions, a complementary validated measurement procedure should be used (e.g., light scattering, time-of-flight) for a more definitive delineation of the critical particle/droplet size distribution parameter and assurance of batch-to-batch reproducibility for inhalation spray drug products. For these complementary procedures, it is crucial that instrumental and operational parameters (e.g., apparatus and accessories, calculation theory, correction principles, software version, sample placement, laser trigger condition, measurement range, beam width) be defined accurately and with sufficient detail for Agency laboratories to assess the adequacy of the methodology. The associated specifications should control the particle/droplet size distribution (e.g., three to four size ranges[11]) of the delivered plume subsequent to spraying under specified experimental and instrumental conditions.

G. Container Closure Systems

This subsection applies to container closure systems for nasal spray and inhalation solution, suspension, and spray drug products. For these drug products, the container closure system consists of the container, closure, pump, and any protective packaging, if applicable. Comments below apply to all product types unless otherwise specified. Comments pertaining to pumps apply to both nasal and inhalation spray drug products. In this guidance the word *pump* refers to all components that are responsible for metering, atomization, and delivery of the formulation to the patient. A properly performing pump should repeatedly spray discrete, accurate, small doses of the formulation in the desired physical form.

The administered dose of nasal and inhalation spray drug products is directly dependent on the design, reproducibility, and performance characteristics of the container closure system. The selection of a suitable pump for a given set of formulation characteristics (e.g., viscosity, density, surface tension, rheological properties) is of paramount importance for the correct performance of the pump and, ultimately, the drug product. Actuation parameters (e.g., force, speed, hold and return times) should also be considered when selecting the pump. Moreover, the design (e.g., number and dimensions of inlet channels, swirl chambers) and performance of the pump, as well as the compatibility of the pump, container, and closure with formulation components, should be thoroughly investigated and established before initiating critical clinical, bioequivalence, and primary stability

[11] Size ranges such as D_{10}, D_{50}, D_{90}, and span $((D_{90} - D_{10})/D_{50})$.

studies. The device should be designed to prevent partial metering of the formulation when used according to the patient instructions for use. The use of some type of actuation counting mechanism for multidose drug products is encouraged to promote patient compliance. If the device includes electronic components that can affect the performance or reliability of the drug product, the applicant should refer to the applicable recommendations outlined in the appropriate guidances from the Center for Devices and Radiological Health (CDRH).[12]

For device-metered nasal or inhalation spray drug products designed for use with replaceable reservoirs, the device should be specific for the intended formulation reservoir only and should not allow use of an alternate reservoir that contains a different formulation. It is also recommended that a mechanism that would prevent unintentional multiple dosing be included, if applicable.

The composition and quality of the materials used in the manufacture of the container closure system components should be carefully selected. For safety considerations, materials should be chosen that minimize or eliminate leachables without compromising the integrity or the performance of the drug product.

The identity and concentration of recurring leachables in the drug product or placebo formulation (i.e., drug product formulation without drug substance) should be determined through the end of the drug product=s shelf life. If possible, the results should be correlated with the extractables profiles of the container closure components determined under the various control extraction study conditions. Evaluation of leachables in the drug product formulation in future routine stability studies may not be needed when such a correlation exists. In general, the levels of extractables should be greater than the levels of leachables for the correlation to be considered valid. For ANDAs, the applicant can compare the extraction profiles of the container and closure components with the leachables profiles of the drug product (or placebo) after storage under accelerated stability conditions for 3 months. If equilibrium is not reached by 3 months, real-time long-term data should be used to establish an appropriate expiration dating period. A commitment should be provided to confirm the results for the drug product (or placebo) on initial production stability batches at or near expiry. If the compared results are within the applicant=s acceptance criteria but there are qualitative differences, the results should be discussed with the responsible review division.

Relevant information (see below) should be provided on the characteristics of each of the critical components of the container closure system to ensure its

[12] Contact CDRH for additional guidance and copies of (1) *Reviewer Guidance for Premarket Notification Submissions* (November 1993), Anesthesiology and Respiratory Devices Branch, Division of Cardiovascular, Respiratory, and Neurological Devices and (2) *Reviewer Guidance for Computer Controlled Medical Devices Undergoing 510(K) Review* (August 1991).

suitability for manufacturing the drug product. Information should also be provided on acceptance criteria, test procedures, and analytical sampling plans (i.e., number of samples tested, individual or composite samples specified, number of replicate analyses per sample) for the critical components. Critical components are defined as (1) those that contact the patient (mouth or nose) or the formulation, (2) those that affect the mechanics of the overall performance of the device, or (3) any protective packaging. For additional information on container closure systems, refer to FDA's guidance for industry on *Container Closure Systems for Packaging Human Drugs and Biologics* (May 1999).

The following information should be included in the application. Reference to information in Drug Master Files (DMFs) for container, closure, and pump information is acceptable if the DMF holder provides written authorization that includes specific reference (e.g., submission date, page number, item name and unique identifier) to the pertinent and up-to-date information (21 CFR 314.420(d)). However, CDER recommends that, at a minimum, the information identified below (with asterisks) be included in the application so that the applicant can ensure continued product quality with respect to the container closure system.

- Fabricators of the container, closure, and the assembled pump*
- Fabricators for each part of the pump
- Unique identifiers for different parts of the pump
- Unique identifiers of the container, closure, and the assembled pump*
- Engineering drawings of the container, closure, and pump components
- Precise dimensional measurements of the container, closure, pump, and pump components*
- Composition and quality of materials of the container, closure, and pump components*
- Control extraction methods and data for elastomeric and plastic components*
- Toxicological evaluation of extractables*
- Acceptance criteria, test procedures, and analytical sampling plans*
  - Physicochemical parameters and dimensional measurements of the container, closure, and pump components*
  - Qualitative and quantitative extractable profiles from the container, closure, and pump components*
  - Performance characteristics of the pump*

Additional information on select topics is provided below.

1. Fabricator, Chemical Composition, and Physical Dimensions

The fabricator, chemical composition (e.g., resins, additives, colorants, adhesives, inks), and physical dimensions of each component and the assembled pump should be specified. The composition of the container, closure, coating material

(if applicable), and individual pump components should be provided. For the materials used in fabrication of the critical components of the container closure system, specific citations should be made, where applicable, to the indirect food additive regulations in Title 21 of the Code of Federal Regulations. The dimensional measurements of metering pump components should be held to very tight tolerances through precision measurements. The applicant can rely on the certificate of analysis for the dimensional controls for the individual pump components for each incoming shipment of assembled pumps. Devices with unique or new delivery mechanisms should be accompanied by a description and drawings that clarify the device operation. Moreover, it is recommended that assembled and disassembled components of the container closure system for all drug products be available, if requested by the Agency, to facilitate the review process.

2. Control Extraction Studies

The purpose of the control extraction study is to define quantitative extractable profiles for elastomeric or plastic packaging components under specified test conditions and to establish an acceptance criterion for each of the extractables from the container, closure, and critical components of the pump used for the submitted batches (e.g., critical clinical, preclinical, biobatch, primary stability, production). For critical components that affect the mechanics of the overall performance of the device but do not contact either the patient (mouth or nose) or the formulation, a qualitative approach for control of the extractable profile may suffice. The extractable profiles of the specified container, closure, and pump components should be established and documented under defined experimental conditions. The documentation should include the sample size, type and amount of solvents, temperature, duration, extraction procedures, analysis procedures, and data. Solvents of various polarities should be used for initial determination of the profiles (e.g., water and appropriate organic solvents).

Extraction studies should be performed, and the profile of each extract should be evaluated both analytically and toxicologically. The application should provide adequate analytical information, obtained using a variety or combination of procedures (e.g., chromatography with mass spectroscopy), to identify and quantify each extractable and establish appropriate acceptance criteria. A toxicological evaluation should be made of the extractables from the container, closure, and critical pump components, and the results submitted in the application. For critical components that only affect the mechanics of the overall performance of the pump, a toxicological evaluation of extractables is not necessary. The appraisal should include appropriate in vitro and in vivo tests and can also be supported by applicable citations and additional safety data. The results of USP Biological Reactivity Tests (USP <87> and <88>) should be submitted. A rationale, based on available toxicological information, should be provided to support acceptance criteria for components in terms of the extractable profiles. Special attention should be paid to elastomeric components because of

the potential for release of additional leachables (e.g., PNAs (polynuclear aromatics), nitrosamines, vulcanization accelerators) into the formulation, which can alter the toxicological profile of the drug product. Since some extractables may be carcinogenic, appropriate risk assessment models may be warranted to establish acceptance criteria. Applicants are encouraged to contact the responsible review division for further guidance.

3. Routine Extraction

Based on the analytical and toxicological evaluation of the extractables from the control extraction studies, the applicant should establish discriminatory test procedures and set appropriate acceptance criteria for the extractable profiles for routine testing for each critical component of the container closure system. This testing will provide continued assurance of the batch-to-batch consistency of the composition and purity of the container and closure components. An extraction test should be performed on every incoming component batch using water and other suitable solvents selected from the control extraction studies, to determine the individual and total extractables. For nasal spray drug products, if the level of extractables for each component is relatively low, it may be appropriate to establish a limit only for the total weight of extractables from each individual critical component.

If a correlation is established between the extractables from the raw materials used for fabrication of the container and closure components and those emanating from the molded components, and assurance is provided that no additional additives are introduced during the fabrication process, then routine extraction studies can be performed on each raw material batch, with a reduced testing schedule of individual component batches.

Test procedures and analytical sampling plans (i.e., number of samples tested, individual or composite samples specified, number of replicate analyses per sample) should be provided. The specificity, linearity, range, accuracy, precision, detection limit, quantitation limit, and robustness of the proposed validated test procedures, including system suitability testing, should be documented with proper standards during validation in the control extraction studies.[13]

4. Acceptance Criteria

The application should include specifications for the container, closure, each component of the pump, the assembled pump, labels, adhesives, ink, and

[13] Guidance relating to validation of analytical procedures is available in the ICH guidances (Q2A) *Text on Validation of Analytical Procedures* (March 1995) and *Q2B Validation of Analytical Procedures: Methodology* (November 1996) and CDER's guidance on *Submitting Samples and Analytical Data for Methods Validation* (February 1987). CDER's 1987 guidance will be superseded by the guidance on *Analytical Procedures and Methods Validation*, when finalized. A notice of availability for a draft version of this guidance published in the *Federal Register* on August 30, 2000 (65 FR 52776).

protective packaging, as applicable. The specifications should include dimensional measurements, particulate matter, physicochemical parameters, and individual and total extractables as outlined above in #3 under the discussion of the routine extraction studies. In addition, the specifications should include performance attributes of the pump (e.g., functionality, pump or spray weight delivery, particle/droplet size distribution, spray pattern, minimum actuation force to achieve desired spray characteristics). Data should be collected using defined actuation parameters (e.g., force, speed, hold and return times). All proposed acceptance criteria should reflect the test results of the pumps used in the submitted drug product batches (e.g., critical clinical, primary stability, biobatch, and production batches, all using same pumps). If the information outlined above is generated by the pump manufacturer through authorized DMFs and is reported by certificate of analysis, applicants should also develop or have access to the analytical and other procedures to verify the reliability of the supplier's test results at appropriate intervals (21 CFR 211.84).

For the extractables profiles and the physicochemical parameters, a reduced acceptance testing schedule can be considered once the applicant establishes the reliability of the supplier's test results. If a reduced acceptance testing schedule is proposed, the applicant should confirm the supplier's results by testing multiple incoming batches of individual components (e.g., container, closure, pump components), some of which were used in preparing the submitted drug product batches (e.g., critical clinical, primary stability, biobatch, production). Also, a commitment should be provided to test a predetermined number of batches of each component used in preparing postapproval drug product batches.

5. Semipermeable Container Closure Systems

Protective packaging (e.g., foil overwrap) is recommended for inhalation drug products packaged in semipermeable containers (e.g., low density polyethylene (LDPE)). The protective packaging mitigates conditions such as ingress of foreign contaminants, loss of solvent, exposure to oxygen. Furthermore, labeling of these products by embossing or debossing is recommended to avoid the potential ingress from other types of labels (e.g., volatile organic chemicals from inks, paper, adhesive components). The levels of the leachables originating from indirect exposure to labels or related materials should be determined with validated methodology that has suitable detection and quantitation limits for the potential leachables. The levels of leached compounds should be appropriately qualified and documented and acceptance criteria established.[14]

H. Drug Product Stability

[14] A draft guidance is under development and will publish soon. When finalized, this guidance will provide additional information on inhalation drug products packaged in semipermeable container closure systems.

Stability studies provide a means for checking the physical and chemical stability of the drug product at various storage conditions, including the compatibility of the formulation with the components of the device, as well as performance of nasal and inhalation spray drug products. The application should contain (1) a complete, detailed stability protocol, (2) stability report and data, and (3) information regarding the suitability of the test procedures employed.

1. Protocols, Commitment, and Data Reporting

A stability protocol is a detailed plan described in an application that is used to generate and analyze stability data to support the retest or expiration dating period for a drug substance or the expiration dating period for a drug product.

The applicant should verify and ensure continued stability of the drug product by placing production batches into the applicant's routine stability testing program. The applicant should provide appropriate statements in the stability protocol committing to conduct and/or complete prescribed studies on production batches of a drug after approval.

For detailed information on the stability protocol, commitment, and data reporting, refer to *Submitting Documentation for the Stability of Human Drugs and Biologics* (the stability guidance) (February 1987).[15] For nasal spray and inhalation solution, suspension, and spray drug products, the stability report should also include the grade, batch number, and source of critical and novel excipients.

The following additional discussion elaborates on specific aspects of stability information for nasal spray and inhalation solution, suspension, and spray drug products that should be included in the application.

a. Specification

The stability test parameters, with appropriate acceptance criteria, should include those test parameters identified in the drug product specification (refer to section III.F) but can exclude the following: for nasal sprays, identity of the drug substance, spray pattern, osmolality, and net content; for inhalation products, identity, osmolality, net content, and content uniformity of the premetered dose units (SCU is not exempt). Test procedures should be stability indicating where applicable. For the parameter of drug content (assay), refer to information provided in sections III.F.1.c and III.F.2.c above. A single primary stability batch of the drug product stored under long-term stability conditions should be

[15] In June 1998, FDA made available a draft guidance document for industry on *Stability Testing of Drug Substances and Drug Products*. When finalized, this guidance will supersede the 1987 stability guidance.

tested for antimicrobial preservative effectiveness at the proposed shelf life for verification purposes.

b. Test Time Points

The stability test intervals should be indicated in the protocol. For NDAs, long-term, accelerated, and, if applicable, intermediate test intervals should be used that are consistent with the recommendations in the ICH guidance *Q1AR Stability Testing of New Drug Substances and Products* (November 2000). For ANDAs, the long-term and intermediate intervals should be consistent with the ICH guidance, but intervals at 0, 1, 2, and 3 months can be used for accelerated testing**.** Tabular presentation of test intervals can be used to add clarity.

c. Container Storage Orientations

The stability of nasal and inhalation drug products can be affected by storage under differing orientations. For example, leachable levels, pump appearance, weight loss, assay, particle size distribution, and SCU can be affected by orientation. Primary stability studies should include storage under different orientations (e.g., upright and inverted or upright and horizontal) to characterize any differences in the behavior under storage and to define optimum storage orientation, if any. Once sufficient data demonstrate that orientation does not affect the product quality, routine stability studies can be conducted on product stored in only one orientation.

Stability storage under multiple orientations may not be necessary for some drug products (e.g., blow-fill mold unit-dose inhalation solutions).

d. Test Storage Conditions

Stability studies should be performed on the drug product with the packaging configuration (i.e., primary, protective) for which approval is sought, using the appropriate test storage conditions. CDER's recommendations on appropriate test storage conditions can be found in the ICH guidance *Q1AR Stability Testing of New Drug Substances and Products* (November 2000). A summary of these recommendations is provided below.

Usually, the test storage conditions in the stability protocol for a drug product intended for storage under controlled room temperature conditions should include (1) accelerated (40"2°C/75"5%RH), (2) intermediate (30"2°C/60"5%RH), if applicable, and (3) long-term (25"2°C/60"5%RH) conditions. Stability studies under the various storage conditions can be initiated concurrently. Accelerated stability

studies alone may not be predictive of the product performance throughout the extrapolated expiration dating period.

For drug products packaged in semipermeable containers (e.g., low density polyethyelene) without protective packaging that are intended for storage under controlled room temperature conditions, the test storage conditions in the stability protocol should include (1) accelerated (40"2°C/NMT 25%RH), (2) intermediate (30"2°C/60"5%RH), if applicable, and (3) long-term (25"2°C/40"5%RH). Additional approaches for testing of drug products packaged in semipermeable containers are described in the ICH guidance *Q1AR Stability Testing of New Drug Substances and Products* (November 2000).

For drug products intended for storage in a refrigerator, the test storage conditions in the stability protocol should include (1) accelerated (25"2°C/60"5%RH), and (2) long-term (5"3°C).

For drug products using sealed glass ampules, humidity control during stability studies is not necessary.

For NDAs, the first three production batches manufactured postapproval should be placed in the accelerated, intermediate (if applicable), and long-term stability testing program using the approved stability protocol. If stability data for the first three production batches were submitted with the original application using the approved protocol and the above cited storage conditions, then it may not be necessary for the first three production batches manufactured postapproval to be placed on stability.

For ANDAs, refer to the stability guidance.

e. Batches, Manufacturing Process, Facilities, Components, and Container Closure System Considerations

To determine drug product stability, a minimum of three batches should be studied to provide an evaluation of batch-to-batch variability. The formulation and container closure system components of the three primary stability batches should be the same as those intended for distribution, which should be the same as those used in the other submitted batches (e.g., critical clinical, biobatch, production). For ANDAs, see the stability guidance for recommendations regarding the number of batches. Stability batches identified in the application should be described in terms of the size, manufacturing method, manufacturing site, testing procedures and acceptance criteria, and packaging. Applications should indicate the type, size, and source of various container and closure components that were used in generating stability data for the identified stability batches (e.g., IND, NDA, ANDA).

f. Quality, Purity, and Source of Drug Substance and Excipients

Data should be provided to demonstrate the quality and purity of drug substance and excipient batches used in the drug product stability batches. The source (e.g., manufacturer, site) of the drug substance used in these drug product batches should be specified. The sources of the excipients used in these drug product batches should be specified where formulations are suspensions or the excipients have a direct impact on the drug product performance. The information on these drug substance batches should include but may not be limited to the purity, synthetic method, synthesis site, micronization site, micronization procedure, and testing. Similar information, such as purity, micronization site and procedure, and testing, should also be provided for excipients that affect the suspension and/or particle characteristics. For inhalation solution, suspension, and spray drug products, purity information should be provided for compendial excipients where purity is not controlled through the associated monographs. This information for the drug substance and the excipients can be duplicated in the stability report or referenced to the specific pertinent section or sections of the drug application.

g. Sampling Plans and Statistical Analysis Approaches and Evaluation

Refer to the stability guidance.

h. Expiration Dating Period

For NDAs, the expiration dating period should be based upon the accelerated, intermediate (if applicable), and long-term stability data from at least three batches of drug product. The data should be statistically analyzed, as appropriate. These primary stability batches should be manufactured, preferably, from three different batches of the drug substance and with different batches of container and closure components, to ensure a statistically acceptable level of confidence for the proposed expiration dating period. See the stability guidance for the determination of the expiration date and for additional recommendations regarding expiration dating periods for ANDAs.

2. Other Stability Considerations

Changes in the manufacturing facility; manufacturing procedure; source, synthesis, or micronization of the drug substance; source or type (design or composition) of container and closure components; or grade of excipient may affect the stability of the drug product. In addition, for excipients used in suspension formulations that may have direct impact on the performance, a change in the source of such excipients may affect the stability of the drug

product. After such changes, additional stability data should be generated for the drug product so that comparability can be assessed and linkages established between the various batches.

If multiple manufacturing facilities, manufacturing processes, or sources of the components (container and closure or formulation) are intended to be used in the manufacturing of the drug product**,** adequate data should be provided to support the different facilities, manufacturing processes, and sources. See the stability guidance for additional guidance.

Appropriate bracketing and matrixing protocols can be used in stability programs for some of these drug products (e.g., solution-based formulations). However, additional justification should be provided for certain complex drug delivery systems where there are a large number of potential drug-device interactions. Applicants are encouraged to contact the appropriate review team for further guidance on bracketing or matrixing before implementing such protocols.[16]

For additional stability considerations, refer to section IV below on drug product characterization studies and the stability guidance.

IV. DRUG PRODUCT CHARACTERIZATION STUDIES

For nasal spray and inhalation solution, suspension, and spray drug products, certain studies should be performed to characterize the performance properties of the drug product and to provide support in defining the optimal labeling statements regarding use (e.g., storage, cleaning, shaking). Delivery systems for nasal and inhalation spray drug products can vary in both design and mode of operation, and these characteristics may be unique to a particular drug product. Studies to define these characteristics will help facilitate correct use and maintenance of the drug product and contribute to patient compliance. For the most part, these should be one-time studies, preferably performed on multiple batches (e.g., two or three) of drug product representative of the product intended for distribution. Additionally, this information will provide a baseline for comparison if, at a later time, the performance characteristics of a drug product are in question. For ANDAs, the applicability of each of the characterization studies outlined below for a given drug product can be discussed with the responsible review division.

[16] In September 2001 (66 FR 49029), the Agency made available a draft guidance on ICH *Q1D Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Drug Products*. Applicants can consult this guidance once issued by FDA in its final form.

A. Priming and Repriming in Various Orientations

For multiple-dose nasal and inhalation spray drug products, studies should be performed to characterize the priming and repriming required for the product after storage in multiple orientations (upright and inverted or upright and horizontal) and after different periods of non-use. SCU and other pertinent parameters should be evaluated. The following information should be established:

- the approximate interval that can pass before the drug product should be reprimed to deliver the labeled amount of medication

- the number of sprays recommended to prime or reprime the unit

Multiple orientation studies should be performed with initial sprays and with sprays near the label claim number. Priming and repriming information will be used to support the proposed labeling statements.

B. Effect of Resting Time

For multiple-dose inhalation spray drug products, a study is recommended to determine the effect of increasing resting time on the first spray of unprimed units, followed immediately by the second and the third sprays. Units should be primed only before initiation of the study. After resting for increasing periods of time (e.g., 6, 12, 24, 48 hours), uniformity of the medication delivered in the first, second, and third sprays (no priming) should be determined. Testing should be performed on units that have been stored in different orientations (i.e., upright and inverted or upright and horizontal). To shorten the length of the study, testing can be performed concurrently on separate samples with progressively longer resting periods.

C. Temperature Cycling

For nasal spray, inhalation suspension, and inhalation spray drug products, a stress temperature cyclic study should be performed to evaluate the effects of high and low temperature variations that may be encountered during shipping and handling on the quality and performance of the drug product. Such a study can consist of 12-hour cycles, with temperatures ranging between freezer temperature (-10 to -20°C) and 40°C for a period of at least 4 weeks. Alternative conditions and duration can be used with appropriate justification. Periodically throughout the study, at the end of a predetermined number of cycles, the samples should be analyzed for appropriate parameters and compared with the control drug product. Test parameters for cycling studies should include, where applicable, droplet size distribution, particle size distribution, microscopic evaluation, appearance, color, clarity, assay, SCU, sterility, and functionality of pump components. A validated container closure integrity test, instead of sterility testing, can be used to assess sterility and demonstrate maintenance of the integrity of the microbial barrier

provided by the container closure system. With regard to appearance of the nasal spray and inhalation drug products, one should consider, as applicable, the discoloration of the formulation, distortion of pump components, pump clogging, and adherence of the drug to the walls of the container, closure, and/or pump components.

D. In Vitro Dose Proportionality

For nasal and inhalation spray drug products with multiple strength suspension formulations, studies should address in vitro dose proportionality between strengths by determining SCU and particle/droplet size distribution.

E. Cleaning Instructions

For nasal and inhalation spray drug products, in-use studies should be performed to determine the frequency of cleaning and related instructions to be included in the labeling.

F. Device Robustness

Device robustness should be studied for nasal and inhalation spray drug products and should address the following:

- For devices that can be reused repeatedly with replaceable reservoirs, a study should be conducted to establish the product performance characteristics in terms of SCU and particle/droplet size distribution throughout the nominal number of sprays of the device.

- Limits of use related to failure of critical device mechanisms should be studied to determine the appropriate replacement intervals for the device.

- The performance characteristics of the device should be studied after different handling situations (e.g., dropping, shaking, vibrating).

For additional information on studies relating to device robustness, see documentation from the Center for Devices and Radiological Health (CDRH).[17]

G. Effect of Dosing Orientation

[17] Contact CDRH for additional guidance and copies of (1) *Reviewer Guidance for Premarket Notification Submissions* (November 1993), Anesthesiology and Respiratory Devices Branch, Division of Cardiovascular, Respiratory, and Neurological Devices and (2) *Reviewer Guidance for Computer Controlled Medical Devices Undergoing 510(K) Review* (August 1991).

For nasal and inhalation spray drug products, studies should be undertaken to determine the comparative performance of the devices in terms of SCU and particle/droplet size distribution at various dosing orientations.

H. Effect of Varying Flow Rates

The effect of varying flow rate should be studied for inhalation spray drug products and should address the following:

- For breath-activated drug products or those that are intended to be marketed with an expansion or holding chamber, spacer, or similar component, a study should be undertaken to determine the SCU and the particle/droplet size distribution as a function of different testing flow rates at a constant volume. The total volume should be limited to 2 liters. This study assesses the sensitivity of the device to widely varying flow rates generated by patients of different age and gender and with different severity of disease.

- Another study for breath-activated products should assess the triggering ranges of flow rates that generate the amount of delivered dose and the corresponding particle/droplet size distribution.

- For drug products with an expansion or holding chamber, spacer, or similar component, a separate study is encouraged to assess the effect of increasing waiting periods (e.g., 0, 5, 10 seconds) between actuation and initiation of inflow, at a specified flow rate, on the SCU and particle/droplet size distribution.

I. Profiling of Sprays Near Container Exhaustion (Tail Off Characteristics)

For nasal and inhalation spray drug products, a study should be conducted to determine the profiles of SCU and droplet (solution) or particle/droplet (suspension) size distribution of each individual spray after the point at which the labeled number of sprays have been dispensed until no more sprays are possible (i.e., the container is empty). SCU testing can be replaced by pump delivery testing for solution formulations. These studies help determine if the target fill and any proposed overfill of the containers are justified, since the tail off characteristics can vary as a function of pump design, container geometry, and formulation. A graphical representation of the findings is also recommended. Refer to sections III.F.1.g, III.F.1.i, III.F.2.o, and III.F.2.q.

J. Effect of Storage on the Particle Size Distribution

For suspension spray drug products, the stability studies on the primary stability batches should determine the effect of storage time and conditions on particle size

distribution through unit life (beginning to end for device-metered products). If stability studies demonstrate an effect on the particle size distribution within unit life, then the routine stability protocol should include particle size distribution testing through unit life. Refer to sections III.F.1.j and III.F.2.m.

K. Plume Geometry

For nasal spray drug products, plume geometry of the spray should be characterized. For discussion of this test, refer to section III.F.2.p for inhalation sprays. Plume geometry does not distinguish between drug substance particles and formulation droplets in the spray or indicate any density gradient for the drug substance, but determines the shape of the entire plume. Therefore, this test is complementary to the spray pattern test (see section III.F.1.h and III.F.2.p). The plume geometry characteristics can be used as a baseline to compare similar nasal spray drug products by different manufacturers or when certain changes are introduced to an already approved drug product.

L. Preservative Effectiveness and Sterility Maintenance

If preservatives are used in the formulation, the minimum content limit should be demonstrated as microbiologically effective by performing a microbial challenge assay of the drug formulated with an amount of preservative equal to or less than the minimum amount specified. For details for this characterization, see the stability guidance.

For device-metered, aqueous-based inhalation spray drug products (as defined in section II.C), studies should be performed to demonstrate the appropriate microbiological quality through the life of the reservoir and during the period of reservoir use. Such testing could assess the ability of the container closure system to prevent microbial ingress into the formulation and/or the growth inhibiting properties of the formulation.

M. Characterization of Nebulizer Specified in the Labeling

For inhalation solution and suspension drug products, a study should be undertaken to determine the delivered dose and the particle/droplet size distribution as per the specified operating parameters and ranges for a given nebulizer.

N. Photostability

Photostability studies should be performed using appropriate test conditions, if warranted by the immediate container, i.e., the formulation in the primary container can receive light exposure. These studies should be conducted in the absence of any additional packaging (e.g., foil overwrap). For additional

guidance, applicants can refer to the ICH guidance *Q1B Photostability Testing of New Drug Substances and Products* (November 1996).[18]

O. Stability of Primary (Unprotected) Package

For a drug product labeled for storage at room temperature, if additional packaging (e.g., foil overwrap for LDPE-contained product) is used to protect the drug product from degradation and/or evaporative effects, adequate stability data conducted at a minimum of 25°C and a maximum of 40 percent RH should be generated for these units without the protective packaging for pertinent parameters. This data can support the establishment of the maximum length of time for product use after the protective packaging is removed. Drug products both newly manufactured and near the end of the proposed expiration dating period should be evaluated.

V. LABELING CONSIDERATIONS

To achieve consistency and uniformity in the content, the product title, and the format of the labeling of nasal spray and inhalation solution, suspension, and spray drug products, the following pertinent information is recommended in the labeling. These comments are not all inclusive, and they are directed mainly at labeling issues unique to NDAs for prescription nasal spray and inhalation solution, suspension, and spray drug products. For additional information regarding the labeling of drug products, see part 201 (21 CFR part 201). In general, labeling for ANDAs should be the same as the reference listed drug.[19]

A. Nasal and Inhalation Spray Drug Products

1. Product Title

To standardize the nomenclature for oral inhalation sprays, the established name of all such drug products should include the designation *(Drug Substance) Inhalation Spray*. For nasal sprays, the drug product would include the name *(Drug Substance) Nasal Spray*. The established name should be followed by a phrase such as *For Oral Inhalation Only*, or *For Nasal Use Only*, as appropriate.

2. Label

The label should bear the following information:

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[18] Additional information on photostability testing will be available in FDA's forthcoming guidance for industry *Stability Testing of Drug Substances and Drug Products* (draft published June 1998) when it is finalized.

[19] For additional information regarding labeling for ANDAs, see § 314.94(a)(8) (21 CFR 314.94(a)(8)).

- $ Established name of the drug product
- $ Amounts of the drug substance delivered from the pump nasal actuator or mouthpiece
- $ Number of medication sprays per container
- $ Net content (fill) weight
- $ Usual dosage
- $ Excipients (established names)
- $ Route of administration
- $ Recommended storage conditions including any warning statements regarding temperature or light exposure
- $ Manufacturer's and/or distributor's name and address
- $ "Rx Only" or "L Only" statement
- $ Lot number
- $ Expiration date
- $ Use period once drug product is removed from protective packaging (if applicable)
- $ Instructions regarding shaking of suspension drug products
- $ NDC number (recommended)

For nasal and inhalation spray drug product devices that can be reused repeatedly with multiple reservoirs, each reservoir should be labeled adequately.

In the case of small labels, only some of the information listed above must be included in the label (21 CFR 201.10(i)). However, all labeling information required by the Federal Food, Drug, and Cosmetic Act (the Act) and the regulations in Title 21 of the Code of Federal Regulations must be included on the carton, outer container, wrapper, and leaflet as appropriate.

3. DESCRIPTION Section of the Package Insert

In addition to the information typically required by FDA regulations for the description of the drug substance and formulation (21 CFR part 201), the package insert should include the following information that is specific for nasal and inhalation spray drug products:

- $ The medication dose delivered to the patient should be expressed by a statement in this section, such as: *Each spray delivers x mcg of drug substance in w mg of suspension or solution equivalent to y mcg of drug substance base (if applicable) from the nasal actuator or mouthpiece.* The term *approximately* should not be used to modify the medication dose delivered.
- $ For suspension formulations, if the drug substance forms solvates or hydrates, this formation should be clearly specified with proper conversion for the active drug shown.
- $ A list of all excipients should be included. Substances should be identified by their established names.

- **$** The number of priming sprays before using the unit for the first time should be included. The number of priming sprays for a unit that has not been used for more than a specified period of time (e.g., 24 hours, 48 hours) should be included.

4. HOW SUPPLIED Section of the Package Insert

The following should be included in nasal and inhalation spray drug product labeling:

- **$** The net content (fill) weight of the container should be stated.
- **$** The number of medication sprays expected throughout the shelf life of the drug product should be indicated for each container fill weight. Qualifying terms such as *at least* and *approximately* should not be used.
- **$** The color and appearance of the container, closure, and pump components should be included.
- **$** A statement should be provided that the correct amount of medication in each spray cannot be ensured after the labeled number of sprays from the unit even though the unit may not be completely empty. In addition, for reusable devices with replacement cartridges or refill units, a statement should be included that these units should be discarded when the labeled number of sprays have been dispensed and this labeling should be applied to these unit, not the device. The device should be labeled with an appropriate replacement or service interval.
- **$** Storage conditions should be clearly stated including any warning statements regarding temperature and light exposure.
- **$** Any preferred storage orientation should be indicated.
- **$** If protective packaging (e.g., foil overwrap) is warranted to ensure product quality and is used for the drug product, this should be clearly stated. In addition, appropriate statements should be included that the contents of the protective packaging should not be used after a specified number of days (e.g., 2 weeks, 30 days) from the date the protective packaging was removed. The length of time specified should be supported by data in the application (refer to section IV.O).
- **$** A statement should be included regarding recommendations for shaking, if warranted (i.e., for suspension products).
- **$** NDC number or numbers (recommended)

5. Patient Package Insert

The instructions to the patient should include the following if applicable:

- **$** Detailed, step-by-step, appropriately illustrated instructions for patient use should be included. The following information is also recommended:

- **$** A figure that displays the various elements of the container closure system.
- **$** Instructions for initial priming and for repriming of the unit.
- **$** A statement cautioning against spraying the eyes with the formulation.
- **$** For inhalation spray drug products, a statement instructing the patient to confirm the absence of foreign objects in the mouthpiece before using the product and after removing the protective mouthpiece cap, where applicable.

- **$** Storage conditions should be clearly stated, including any warning statements regarding temperature and light exposure. A statement should be included regarding recommendations for shaking, if warranted (i.e., for suspension products). Any preferred storage orientation should be noted.
- **$** If protective packaging was used for the drug product, appropriate statements should be included that the contents of the protective packaging should not be used after a specified number of days (e.g., 2 weeks, 30 days) from the date the protective packaging was removed (refer to section IV.O).
- **$** Appropriate cleaning instructions should be included (if applicable).
- **$** A statement should be included that the correct amount of medication in each spray cannot be ensured after the labeled number of sprays even if there is evidence that the unit is not completely empty. A statement instructing the patient to keep track of the number of sprays used from the container should also be included unless a counter mechanism is incorporated into the device.

B. Inhalation Solutions and Suspensions

1. Product Title

To standardize the nomenclature for inhalation solutions, the established name of all such drug products should include the designation *(Drug Substance) Inhalation Solution*. For inhalation suspensions, the drug product would include the name *(Drug Substance) Inhalation Suspension*. The established name should be followed by a phrase such as *For oral inhalation only*.

2. Label

The label should bear the following information:

- **$** Established name of the drug product
- **$** Amount of the drug substance per container and concentration of drug substance in the formulation
- **$** Net content (fill) weight
- **$** Usual dosage

- $ Excipients (established names)
- $ Route of administration
- $ Recommended storage conditions including any warning statements regarding temperature and light exposure
- $ Manufacturer's and/or distributor's name and address
- $ "Rx Only" or "L Only" statement
- $ Lot number
- $ Expiration date
- $ Use period once drug product is removed from protective packaging (if applicable)
- $ Instructions regarding shaking of suspension drug products
- $ NDC number (recommended)

In the case of small labels, only some of the information listed above must be included in the label (21 CFR 201.10(i)). However, all labeling information required by the Act and the regulations in Title 21 must be included on the carton, outer container, wrapper, and leaflet as appropriate.

3. DESCRIPTION Section of the Package Insert

In addition to the information typically required by FDA regulations for the description of the drug substance and formulation (21 CFR part 201), the package insert should include the following information that is specific for inhalation solution and suspension drug products:

- $ For suspension formulations, if the drug substance forms solvates or hydrates, this formation should be clearly specified with proper conversion for the active drug shown.
- $ A list of all excipients should be included. Substances should be identified by their established names.
- $ Delivered dose and description of particle/droplet size distributions that could be expected from an identified nebulizer under specific and defined operating conditions should be provided (refer to section IV.M).

4. HOW SUPPLIED Section of the Package Insert

The following should be included in inhalation solution and suspension drug product labeling:

- $ The net content (fill) weight of the container should be stated.
- $ Storage conditions should be clearly stated including any warning statements regarding temperature and light exposure.
- $ A statement should be included indicating that the contents of any partially used container should be discarded (e.g., unit dose presentations).
- $ If protective packaging (e.g., foil overwrap) is used for the drug product, this should be clearly stated. In addition, appropriate statements should be

included that the drug product should not be used after a specified number of days (e.g., 2 weeks, 30 days) from the date the protective packaging was removed. The length of time specified should be supported by data in the application (refer to section IV.O).

- **$** A statement regarding any recommendations for shaking should be included, if warranted (i.e., for suspension products).
- **$** Any preferred storage orientation should be noted for inhalation suspensions, if applicable.
- **$** NDC number or numbers (recommended)

5. Patient Package Insert

The instructions to the patient for inhalation solution and suspension drug products should include the following if applicable:

- **$** Instructions for proper opening of containers and transfer of formulation to the specified nebulizer should be included.
- **$** A statement that the contents of any partially used container should be discarded should be included in this section.
- **$** Storage conditions should be clearly stated, including any warning statements regarding temperature and light exposure. A statement should be included regarding recommendations for shaking, if warranted (i.e., for suspension products).
- **$** Any preferred storage orientation should be noted for inhalation suspensions, if applicable.
- **$** If protective packaging was used, appropriate statements should be included that the drug product should not be used after a specified number of days (e.g., 2 weeks, 30 days) from the date the protective packaging was removed.

GLOSSARY OF TERMS

Acceptance Criteria: Numerical limits, ranges, or other criteria for the test described.

Batch: A specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture (21 CFR 210.3(b)(2)).

Container Closure System: The sum of packaging components that together contain, protect, and deliver the dosage form. This includes primary packaging components and secondary packaging components if the latter are intended to provide additional protection to the drug product (e.g., foil overwrap). The container closure system also includes the pump for nasal and inhalation sprays. For nasal spray and inhalation solution, suspension, and spray drug products, the critical components of the container closure system are those that contact either the patient or the formulation, components that affect the mechanics of the overall performance of the device, or any protective packaging.

Drug Product: The finished dosage form and the container closure system.

Drug Substance: An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body (21 CFR 314.3(b)).

Excipient: Any intended formulation component other than the drug substance.

Extractables: Compounds that can be extracted from elastomeric or plastic components of the container closure system when in the presence of a solvent.

Expiration Dating Period: The time period during which a drug product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on the container label.

Inhalation Solutions, Suspensions, and Sprays: Drug products that contain active ingredients dissolved or suspended in a formulation, typically aqueous-based, which can contain other excipients and are intended for use by oral inhalation. Aqueous-based drug products for oral inhalation must be sterile (21 CFR 200.51). Inhalation solutions and suspensions are intended to be used with a specified nebulizer. Inhalation sprays are combination products where the components responsible for metering, atomization, and delivery of the formulation to the patient are a part of the container closure system.

Leachables: Compounds that leach into the formulation from elastomeric or plastic components of the drug product container closure system.

Nasal Sprays: Drug products that contain active ingredients dissolved or suspended in a formulation, typically aqueous-based, which can contain other excipients and are intended for use by nasal inhalation. Container closure systems for nasal sprays include the container and all components that are responsible for metering, atomization, and delivery of the formulation to the patient.

Overfill: For the purposes of this guidance, the excess of theoretical deliverable volume or weight of the drug product formulation that ensures (1) transfer of the dose of drug product declared in the labeling (unit dose) or (2) delivery of the number of dosage units declared in the labeling (multiple-dose).

Packaging Component: Any single part of a container closure system.

Placebo: A dosage form that is identical to the drug product except that the drug substance is absent or replaced by an inert ingredient.

Primary Packaging Component: A packaging component that is or may be in direct contact with the dosage form.

Primary Stability Batch: A batch of a drug substance or drug product used in a formal stability study, from which stability data are submitted in an application for the purpose of establishing the expiration dating period.

Primary Stability Data: Data on the drug product stored in the proposed container closure system for marketing and under storage conditions that support the proposed shelf life.

Protective Packaging: The secondary packaging component that provides protection essential for product quality. This packaging (such as a foil overwrap) can provide, for example, protection from light, ingress of moisture, oxygen, foreign contaminants, or loss of solvent.

Pump: All components of the container closure system that are responsible for metering, atomization, and delivery of the formulation to the patient.

Secondary Packaging Component: A packaging component that is not and will not be in direct contact with the dosage form.

Specification: The quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in the approved application to confirm the quality of drug substances, drug products, intermediates, raw material reagents, components, in-process materials, container closure systems, and other materials used in the production of drug substances or drug products.

Specified Impurity: An identified or unidentified impurity that is selected for inclusion in the drug substance or drug product specification and is individually listed and limited to ensure the reproducibility of the quality of the drug substance and/or drug product.