DRAFT-Not for Implementation

Guidance for Industry

Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products

CHEMISTRY, MANUFACTURING, AND CONTROLS DOCUMENTATION

DRAFT GUIDANCE

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

May 1999
CMC

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GUIDANCE FOR INDUSTRY[1]

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Chemistry, Manufacturing, and Controls Documentation

(Due to the complexity of this draft document, please identify specific comment by line number. Use the pdf version of the document whenever possible.)

I. INTRODUCTION

This document provides guidance for industry on the chemistry, manufacturing, and controls (CMC) documentation to be submitted in new drug applications (NDAs) and abbreviated new drug applications (ANDAs) for nasal spray and inhalation solution, suspension, and spray drug products. This guidance also covers CMC information recommended for inclusion in the application regarding the components, manufacturing process, and associated controls with each of these areas. The recommendations in this guidance should also be considered during the investigational stages and phased in by the initiation of critical clinical studies to provide supporting documentation for the NDA. The guidance does not address propellant-based inhalation and nasal aerosols (respectively also known as oral and nasal metered-dose inhalers, MDIs), inhalation powders (also known as dry powder inhalers, DPIs), and nasal powders. Information on these dosage forms will be provided in the guidance for industry on *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products — Chemistry, Manufacturing, and Controls Documentation* (October 1998), when finalized.

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 acceptable approaches for submitting CMC-related regulatory information. Alternative approaches may be used. Applicants are encouraged to discuss significant departures from the approaches outlined in this guidance with the appropriate Agency division before implementation to avoid expending resources on development avenues that may later be deemed unacceptable.

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[1]This guidance has been prepared by the Inhalation Drug Products Working Group of the Chemistry, Manufacturing, and Controls Coordinating Committee (CMC CC) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA). This guidance represents the Agency's current thinking on CMC documentation to be submitted in NDAs and ANDAs for nasal spray and inhalation solution, suspension, and spray drug products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

Reference to information in Drug Master Files (DMFs) for particular portions of the CMC section of the application is acceptable if the DMF holder provides written authorization that includes specific reference (e.g., submission date, page number, item name and number) 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 use metering spray pumps. Nasal sprays are applied to the nasal cavity for local and/or systemic effects. A nasal spray unit may be designed for unit dosing or may discharge up to several hundred metered sprays of formulation containing the drug substance (typically in microgram quantities).

Although similar in many features to other drug products, nasal sprays have unique differences with respect to formulation, container closure system, manufacturing, in-process and final controls, and stability. These differences need to be considered during the development program because they can affect the ability of the product to deliver reproducible doses to patients over the life of the product as well as the product's efficacy. 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 may 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 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.

B. Inhalation Solutions and Suspensions

Inhalation solution and suspension drug products are sterile, typically aqueous-based formulations, that contain therapeutically active ingredients and may also contain additional excipients. 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(s).

These drug products are normally designed for unit dosing. The container closure system for these drug products consists of the container and closure, and may include protective packaging (e.g., foil laminate overwrap).

C. Inhalation Sprays

An inhalation spray drug product consists of the formulation and the container closure system. The formulations are sterile, typically aqueous based, and, by definition, do not contain any propellant. The products contain therapeutically active ingredients and may also contain additional excipients. The formulation may be in unit-dose or multidose presentations. The dose is delivered by the pump components of the container closure system to the lungs by oral inhalation for local and/or systemic effects. The container closure system consists of the container, closure, and pump, and may 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 size distribution, since these parameters directly 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., aerosol generators, electronic features, and 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(s) or manufacturing process that may 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.

III. DRUG PRODUCT

A. 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 necessary 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. 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 drug product. These 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 fill weight 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 excess for an ingredient should be designated as such and the percent excess shown, scientifically justified, and documented. For these products, excesses should be included only for justified reproducible manufacturing losses. Any intended change in the formulation from

that used in the submitted batches (e.g., clinical, biobatch, primary stability, production) should be clearly indicated.

The composition of suspension formulations is crucial, particularly in defining the physical stability and the performance characteristics of the drug product. The density and suspension properties of the solid material(s) 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 may 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 Ingredient(s)

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 may 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, pKa(s), and specific rotation.

Appropriate acceptance criteria and tests should be instituted to control those drug substance parameters considered key to ensuring reproducibility of the physicochemical properties of the drug substance. Specification parameters may include color, appearance (visual and microscopic), specific identification, moisture, residue on ignition, specific rotation, assay, microbial limits (10-gram sample size, USP <61>), melting range, particle size distribution, surface area, crystalline form(s), residual solvents, and heavy metals. Some of these parameters may not be pertinent for drug substance used in solution formulations.

For suspension formulations, the specification submitted in the application should include controls for particle size distribution and crystalline forms (e.g., shape, 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, software version and calculation algorithms, 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, specifications for amorphous content and foreign particulates that may result from a micronization process should be included.

The purity of the drug substance and its impurity profile should be characterized and controlled with appropriate specifications. Important impurity-related parameters may include organic volatile impurities and/or residual solvents, heavy metals, residual organics and inorganics (e.g., reagents, catalysts), and related substances (synthetic and degradants). Any recurring impurity found in the drug substance at a concentration of 0.1 percent or greater, relative to the parent drug substance, should be identified and qualified. In addition to toxicological considerations, justification of acceptance criteria for the drug substance impurities should be based on levels of impurities found in the submitted batches (e.g., clinical, biobatch, primary stability, production). When additional guidance on toxicological qualification is needed, the applicant is encouraged to contact the responsible review division.

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.

2. Excipients

Because of the sensitive nature of the patient population, excipients used in oral inhalation drug products should be completely characterized and strict quality controls should be applied. For suspension formulations, a similar level of control should be applied for excipients that have an effect on the suspension and/or particle characteristics, to ensure consistent safety, quality, stability, performance, and/or effectiveness of the drug product.

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., clinical, biobatch, primary stability, production). However, for excipients used in suspension formulations that may have direct impact on the performance of the drug product, the sources should be identified and test results from multiple batches should be provided. Likewise, when the supplier of an excipient is changed, the new supplier's ability to provide material that meets the same acceptance criteria should be assessed and supporting data should be provided.

For noncompendial excipients, adequate DMFs with appropriate authorization should be submitted to the Agency. The DMFs should include analytical procedures and acceptance criteria and a brief description of the manufacture and controls.

For compendial excipients that affect the performance of the drug product (e.g., droplet and particle size distribution, spray content uniformity, spray pattern), *United States Pharmacopeia* (USP) or *National Formulary* (NF) monograph acceptance criteria and tests alone may not be adequate for controlling key characteristics of the excipient and should be supplemented, as appropriate. A full description of the acceptance criteria and the test procedures used to ensure the identity, assay, quality, and purity of each excipient should be submitted. For excipients that are in suspension, the same type of additional control parameters and testing described for active ingredients in suspension (e.g., particle size distribution, crystal forms, amorphous content, foreign particulates) should be considered (see section III.C.1).

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 or have access to all of the manufacturer's analytical and other test procedures to allow them to establish the reliability of the test results at appropriate intervals (21 CFR 211.84). The applicant should confirm the supplier's results by testing (1) an adequate number of batches of each excipient used in preparing the submitted drug product batches (e.g., clinical, primary stability, biobatch, and production batches) and (2) a predetermined number of batches of each excipient used in preparing postapproval drug product batches. When excipients for suspension formulations play a critical role in the quality and performance of the drug product, multiple incoming batches of these excipients should be tested to confirm the supplier's test results.

The suitability of the physicochemical properties of the excipients to be administered via the inhalation route 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 drug products, (2) excipients that have been used previously in humans but not by the inhalation route, and (3) novel excipients not previously used in humans. The extent of toxicological investigation needed 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.

When USP or NF monograph materials are used, and the associated specifications do not provide adequate assurance for inhalation use of these materials with regard to the assay, quality, performance, and purity, monograph specifications should be supplemented with appropriate specifications to ensure batch-to-batch reproducibility of the components. The acceptance criteria should reflect the data for the excipients used in the submitted batches (e.g., clinical, biobatch, primary stability, production).

D. Manufacturers

The name, street address, building number, and Central File Number (CFN), if available, of each facility involved in the manufacturing 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 operations of the drug product, including all contractors (e.g., test laboratories, packagers, labelers). Excipient manufacturers should be identified by name and address.

E. Method(s) of Manufacture and Packaging

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

All inhalation solutions, suspensions, and spray drug products should be manufactured as sterile products, and their sterility should be ensured through the expiration dating period.

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

A copy of the actual (executed) batch record and in-process controls should be submitted, as appropriate, for representative batches (e.g., clinical, biobatch, primary stability, production). A schematic diagram of the proposed production process, a list of in-process controls, and a master batch production and controls record should be submitted. A description of the packaging operations and associated in-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 should be appropriately justified.

A description of in-process controls, analytical tests, and appropriate data to support the acceptance criteria should be provided. In-process controls should be performed at specified production steps and may include, for example, assay, osmolality, pH, viscosity, consistency of filling, quality of sealing, and delivery performance (nasal and inhalation sprays).

If protective packaging (such as an overwrap) is used for the drug product (e.g., to prevent of ingress of foreign contaminants or solvent loss or to protect from exposure to light or ingress of oxygen), the application should include a description of the primary and protective packaging operations and relevant in-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.

For inhalation drug products packaged in semipermeable containers (e.g., low density polyethylene (LDPE)), labeling by embossing or debossing is recommended to avoid the potential ingress of leachables from other types of labels (e.g., inks, paper, adhesive components). Alternatively, if labels are used for inhalation drug products in semipermeable containers, the absence of leachables originating from the labels or related materials should be demonstrated for the product. Procedures used for these analyses should be validated and have suitable detection and quantitation limits for the potential leachables. Furthermore, any of these leachables present in drug products for inhalation use should be appropriately qualified and documented.

F. Specifications for the Drug Product

A complete description of the acceptance criteria and analytical procedures with analytical sampling plans 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 accuracy, detection limit, quantitation limit, specificity, precision, linearity, and robustness of the proposed validated test procedures, including system suitability testing, should be documented in sufficient detail to permit validation by Agency laboratories.[2]

[2]ICH guidances *Q2A Text on Validation of Analytical Procedures* and *Q2B Validation of Analytical Procedures: Methodology.*

Comprehensive and well-defined in vitro performance characteristics should be established before initiating critical clinical or bioequivalence studies. Appropriate, validated test procedures and corresponding acceptance criteria that are reflective of the test results for submitted batches (e.g., 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.

a. Appearance, Color, and Clarity

The appearance of the content of the container (i.e., formulation) and the container closure system (e.g., pump components, inside of the container) should conform to their respective descriptions 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(s) is recommended to verify the identity of the drug substance in the drug product. Chromatographic retention time alone is not an adequate method to ensure the identity of the drug substance in the drug product. If the drug substance is a single enantiomer, then at least one of the methods should be specific for this property.

c. Drug Content (Assay)

The assay of drug substance in the entire container should be determined analytically with a stability indicating procedure. This test provides assurance of consistent manufacturing (e.g., formulation, filling, sealing). The acceptance criteria should be tight enough to ensure conformance in other related attributes (e.g., spray content uniformity). A suitable assay procedure should be designed to address any degradation of the drug substance, adherence of the drug substance to the container and closure components, and the potential effect of formulation evaporation and/or leakage.

d. Impurities and Degradation Products

The levels of degradation products and impurities should be determined by means of stability indicating procedure(s). Acceptance criteria should be set for individual and total degradation products and impurities. For identification and qualification thresholds, refer to the appropriate guidance. 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.

e. Preservative(s) and Stabilizing Excipient(s) 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. Refer to section III.F.1.o below.

f. Pump Delivery

A test to assess pump-to-pump reproducibility in terms of drug product performance and to evaluate the metering ability of 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 individual sprays to within ±15 percent of the target weight and their mean weight to within ±10 percent of the target weight.

g. Spray Content Uniformity (SCU)

The spray discharged from the nosepiece should be thoroughly analyzed for the drug substance content of multiple sprays from 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. The number of sprays per determination should not exceed the number of sprays per single dose. A single dose represents the minimum number of sprays per nostril specified in the product labeling. To ensure reproducible in vitro dose collection, the procedure should have controls for actuation parameters (e.g., stroke length, depression force). The test may be performed with units primed following the instructions in the labeling. The amount of drug substance delivered from the nosepiece should be expressed both as the actual amount and as a percent 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 nosepiece, of an appropriate number (n = 10 is recommended) 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:

- The amount of active ingredient per determination is not outside of 80–120 percent of label claim for more than 1 of 10 containers, none of the determinations is outside of 75–125 percent of the label claim, and the mean is not outside of 85–115 percent of label claim.

- If 2 or 3 of the 10 determinations are outside of 80–120 percent of the label claim, none is outside of 75–125 percent of label claim, and the mean is not outside of 85–115 percent of label claim, an additional 20 containers should be sampled (second tier). For the second tier of testing of a batch, the amount of active ingredient per determination is not outside of 80–120 percent of the label claim for more than 3 of all 30 determinations, none of the 30 determinations is outside of 75–125 percent of label claim, and the mean is within 85–115 percent of label claim.

h. Spray Content Uniformity (SCU) Through Container Life

The purpose of this test is to assess whether the product delivers the labeled number of full medication sprays meeting SCU acceptance criteria throughout the life of the nasal spray unit. The test involves determining the SCU from the beginning of unit life and at the label claim number of sprays per container for an appropriate number of containers (n = 5 is recommended). The following acceptance criteria are recommended.

- The amount of active ingredient per determination is not outside of 80–120 percent of label claim for more than 1 of 10 determinations from five containers, none of the determinations is outside of 75–125 percent of the label claim, and the means for each of the beginning and end determinations are not outside of 85–115 percent of label claim.

- If 2 or 3 of the 10 determinations are outside of 80–120 percent of the label claim, none is outside of 75–125 percent of label claim, and the means for each of the beginning and end determinations are not outside of 85–115 percent of label claim, an additional 10 containers are sampled at the beginning of unit life and at the label claim number of sprays (second tier). For the second tier of testing of a batch, the amount of active ingredient per determination is not outside of 80–120 percent of the label claim for

more than 3 of all 30 determinations, none of the 30 determinations is outside of 75–125 percent of label claim, and the means for each of the beginning and end determinations are not outside of 85–115 percent of label claim.

i. Spray Pattern and Plume Geometry

Characterization of spray pattern and plume geometry are important for evaluating the performances of the pump and nozzle. 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 should typically 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.r and for nasal spray drug products in section IV.K.)

The proposed test procedure for spray pattern, including analytical sampling plans, 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 nosepiece and the collection surface, number of sprays per spray pattern, position and orientation of the collection surface relative to the nosepiece, and visualization procedure should be specified. The acceptance criteria for spray pattern should include the **shape** (e.g., ellipsoid of 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, 1.00–1.20). The spray pattern should be determined, preferably by a procedure specific for the drug substance, at different distances (e.g., two) from the nosepiece to provide greater discriminatory capability to the test. Variability in the test can be reduced by the development of a sensitive detection procedure and by providing procedure-specific training to the analyst.

j. 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. Appropriate and validated dynamic plume droplet size analytical procedures should be described in sufficient detail to allow accurate assessment by Agency laboratories (e.g., apparatus and accessories, software

version and calculation algorithms, sample placement, laser trigger condition, measurement range, beam width).

k. Particle Size Distribution (Suspensions)

For suspension nasal sprays, the specification should include controls for the particle size distribution of the drug substance particles in the formulation. This quantitative procedure should be appropriately validated in terms of its sensitivity and ability to detect shifts that may occur in the distribution. The acceptance criteria should control the complete distribution and should reflect the data obtained for the submitted batches (e.g., clinical, preclinical, biobatch, primary stability, production).

l. Microscopic Evaluation (Suspensions)

This test, which involves a qualitative and semiquantitative microscopic examination of the suspension formulations, is complementary to particle size distribution testing (section III.F.1.k) for both release and stability purposes. For example, the examination provides information on the presence of large particles and changes in morphology of the drug substance particles, extent of agglomerates, and crystal growth. Additionally, where changes in the solid state of the drug substance can affect the bioavailability, performance, stability, or other properties of the drug product, microscopic evaluation or other appropriate procedures are recommended to control and monitor changes that are observed on stability.

m. Foreign Particulates

For both solution and suspension nasal sprays, there should be validated tests and associated acceptance criteria for foreign particulates. Foreign particulates may originate during manufacturing, from formulation components, and, in particular, from the container and closure components. Levels of foreign particulates in the drug product may increase with time, temperature, and stress.

n. 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 pathogens. Acceptance criteria should be reflective of the data for the submitted batches (e.g., clinical, preclinical, biobatch, primary stability, production), but at a minimum should meet the recommended microbial limits

acceptance criteria in USP <1111>, Microbiological Attributes for Nonsterile Pharmacopeial Articles. 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. For a description of this test, refer to the procedure in USP <61>.

o. Preservative Effectiveness

For nasal sprays that contain a preservative(s), stability testing should include microbial challenge studies performed on the first three production batches of drug product. For more details about this parameter in terms of stability testing, see section III.B.4. in FDA's guidance *Submitting Documentation for the Stability of Human Drugs and Biologics* (February 1987).[3] Also refer to section III.F.1.e above.

p. Net Content and Weight Loss (Stability)

Nasal spray drug products should include acceptance criteria for net content and weight loss on stability. Since storage orientation plays a key role in any weight loss, the drug product should be stored in upright and inverted or upright and horizontal positions to assess this characteristic.

The total net content of all formulation components in the entire container should be determined. The net content of each of 10 test containers should be in accordance with the release specification. For a description of this test, refer to the procedure in USP Chapter <755> Minimum Fill.

q. Leachables (Stability)

The drug product should be evaluated for compounds that leach from elastomeric or plastic components of the container closure system, such as nitrosamines, monomers, plasticizers, accelerators, antioxidants, and vulcanizing agents. The development of appropriate analytical procedures to identify, monitor, and quantify the leached components in the drug product should be done during investigational studies. These validated 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

[3]The 1987 stability guidance will be superseded by FDA's draft guidance for industry *Stability Testing of Drug Substances and Drug Products* (June 1998) once it is issued in final form.

additional discussion, see the container closure system section of this guidance (section III.G).

r. pH

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

s. Osmolality

The osmolality of the formulation should be tested and controlled with an appropriate procedure and acceptance criterion.

2. Inhalation Solutions, Suspensions, and Sprays

a. Appearance, Color, and Clarity

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

b. Identification

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

c. Drug Content (Assay)

See nasal sprays, section III.F.1.c. In addition, 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.

d. Impurities and Degradation Products

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

e. Preservative(s) and Stabilizing Excipient(s) Assay

If the use of a preservative(s) or stabilizing excipient(s) is justified, see nasal sprays, section III.F.1.e.

f. Sterility

All inhalation solutions, suspensions, and spray drug products should be sterile. For test methodology, refer to USP <71> Sterility Tests.

g. Preservative Effectiveness

If the use of a preservative(s) is justified, see nasal sprays, section III.F.1.o.

h. Foreign Particulates

See nasal sprays, section III.F.1.m. The acceptance criteria should **also** include limits for foreign particulates less than 10 micrometers (μm).

i. pH

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

j. Osmolality

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

k. Net Content and Weight Loss (Stability)

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

l. Leachables (Stability)

See nasal sprays, section III.F.1.q. Additionally, for inhalation solutions and suspensions packaged in semipermeable containers (e.g., low density polyethylene) with protective packaging or if their immediate containers bear paper labels (including, for example, inks, paper, adhesives components), the absence of the ingress of volatile components from the packaging or labels should be demonstrated. Procedures used for these determinations should be validated and have suitable detection and quantitation limits for the potential leachables.

m. Particle Size Distribution (Suspensions)

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

n. Microscopic Evaluation (Suspensions)

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

o. Pump Delivery for Inhalation Sprays

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

p. Spray Content Uniformity (SCU) for Inhalation Sprays

The recommendations for acceptance criteria and tests for SCU from the 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.

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

q. Spray Content Uniformity (SCU) Through Container Life for Inhalation Sprays (Device-Metered)

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. Refer to nasal sprays (section III.F.1.h.) and the discussion of the SCU tests and acceptance criteria above (section III.F.2.p.).

r. 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 may be evaluated by a variety of procedures (e.g., the time sequence sound-triggered high speed flash photography method, video tape recording and taking pictures of different frames). The approaches used should allow monitoring the plume development to define the shape of the complete 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 microsecond(s)) for visualization after spraying, and the examination orientations (e.g., from top and side). 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, and spray cone angle from two orientations, i.e., top and side). Variability in tests involving manual manipulations can be reduced by providing procedure-specific training to the analyst.

s. Particle/Droplet[4] 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 1–5 µm.

From a pharmaceutical viewpoint, the most important parameter for an inhalation product is usually the aerodynamic particle/droplet size distribution of the outgoing spray. 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.

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(s) 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. Additionally, criteria should be provided in the application for the qualification of each cascade impactor. It is recommended that all cascade impactors used in support of the drug product in the application be of the same design.

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

The number of sprays needed 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. 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 may 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 may be proposed in terms of 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. Furthermore, 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.

Inhalation spray drug products may vary widely in design and mode of operation. These differences may lead to particle/droplet size distribution properties that are unique for the drug product and that cannot be characterized by cascade impaction alone. Therefore, for more definitive delineation of the critical particle/droplet size distribution parameter and assurance of batch-to-batch reproducibility for inhalation spray drug products, a complementary validated measurement procedure should be used (e.g., light scattering, time-of-flight). For these complementary procedures, it is crucial that instrumental and operational parameters (e.g., apparatus and accessories, software version and calculation algorithms, 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[5]) of the delivered plume subsequent to spraying under specified experimental and instrumental conditions.

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

G. Container Closure Systems

The following section applies to container closure systems for nasal spray and inhalation solution, suspension, and spray drug products. Comments below apply to all product types unless otherwise specified. Comments pertaining to pumps apply to both nasal and inhalation spray drug products.

The clinical efficacy of nasal and inhalation spray drug products is directly dependent on the design, reproducibility, and performance characteristics of the container closure system. For these drug products, the container closure system consists of the container, closure, pump, and any protective packaging, if applicable. In this guidance the word *pump* refers to all components that are responsible for metering, aerosolization, 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 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 studies. The device should be designed to prevent partial metering of the formulation. The use of some type of dose counting mechanism for these products is encouraged. 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.

If the device includes electronic components that may affect the performance 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).[6]

The composition and quality of the materials used in the manufacture of the container closure system components should be carefully selected. For safety considerations,

[6]Contact CDRH for drafts 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).

materials that minimize or eliminate leachables without compromising the integrity or the performance of the drug product should be chosen.

The identity and concentration of the leachables in the drug product or placebo formulation (i.e., drug product formulation without drug substance) through the end of the drug product's shelf life should be determined. If possible, the results should be correlated with the extractables profile(s) of the container closure components determined under the various control extraction study conditions. Such a correlation may obviate the need to evaluate leachables in the drug product formulation in future routine stability studies. For ANDAs, the applicant may compare the extraction profiles of the container and closure components with the leachables profile(s) of the drug product (or placebo) after storage under accelerated stability conditions for 3 months, as long as a commitment is 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.

Complete information (see below) should be provided on the characteristics of, and acceptance criteria, test procedures, and analytical sampling plans used for each component of the container closure system to ensure its suitability for manufacturing the drug product. For additional information on container closure systems, refer to FDA's guidance for industry *Submitting Documentation for Packaging for Human Drugs and Biologics* (February 1987).[7]

The following information should be included in the drug application:

- Source(s) and fabricator(s) of the container, closure, and the assembled pump
- Source(s) and fabricator(s) for each part of the pump
- Item numbers for different parts of the pump
- Item numbers of the container, closure, and the assembled pump
- Schematic engineering drawings of the container, closure, and pump components
- Precise dimensional measurements of the container, closure, and pump components
- Composition and quality of materials of the container, closure, and pump components
- Control extraction studies for elastomeric and plastic components
- Toxicological evaluation of extractables

[7] The 1987 packaging guidance will be superseded by FDA's draft guidance for industry *Submission of Documentation in Drug Applications for Container and Closure Systems Used for the Packaging of Human Drugs and Biologics* (July 1997) once it is issued in final form.

- Acceptance criteria, test procedures, and analytical sampling plans
  - Physicochemical parameters and dimensional measurements of the container, closure, and pump components
  - Qualitative and quantitative extractable profile(s) from the container, closure, and pump components
  - Performance characteristics of the pump

Additional information on select topics is provided below.

1. Source, Chemical Composition, and Physical Dimensions

The source, chemical composition (e.g., resins, additives, colorants, adhesives, inks), and physical dimensions of each component should be specified. The dimensional measurements of metering pump components should be held to very tight tolerances through precision measurements. The composition of the container, closure, coating material (if applicable), and individual pump components should be provided in the application and/or an appropriately referenced DMF. 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. Critical components are defined as those that contact either the patient or the formulation, components that affect the mechanics of the overall performance of the device, or any necessary protective packaging. 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 submitted to facilitate the application review process.

2. Control Extraction Studies

The purpose of the control extraction study is to define an acceptable quantitative extractable profile for elastomeric or plastic packaging components under specified test conditions and to establish acceptance criteria for each of the extractables from the container, closure, and critical components of the pump used for the submitted batches (e.g., clinical, preclinical, biobatch, primary stability, production). 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 analytical sampling plan, 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. Typically, the extraction solvents would include 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. The appraisal should include appropriate in vitro and in vivo tests and may 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 profile(s). Special attention should be paid to elastomeric components because of the potential for release of additional leachables (e.g., PNAs, nitrosamines, vulcanization accelerators) into the formulation which may alter the toxicological profile of the drug product. Since some extractables may be carcinogenic, appropriate risk assessment models may be needed 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 profile(s) for routine testing for each container, closure, and individual pump component. This testing will provide continued assurance of the batch-to-batch consistency of the quality 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. However, for nasal spray drug products, if the level of extractables for each component is very low, it may be appropriate to establish a limit only for the total weight of extractables from each individual critical component.

Test procedures and analytical sampling plans should be provided. The accuracy, precision, specificity, sensitivity, and ruggedness of each procedure should be

documented with proper standards during validation in the control extraction studies.

4. Acceptance Criteria

The application should include specifications for the container, closure, each component of the pump, the assembled pump, labels, adhesives, ink, and secondary protective packaging, as applicable. The specifications should include dimensional measurements, physicochemical parameters, individual and total extractables for the container, closure, and individual pump components as outlined above under the discussion of the routine extraction studies. In addition, the specifications should include performance attributes of the pump (e.g., functionality, actuation force, pump or spray weight delivery, particle/droplet size distribution, spray pattern). 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., clinical, primary stability, biobatch, and production batches, all using identical 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 necessary 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, a reduced acceptance testing schedule may be considered once the applicant establishes the reliability of the supplier's test results. The applicant should confirm the 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., clinical, primary stability, biobatch, and production), and a predetermined number of postapproval drug product batches.

H. Drug Product Stability

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 data, and (3) information regarding the suitability of the test procedures employed.

1. Content of Stability Protocol

The stability protocol should be comprehensive and should include information on the following aspects:

- Test parameters and acceptance criteria
- Test procedure references
- Test intervals
- Container storage orientations
- Test storage conditions
- Type, size, and source of container and closure components
- Grades and manufacturers of drug substance and excipients
- Type, size, and number of batches
- Identification of manufacturing facilities for each stability batch (e.g., IND, NDA, ANDA, postapproval batches)
- Analytical sampling plans
- Statistical analysis approaches and evaluation for NDAs
- Content and format of stability data
- Commitments
- Expiration Dating Period

For general guidance on information to support drug product stability and content and format of stability reports, refer to FDA's guidance for industry *Submitting Documentation for the Stability of Human Drugs and Biologics* (February 1987).[8] The following additional discussion elaborates on specific aspects of information for nasal spray and inhalation solution, suspension, and spray drug products that should be included in the application.

a. Test Parameters, Acceptance Criteria, and Procedures

The stability test parameters, with appropriate acceptance criteria, should include those test parameters identified in the release specifications of the drug product (refer to section III.F) with the following exceptions: for nasal sprays, identity of the drug substance, spray pattern, osmolality, and net content; for inhalation products, identity, osmolality, and net content. 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. Testing for preservative effectiveness should be performed, if applicable, on the primary stability batches submitted in the application and for the first three production batches of drug product stored under long-term stability conditions.

[8]The 1987 stability guidance will be superseded by FDA's draft guidance for industry *Stability Testing of Drug Substances and Drug Products* (June 1998) once it is issued in final form.

b. Test Intervals

The stability test intervals should be indicated in the application. Long-term test intervals (e.g., 0, 3, 6, 9, 12, 18, 24 months), accelerated test intervals of a minimum of four test time-points for 6 months (e.g., 0, 1, 3, 6 months), and intermediate test intervals (e.g., 0, 3, 6, 9, 12 months) should be included. For ANDAs, the same long-term and intermediate conditions should be used, but intervals at 0, 1, 2, and 3 months can be used for accelerated testing. However, confirmation by the Office of Generic Drugs of the acceptability of the proposed study duration is recommended. Tabular presentations of the test intervals may be used for added clarity.

c. Container Storage Orientations

The stability of nasal and inhalation drug products may be affected by storage under differing orientations. For example, leachable levels, pump appearance, weight loss, assay, particle size distribution, and SCU may be affected by orientation. 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.

d. Test Storage Conditions

Stability studies should be performed on the drug product with the packaging configuration (i.e., primary, secondary or additional protective) intended for marketing using the appropriate test storage conditions.

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 may be initiated concurrently. Due to the complexity of these types of drug products, accelerated stability studies alone may not be predictive of the product performance throughout the extrapolated expiration dating period.

For drug products intended for storage under controlled room temperature conditions and packaged in semipermeable containers (e.g., low density polyethyelene) without protective packaging, the above test storage conditions should be replaced with the following conditions: (1) accelerated

(40±2°C/15±5%RH), (2) intermediate (30±2°C/40±5%RH), if applicable, and (3) long-term (25±2°C/40±5%RH).

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 *Submitting Documentation for the Stability of Human Drugs and Biologics* (February 1987).[9]

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

To determine drug product stability, three batches provide a minimally acceptable evaluation of batch-to-batch variability and represent a compromise between statistics and economics. The three batches should be prepared from the formulation and container closure system components intended for marketing, which should be the same as those used in submitted batches (e.g., clinical, biobatch, primary stability, production). For ANDAs, see *Submitting Documentation for the Stability of Human Drugs and Biologics* (February 1987)[10] 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(s) of the drug substance and excipients used in these drug product batches should be specified. The information on these drug substance batches should include but

[9]Ibid.

[10]Ibid.

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 and for noncompendial excipients.

g. Sampling Plans and Statistical Analysis Approaches and Evaluation

Refer to *Submitting Documentation for the Stability of Human Drugs and Biologics* (February 1987).[11]

h. Stability Commitment

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 commitment, refer to *Submitting Documentation for the Stability of Human Drugs and Biologics* (February 1987).[12]

i. Expiration Dating Period

The expiration dating period should be based upon full shelf-life stability studies of at least three batches of drug product, preferably manufactured from three different batches of the drug substance and using different batches of container and closure components, to ensure a statistically acceptable level of confidence for the proposed expiration dating period. For ANDAs, see *Submitting Documentation for the Stability of Human Drugs and Biologics* (February 1987)[13] for recommendations regarding expiration dating periods.

2. Other Stability Considerations

Any change in the manufacturing facility; manufacturing procedure; source, synthesis, or micronization of the drug substance; source or type (design or

[11]Ibid.

[12]Ibid.

[13]Ibid.

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 necessary 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 stability data should be generated from each different facility, process, or source. Stability studies should be performed on all sizes of the drug products (e.g., trade and sample sizes).

In general, the use of bracketing and matrixing protocols may not be appropriate for some of these drug products. If applicants believe that a bracketing or matrixing protocol is justified, then they are encouraged to contact the appropriate review team for further guidance.

For additional stability considerations, refer to section IV below on drug product characterization studies and *Submitting Documentation for the Stability of Human Drugs and Biologics* (February 1987).[14]

IV. DRUG PRODUCT CHARACTERIZATION STUDIES

For nasal spray and inhalation solution, suspension, and spray drug products, certain studies should be performed to characterize the optimum performance properties of the drug product and to support appropriate labeling statements. Delivery systems for nasal and inhalation spray drug products may 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 are one-time studies, usually performed on three batches of drug product representative of the product intended for marketing. 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 should be discussed with the responsible review division.

[14] Ibid.

A. Priming/Repriming in Various Orientations

For nasal and inhalation spray drug products, studies should be performed to characterize the priming and repriming requirements for the product in different orientations (upright and inverted or upright and horizontal) after different periods of non-use. SCU and other pertinent parameters should be evaluated. The approximate interval that may pass before the drug product needs to be reprimed to deliver the labeled amount of medication and the number of sprays needed to prime or reprime the unit should be determined. Multiple orientation studies should be performed with initial sprays and with sprays corresponding to a fill of 50 percent of the nominal container capacity when fitted with the pump (which will correspond to greater than 50 percent relative to labeled number of sprays). Priming and repriming information will be used to support the proposed labeling statements.

B. Effect of Resting Time

For 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 are only primed, if needed, prior to 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 which have been stored in different orientations (i.e., upright and inverted or upright and horizontal). To shorten the length of the study, testing may 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 may consist of three or four 6-hour cycles per day, between subfreezing temperature and 40°C for a period of at least 4 weeks. 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, SCU through container life, and sterility and functionality of pump components. 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 strengths, studies should address in vitro dose proportionality between strengths (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 Ruggedness

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

(1) For devices that may be reused repeatedly with replaceable reservoirs, a study should be conducted to establish the product performance characteristics (SCU, particle/droplet size distribution) throughout the life of the device.

(2) Limits of use related to failure of critical device mechanisms should be studied to determine the necessary replacement intervals for the device.

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

G. Effect of Orientation

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

For inhalation spray drug products that are breath-activated or 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.

For breath-activated inhalation sprays, another study should assess the triggering ranges of flow rates needed to generate the amount of delivered dose and the corresponding particle/droplet size distribution.

For inhalation spray drug products with an expansion or holding chamber, spacer, or similar component, a separate study 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 is encouraged.

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 delivered drug substance 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). These studies help determine if the target fill and any proposed overfill of the containers are justified, since the tail off characteristics may vary as a function of pump design, container geometry, and formulation. A graphical representation of the findings is also recommended.

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/droplet size distribution through unit life. Refer to sections III.F.1.k and III.F.2.s.

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.r 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.i). The plume geometry characteristics may 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 a preservative(s) is used in the formulation, the minimum acceptable limit for the content of preservatives 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 as acceptable. For details for this characterization, see section III.B.4 in *Submitting Documentation for the Stability of Human Drugs and Biologics* (February 1987).[15]

For device-metered inhalation spray drug products, studies should be performed to demonstrate the maintenance of sterility through the life of the reservoir during use.

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 may refer to the ICH guidance *Q1B Photostability Testing of New Drug Substances and Products* (November 1996).[16]

O. Stability of Primary (Unprotected) Package

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 40%RH should be generated for these units without the protective packaging for pertinent parameters to establish the maximum length of time for 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

[15]The 1987 stability guidance will be superseded by FDA's draft guidance for industry *Stability Testing of Drug Substances and Drug Products* (June 1998) once it is issued in final form..

[16]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.

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 21 CFR part 201. In general, labeling for ANDAs should be the same as the reference listed drug.

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. Labels

The label(s) should bear the following information:

- Established name of the drug product
- Amounts of the drug substance delivered from the pump nosepiece 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 "℞ Only" statement
- Lot number
- Expiration date
- Use period once drug product is removed from protective packaging (if applicable)
- NDC number(s)
- The instruction *Shake well before using* for suspension formulations

For nasal and inhalation spray drug product devices that may 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 under FDA regulations for the description of the drug substance and formulation, 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 nosepiece 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 sprays per container should be included.
- The number of priming sprays needed before using the unit for the first time and in cases where the unit 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. Additionally, a statement should be included that the unit or container (for nasal or inhalation sprays with reuseable devices) should be discarded when the labeled number of sprays has been dispensed.
- 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) was deemed necessary 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.N).
- A statement should be included regarding any requirements for shaking, if necessary (i.e., for suspension products).
- NDC number(s)

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 any requirements for shaking, if necessary (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.N).
- 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.

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. Labels

The label(s) 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 "℞ Only" statement
- Lot number
- Expiration date

- Use period once drug product is removed from protective packaging (if applicable)
- NDC number(s)
- The instruction *Shake well before using* for suspension formulations

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 under FDA regulations for the description of the drug substance and formulation, 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.L).

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 content 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.N).

- A statement regarding any requirements for shaking should be included, if necessary (i.e., for suspension products).
- Any preferred storage orientation should be noted for inhalation suspensions, if applicable.
- NDC number(s)

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 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 any requirements for shaking, if necessary (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 content 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.

GLOSSARY OF TERMS

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. The container closure system also includes the pump for nasal and inhalation sprays.

Drug Product: The formulation and the container closure system constitute the drug product.

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: Formulation component(s) 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(s).

Expiration Dating Period: The time interval during which all batches of a drug product are expected to remain within approved specifications after manufacture. Expiration dating period will be used to determine the expiration date of the drug product.

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

Leachables: Compounds that leach from elastomeric or plastic components of the container closure system of nasal spray, and inhalation solution, suspension, and spray drug products as a result of direct contact with the formulation.

Nasal Sprays: Drug products that contain active ingredient(s) dissolved or suspended in a formulation, typically aqueous-based, which may 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, aerosolization, and delivery of the formulation to the patient.

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

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

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

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

Specification: A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described. Specifications establish a set of criteria to which a drug substance or drug product should conform using the approved analytical procedure to be considered acceptable for its intended use.

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.

ABBREVIATIONS

CFR: Code of Federal Regulations
mcg: microgram(s)
mg: milligram(s)
NF: National Formulary
PNA: polynuclear aromatic
SCU: spray content uniformity
USP: United States Pharmacopeia