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Guidance for Industry

Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) 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DRAFT GUIDANCE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)**
October 1998
CMC

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November 5, 1998

98D-0997

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(Due to the length and complexity of this draft guidance, please identify specific comment by line number.)

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 metered dose inhalation aerosols and metered dose nasal aerosols (also known as oral and nasal metered dose inhalers respectively or MDIs) and inhalation powders (also know-n as dry powder inhalers or DPIs). This guidance also covers CMC information recommended for inclusion in the application regarding the components, manufacturing process, and controls associated with each of these areas. The recommendations in this guidance should also be considered for investigational drug applications (INDs). The guidance does not address inhalation solutions and aqueous nasal sprays.

The guidance sets forth information that should be provided to ensure continuing drug product quality and performance characteristics for MDIs and DPIs. The guidance does not impose mandatory requirements but does put forth 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.

Reference to information in Drug Master Files (DMFs) for 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.

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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 inhalation 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.

II. BACKGROUND

A. Metered-Dose Inhalers (MDIs)

Metered-dose inhalers have grown in popularity since their introduction in the late 1950s, and they are currently used by over 25 million Americans for a variety of diseases, such as asthma, chronic obstructive pulmonary disease (COPD), and other lung diseases characterized by obstruction of airflow and shortness of breath.

Metered-dose inhaler products contain therapeutically active ingredients dissolved or suspended in a propellant, a mixture of propellants, or a mixture of solvents, propellants, and/or other excipients in compact pressurized aerosol dispensers. An MDI product may discharge up to several hundred metered doses of one or more drug substances. Depending on the product, each actuation may contain from a few micrograms (mcg) up to milligrams (mg) of the active ingredients delivered in a volume typically between 25 and 100 microliters.

Although similar in many features to other drug products, MDIs have unique differences with respect to formulation, container, closure, 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 MDIs are listed below:

1. The container, the valve, the actuator, the formulation, any associated accessories (e.g., spacers), and protective packaging collectively constitute the drug product. Unlike most other drug products, the dosing and performance and, therefore, the clinical efficacy of a MDI may be directly dependent on the design of the container and closure system (CCS).

2. The fraction of the formulation delivered to the patient consists of a mixture of micronized (or solubilized) drug substance in the desired physical form, which may be within a residual matrix of oily excipient material, propellant, and/or solvent.

3. Fixed portions of medication from a multidose container can be directly administered to the patient without contamination or exposure of the remaining material under normal use conditions. Conversely, portions of the immediate container's content cannot be removed from a pressurized container for further modification or manipulation.

4. The aerosolization of materials from a pressurized container is a complex and rapid sequence of events. When the content of the metering chamber is released, it undergoes volume expansion and forms a mixture of gas and liquid before being discharged as a jet through the orifice of the actuator. Within the expanding jet, the droplets undergo a series of processes. Subsequent to the aerosolization and dispersion of the drug product into a multitude of droplets, and during the propulsion of these droplets from the actuator to the biological target, the drug substance particles in the droplets become progressively more concentrated due to rapid evaporation of the volatile propellant components.

5. The concept of classical bioequivalence and bioavailability is usually not applicable for oral inhalation aerosols. The dose administered is typically so small that blood or serum concentrations are generally undetectable by routine analytical methods. Moreover, bioequivalency studies are complicated by the fact that only approximately 10–1 5 percent of the dose reaches the biological target. The remainder of the dose, trapped in the mouth and pharynx, is swallowed and absorbed through the gastrointestinal (GI) tract. Thus, even if determination of blood or serum concentrations were possible, additional and more extensive studies would be necessary to distinguish the contributions of the drug absorbed from the pulmonary, buccal, and GI routes.

6. Clinical efficacy assessment of inhalation aerosols requires consideration of several parameters, such as:

- Variability in the disease itself (ventilator and anatomic or pathologic factors);
- Administration skills and practices, for example, breath holding and its duration, patient inspiratory flow rate, discharging either via closed lips around the mouthpiece or into the open mouth, coordination of aerosol discharge (actuate and breathe) and inhalation by the patient, add-on devices (e.g., spacers, chambers), proper priming of the valve and cleaning practices for the actuator, proper handling and fitting of the actuator to the valve stem;
- Presence of other drugs (i.e., when disease states require a multidrug treatment) which may exacerbate differences between products;
- Drug product variability due to physical characteristics and controls of the drug substance, optimized formulation, valve and actuator design, manufacturing process and in-process controls, and so on.

B. Dry Powder Inhalers **(DPIs)**

At present, dry powder inhalers are not used as commonly in the United States as are MDIs. Technical challenges have resulted in a greater variety in design and function of DPIs relative to MDIs. Current designs include **pre-metered** and device-metered **DPIs**, both of which can be driven by patient inspiration alone or with power-assistance of some type. Pre-metered DPIs contain previously measured doses or dose fractions in some type of units (e.g., single or multiple presentations in blisters, capsules, or other cavities) that are subsequently inserted into the device during manufacture or by the patient before use. Thereafter, the dose may be inhaled directly from the pre-metered unit or it may be transferred to a chamber before being inhaled by the patient. Device-metered DPIs have an internal reservoir containing sufficient formulation for multiple doses that are metered by the device itself during actuation by the patient. The wide array of DPI designs, many with characteristics unique to the design, will present challenges in developing information in support of an application. Regardless of the DPI design, the most crucial attributes are the reproducibility of the dose and particle size distribution. Maintaining these qualities through the expiration dating period and ensuring the functionality of the device through its lifetime under patient-use conditions will probably present the most formidable challenge.

DPIs are complex drug products that differ in many aspects from more conventional drug products as well as from MDIs. The unique characteristics of DPIs should be considered during development, particularly with respect to formulation, manufacturing, container and closure system or device, and both in-process and final controls. Several key distinctions of DPIs are listed below:

1. The device with all of its parts, including any protective packaging (e.g., overwrap), and the formulation together constitute the drug product. Unlike most other drug products, the dosing and performance and therefore the clinical efficacy of a DPI may be directly dependent on the design of the device.

2. The portion of the formulation that is delivered by inhalation to the patient consists of the neat drug substance controlled to a suitable particle size distribution (e.g., micronized, spray-dried) or the drug substance contained within a matrix of excipients.

3. Energy is required for dispersion and aerosolization of the formulation and the drug substance. Whereas MDIs use energy stored in a liquefied gas propellant under pressure for aerosolization and dispersion, DPIs may rely on several energy sources, including energy from patient inspiration, from compressed gas, or from a motor-driven impeller.

4. Whereas MDIs administer doses of the drug substance formulation to the patient without contamination of the remaining formulation under normal use conditions, this is not necessarily the case with DPIs. In particular, device-metered DPIs can be susceptible to contamination (e.g., moisture, microbial) of the remaining doses. Contamination aspects under both in-use and abuse conditions should be considered during development of the drug product.

5. In DPIs, complex and subtle interactions may occur between the drug substance, carrier(s), and components of the container and closure system that significantly affect the safety and effectiveness of the drug product. For example, gravitational, fluid dynamic, and other interactive forces, such as electrostatic, van der Waals, and capillary forces, together are responsible for different fluidization behaviors exhibited by different powders in an inhaler. Electrostatic charge interactions influence the overall efficiency of a DPI, since such forces are considered to be significant for attraction and adhesion between the drug substance particles, excipient particles, and device surface. Additionally, particle size distribution, particle morphology, and moisture content can greatly influence the bulk properties of the formulation and the product performance.

6. The issues of classical bioequivalence and bioavailability (point 5 in section II.A) and clinical efficacy assessment (point 6 in section II .A) that were discussed for MDIs apply equally to DPIs.

In summary, MDIs and DPIs have many distinctive features that should be considered when developing documentation supporting an application. Furthermore, modification or alteration of these products due to changes in components of the drug product or changes in the manufacturers or manufacturing process should be carefully evaluated for effect on the safety, clinical effectiveness, and stability of the product. The type and extent of scientific supportive information needed for such changes could be more extensive than that needed for similar changes in more conventional drug products.

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 MDI and DPI drug products.

III. DRUG PRODUCT

MDIs and DPIs are complex units, the quality and reproducibility of which can be better ensured by appropriate controls of all components (active ingredients, excipients, device components, protective packaging) used in the drug product, controls during manufacture of the drug product,

and controls for the drug product. In particular, consistent dosing and particle size distribution for these products should be maintained throughout the expiration dating period.

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 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

1. MDIs

The composition of an MDI formulation is crucial, particularly in defining the physical stability and the performance characteristics of a suspension MDI. In suspension inhalation aerosols, the drug substance can float or settle depending on the relative densities of the drug substance and the liquid phase of the formulation. Moreover, the formulation composition will have a direct effect on the degree or extent of agglomeration or suspendibility of the drug substance particles. Preferential interaction of the suspended drug substance with the various internal container and closure system components (e. g., adherence of the drug substance to the walls of the container or valve 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 medication dose delivery and particle size distribution. Additionally, in a typical MDI, the propellant(s) and cosolvent(s) constitute the majority of the formulation composition, and the type and amount of these components determine the internal pressure of an inhalation aerosol, a critical parameter related to the MDI performance.

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 actuation delivered at the valve. The amount of active ingredient delivered per actuation from the mouthpiece

should be provided. 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, the percent excess shown, scientifically justified, and documented. Information on the density of the formulation should be included. Any intended change in the formulation from that used in the submitted batches (e.g., clinical, biobatch, primary stability, production) should be clearly indicated.

2. DPIs

The composition of the formulation of a DPI has a direct effect on the stability of the formulation as well as on the dosing performance of the product. A carrier may be used for a DPI, for example, as a bulking agent to enhance reproducible dose metering. The suitability of a carrier is dependent on its chemical and physical characteristics, which can have direct effect on the performance of the product (e.g., ease of entrainment of the formulation, energy input necessary for dispersion and aerosolization of the active ingredient from the carrier, hygroscopicity of the formulation). Hygroscopicity can result in uptake of moisture by the formulation which may affect the particle size distribution of the emitted drug substance, the stability of the drug substance, the dose hold-up in the device, and hence the delivered dose.

The application should include a statement of the quantitative composition of the drug product, specifying the name and amount of each active and excipient contained in a stated quantity of the formulation. These amounts should be expressed in concentration (i.e., amount per unit weight), as well as amount per metered dose and emitted dose at the mouthpiece under defined test conditions (e.g., flow rate, duration). For device-metered DPIs, the target formulation fill weight should also be indicated. 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, the percent excess shown, scientifically justified, and documented in the submission.

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 to be used in inhalation drug products should be included in the application. Important properties of the drug substance

may include, but are not necessarily limited to, density, particle size distribution, particle morphology, solvates and hydrates, clathrates, morphic forms, amorphous forms, volubility profile, moisture and/or residual solvent content, microbial quality, pH profile and 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. Key specification parameters may include color, appearance (visual and microscopic), specific identification, moisture, residue on ignition, specific rotation, assay, microbial limits (10 g sample size, USP <61>), melting range, particle size distribution, surface area, crystalline form(s), residual solvents, and heavy metals. Micronized drug substance is typically used in DPIs or MDIs containing a suspension of drug substance. Specifications for control of particle size distribution and crystalline forms (e.g., shape, texture, surface) of the drug substance, parameters often critical for reproducible drug product performance, should be included in the application.

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 inorganic (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). For additional guidance on toxicological qualification, the applicant is encouraged to contact the responsible review division.

In general, acceptance criteria for all parameters defining the physiochemical properties should be based on historical data, thereby providing continuity of quality and reproducible performance of future batches of the drug substance.

2. Excipients

For most MDIs and DPIs, excipients (when used) comprise a significant portion of the formulation content by weight and their quality has a substantial effect on the safety, quality, stability, performance, and effectiveness of such drug products. The sensitive nature of the patient population warrants complete characterization

and strict quality control of these excipients to ensure consistency in the above properties.

The source of each excipient should be identified in the application. Each source should be assessed, and the material supplied should meet appropriate acceptance criteria based on test results for several batches of excipients that were used in preparing the submitted batches of drug product (e.g., clinical, biobatch, primary stability, production). 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.

Adequate DMFs with appropriate authorization should be submitted to the agency for major (e.g., propellant, carriers) and noncompendial excipients. A full description of the acceptance criteria and the test methods used to ensure the identity, assay, functionality, quality, and purity of each excipient should be submitted. If these materials are accepted based upon certificates of analysis from the manufacturers with a specific identification test, the applicant should also develop validated methods or have access to all of the manufacturer's analytical and other test methods to allow the applicant to verify the reliability of the test results at appropriate intervals (21 CFR 211. 84).

The suitability of excipients to be administered by the inhalation route should be thoroughly investigated and documented in terms of the physiochemical properties. 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 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 *United States Pharmacopeia* (USP) or *National Formulary* (NF) monograph materials are used and the associated specifications do not provide adequate assurance for inhalation use with regard to the assay, quality, performance, and purity, the monograph specifications should be supplemented with additional appropriate acceptance criteria and tests to ensure lot-to-lot reproducibility of the components. For example,

- When Dehydrated Alcohol, USP is used as a cosolvent in MDIs, additional discriminatory specifications for water content (e.g., Karl Fischer) and impurities should be included.

- When Lecithin, NF, a surfactant, is used in MDI formulations, additional acceptance criteria and tests controlling the complete compositional profile should be used (e.g., levels of phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl inositol, lysophosphatidyl choline, phosphatidic acid, triglycerides, fatty acids, carbohydrates).

- When Oleic Acid, NF is used as a surfactant in MDI formulations, additional specifications should be included for identification, assay, and for characterization and control of the compositional profile of impurities (e.g., individual specified fatty acids, unknowns).

- Compendia propellants (e.g., CFC- 11, CFC- 12, and CFC- 114) should be completely controlled by additional acceptance criteria and validated test methods for assay and related impurities (based on historical data). See recommendations in Table 1.

- Lactose Monohydrate, a commonly used carrier excipient for DPIs, is covered by a *National Formulary* monograph. However, the monograph acceptance criteria and tests alone are not adequate for controlling key physicochemical characteristics of this excipient and should be supplemented if this excipient is used in the formulation of an inhalation drug product. For example, lactose carrier particles with low surface roughness may more effectively redisperse drug particles in an inhaled stream. Similarly, different morphic and amorphous forms of lactose may adhere differently to the drug substance particles and produce varying aerosolization behavior. Because the compendia monograph does not address the control for particle morphology and amorphous content, it should be supplemented with appropriate acceptance criteria and tests for control of these parameters in the application. Moreover, other additional recommended parameters for lactose include particle size distribution, quantitative color and clarity, assay, impurities and degradants, solvents, water content, microbial limits (total aerobic count, total mold and yeast, absence of pathogens), pyrogens, and/or bacterial endotoxins test, and specific and quantitative protein content. Protein determination may be performed by an adequate combination of specific and/or general methods (e.g., ELISA, Western Blot, amino acid analysis, Kjeldahl, Lowry, spectrophotometric assay).

For noncompendial excipients (e.g., HFA-134a, HFA-227 propellants), comprehensive acceptance criteria reflecting the data for the excipient batches used in the submitted drug product batches (e.g., clinical, biobatch, primary stability, production) should be included to ensure consistent quality of future incoming material. For additional guidance on pharmacological and toxicological considerations, the applicant should consult available CDER guidances or contact the responsible review division. For example, for noncompendial propellants, such as HFA-134a, acceptance criteria and tests should be included for the following parameters: identity, appearance, assay (e.g., not less than 99.9%), acidity, total residue, moisture content, related impurities, and unrelated impurities (e.g., CO, N_2, O_2 gases). The related impurities acceptance criteria limits shown in Table II may be adopted for HFA-134a.

Table I. Recommended Assay and Impurities Acceptance Criteria for Various Compendia Propellants

Impurity'	CFC- 11 Acceptance Criteria (ppm)	CFC-12 Acceptance Criteria (ppm)	CFC-114 Acceptance Criteria (ppm)
HFC-152a		10	
HCFC-21	75	50	
HCFC-22	10	250	50
HCFC-123	10		200
HCFC-124			50
HCFC-124a			50
HCFC-133a	10	10	20
CFC-11	99,8°A purity	2000	500
CFC-12	2000	99.8% purity	1000
CFC-13	10	300	
CFC-I 13	75	10	50
CFC-113a	15		50
CFC-114	40	150	99.8% purity
CFC-115		15	300
CFC-217			200
CFC-319			10
BCFC- 12B1	15	15	
CFC-1112a	10	10	10^2
Methyl Chloride	10	40	
Dichloromethane	50	10	
Chloroform	20	10	
Carbon Tetrachloride	20	10	
Total Chloromethanes	50	50	
Total Unspecified	I 20	I 20	20
Total Impurities	2000	2000	2000

'No number for an impurity indicates its absence (below detection limit of method).

'Acceptance criteria under evaluation.

Table II. Recommended Assay and Impurities Acceptance Criteria for HFA-134a Propellant

Impurity	HFA- 134a Acceptance Criteria (ppm)	Impurity	HFA-134a Acceptance Criteria (ppm)
HCC-40	5	HCFC-133a	5
HFC-23	5	HCFC-161	30
HFC-32	5	HCFC-1121	5
HFC-125	5	HCFC- 1122	5
HFC-134	1000	HCFC- 1122a	5
HFC-143a	10	CFC- 11	5
HFC- 152	5	CFC- 12	100
HFC- 152a	300	CFC-12B1	5
HFC-245cb	5	CFC- 13	5
HFC-1123	5	CFC-113	5
HFC-1132	5	CFC-114	5
HFC-1225ye	5	CFC-114a	25
HFC-1234yf	5	CFC-115	5
HFC-1243zf	5	CFC-1112a	5
HFC-1336mzz	5	FC- 13 18my-T	5
HCFC-22	50	FC- 13 18my-C	5
HCFC-31	5	Total unsaturates (including HCFC- 11 22)	5
HCFC-123	5	Individual unidentified impurities	5
HCFC-123a	5	Total unidentified impurities	10
HCFC-124	100	Other organic impurities	50
HCFC-124a	5	Any other identified saturated impurity	5
HCFC-132b	5	Total impurities	1000
		Assay	99.9%

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 and excipients 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).

E. Method(s) of Manufacture and Packaging

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

If micronization is used for the drug substance or excipient(s), 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. Attention should be paid to potential contamination of the micronized material during the process from the grinding parts, compressed gas, and collecting filter (e.g., oil, moisture, other contaminants). The moisture content in the micronized material should be tightly controlled for drug substances or formulations that are chemically or physically sensitive to moisture. The moisture content, particle size distribution, particle morphology (shape and texture), bulk density, as well as impurities, degradants, and contaminants in the drug substance and drug products should be controlled with appropriate acceptance criteria and test methods to ensure lot-to-lot reproducibility.

A copy of the actual (executed) batch record and in-process controls should be filed, as appropriate, for representative submitted 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. Information on the lag or equilibration time instituted before the release of MDIs, as well as a description of the packaging operation for MDIs and DPIs 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 time, temperature, and moisture) to decrease controllable process variability and increase consistency in the quality of the drug product.

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 under actual operating conditions. For MDIs, in-process controls may include, for example, assay of the suspension or solution, moisture level, consistency of filling of both the concentrate and the propellant, valve crimp measurements, quality of sealing, in-line leak testing under stress conditions, and performance of the valve. For DPIs, in-process controls may include assay of bulk formulation, moisture level, consistency of filling operation, particle size distribution, quality of sealing of unit dose and protective packaging, and so on.

Additionally, a description of the primary and protective packaging operation and relevant in-process controls for this operation should also be included. For example, when blister units, foil-foil, or protective packaging are used, it should be ensured that the seal area functions properly in terms of adhesion (e.g., heat seal, adhesive) or mechanical seal. 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.

F. Specifications for the Drug Product

A complete description of release acceptance criteria, analytical methods, and 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, sensitivity, specificity, reproducibility, and ruggedness of the proposed validated test methods should be documented in sufficient detail to permit duplication and verification by Agency laboratories. Comprehensive and well-defined in vitro performance characteristics of inhalation drug products should be established before initiating critical clinical studies. Appropriate, validated test methods 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. MDIs

The following test parameters are recommended for MDI drug products. Appropriate acceptance criteria and validated test methods should be established for each test parameter.

a. Appearance and Color

The appearance of the content of the container and the appearance of the container and closure system (i.e., the valve and its components and the 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

Specific identification tests are 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 chiral, then at least one of the methods used for identification should be specific for this property.

c. 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 acceptance criteria proposed in the *Pharmacopeial Forum (1996,* Vol. 22, p. 3098). Furthermore, appropriate testing should be done to show that the drug product does not support the growth of microorganisms and that microbial quality is maintained throughout the expiration period. The minimum sample size should be 10 grams or the full content often containers (USP <61>).

d. Water or Moisture Content

Testing for the presence of water in the container should be performed, particularly for suspension formulations. Water or moisture should be strictly limited to prevent changes in particle size distribution, morphic form, and other changes such as crystal growth or aggregation.

e. Dehydrated Alcohol Content

If alcohol is used as a cosolvent in the formulation, there should be a specific assay with acceptance criteria for this excipient.

f. Net Content (Fill) Weight

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

g. Drug Content (Assay)

The concentration of drug substance in the entire container should be determined analytically with a stability indicating method. The acceptance criteria should be tight enough to ensure conformance in other related attributes (e.g., dose content uniformity). Although this test may not be directly relevant in terms of performance of inhalation aerosols, it provides assurance of consistency concerning the manufacture of the drug product (e.g., formulation, filling, crimping, and sealing).

h. Impurities and Degradation Products

The levels of degradation products and impurities should be determined by means of stability indicating methods. Acceptance criteria should be set for individual and total degradation products and impurities. For identification and qualification thresholds, refer to the appropriate guidance. Individual impurities or degradation products appearing at levels 0.10 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.

i. Dose Content Uniformity

Because of the complexity of the discharged dose, the medication available at the mouthpiece of the actuator should be thoroughly analyzed for an individual container, among containers, and among batches. This test may be regarded as providing an overall performance evaluation of a batch, assessing the formulation, the manufacturing process, the valve, and the actuator. The number of actuations per determination should not exceed the number of actuations in the minimum dose approved in the labeling. A stability indicating method should be used. The amount of drug substance discharged should be expressed both as the actual amount and as a percent of label claim from the actuator. The USP Unit Spray <601> sampling apparatus may be used. This test is designed to demonstrate the uniformity of medication per actuation or dose, consistent with the label claim, discharged from the mouthpiece of a sample of an appropriate number of

containers from a batch (n = 10 is recommended) . The primary purpose is to ensure dose uniformity within discharges from multiple containers of a batch. The following acceptance criteria are recommended:

- The amount of active ingredient per determination is not outside of 80–1 20 percent of label claim for more than one often containers, none of the determinations is outside of 75–125 percent of the label claim, and the mean is not outside of 85–1 15 percent of label claim. If two or three of the ten determinations are outside of 80–1 20 percent of the label claim, none is outside of 75–125 percent of label claim, and the mean is not outside of 85–1 15 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 80–1 20 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.

j. Dose Content Uniformity Through Container Life

The purpose of this testis to assess w-hether the product delivers the labeled number of full medication doses throughout the life of the MDI unit, and ensure that there is dose content uniformity for discharges within the same container. This test involves determining the dose content uniformity at the beginning of unit life, at the actuations corresponding to 50 percent of the fill weight (which may correspond to greater than 50 percent relative to the labeled number of actuations depending on overfill), and at the label claim number of actuations per container for an appropriate number of containers (n= 3 is recommended). The number of actuations per determination should not exceed the number of actuations in the minimum dose approved in the labeling. The rate of discharging between determinations should be such that it does not create excessive chilling of the MDI unit. The following acceptance critieria are recommended:

- The amount of active ingredient per determination is not outside of 80–1 20 percent of label claim for more than one of nine determinations from three containers, none of the determinations is outside of 75–125 percent of the label claim, and means for each of the beginning, middle, and end determinations are not outside of 85– 115 percent of label claim. If two or three of the nine 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, middle, and end determinations are not outside of 85–1 15 percent of label claim, an additional six containers should be sampled at the beginning, middle and end of the canister (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 27 determinations, none of the 27 determinations is outside of 75–125 percent of label claim, and the means for each of the beginning, middle, and end determinations are not outside of 85–1 15 percent of label claim.

k. Particle Size Distribution

One form of control which is more critical for inhalation aerosols than for most other conventional drug products is particle size distribution of the delivered dose. This parameter is dependent on the formulation, the valve, and the mouthpiece. The optimum aerodynamic particle size distribution for most inhalation aerosols has generally been recognized as being in the range of 1 –5 microns.

From a pharmaceutical viewpoint, the most important parameter for an inhalation product is usually the aerodynamic particle size distribution of the outgoing aerosol. The aerodynamic particle size distribution is influenced by the characteristics of the spray of the drug product, as well as other factors, and is not solely determined by the size of the individual drug substance particles initially suspended in the formulation.

A multistage cascade impactor fractionates and collects particles of one or more drug components 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 size fraction of the dose. It also provides information that allows for 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, the size and shape of the expansion chamber, or inlet stem, the selection of impaction surfaces, and the method, accessories, and adapters by which the inhalation aerosol is introduced 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.

Other critical variables that should be specified and controlled in such a test procedure are relative humidity and temperature. Particles may undergo changes during their passage into or through the cascade impactor depending on humidity and temperature conditions. The most common problems associated with humidity are hydroscopic growth and aggregation of particles. Creating atmospheres of controlled temperature and relative humidity by introducing equilibrated air into the system can minimize variability from these sources.

The number of actuations needed to determine particle size distribution by multistage cascade impactor should be kept to the minimum justified by the sensitivity of the analytical method 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 actuation variation.

The aerodynamic particle size distribution analysis and the mass balance obtained (drug substance deposited on surfaces from the valve 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 actuation 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 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*, *respirable dose,* or *fine particle mass* are not considered adequate to characterize the particle size distribution of the whole dose.

1. Microscopic Evaluation

Before the advent of the impactor particle sizing methods, microscopic examination of the formulation was used to determine drug substance particle size. This method is relatively crude in measurement capability, is subjective, and does not provide a profile of the aerodynamic size of the delivered particles of

drug substance. Furthermore, microscopy does not usually account for density of the particles and may not easily distinguish between, for example, two drug substances in a formulation. However, microscopic examination of the formulation has certain merits and, therefore, should be retained for release and stability purposes. For example, the examination provides information on the presence of large particles, changes in morphology of the drug substance particles, extent of agglomerates, crystal growth, and foreign particulate matter. Additionally, where the crystalline form of the drug substance can affect the bioavailability, performance, stability, or other properties of the drug product, microscopic evaluation or other appropriate methods are recommended to control and monitor the morphic form if changes are observed on stability.

m. Spray Pattern and Plume Geometry

Characterization of spray pattern and plume geometry are important for evaluating the performances of the valve and the actuator. Various factors can affect the spray pattern and plume geometry, including the size and shape of the actuator orifice, the design of the actuator, the size of the metering chamber, the size of the stem orifice of the valve, the vapor pressure in the container, and the nature of the formulation. Currently, it is recommended that spray pattern testing should be performed on a routine basis as a quality control for the drug product. However, the characterization of plume geometry should be established during the development of the product and is not necessarily tested routinely thereafter (refer to discussion of plume geometry testing in section IV.A. 10).

The proposed test method for spray pattern, including sampling plans, should be provided in detail to allow their duplication by Agency laboratories. For example, in the evaluation of the spray pattern, the actuation distance between the mouthpiece and the plate, number of actuations per spray pattern, position and orientation of the plate relative to the mouthpiece, and visualization method 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 (mm) 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 method specific for the drug substance, at different distances (e.g., two) from the mouthpiece to provide greater discriminatory capability to the test. Variability in the test can be reduced by developing a sensitive detection method and by providing method-specific training to the analyst.

n. Leak Rate

To maintain optimal performance characteristics for the drug product, acceptance criteria for the leak rate should be based on historical data including primary stability data using the test and sampling plan described in the USP <601>. Leak rate testing should be performed in addition to both the on-line leak test which culls out the occasional gross leakers and the testing that follows the lag or equilibration time instituted before the release of MDIs. The leak rate test is important in stability studies because it may provide information on pressure loss and may predict, at subsequent test stations, failures in testing for dose content uniformity through container life (see section III.F. 1 j). It should be noted, however, that leak rates are not necessarily constant over time.

Leak rates for propellants within the same drug product line are usually independent of the formulation volume filled, since the containers and closures (i.e., seals) used are usually the same. As a result, selective leakage of the propellants may concentrate the content of a smaller container faster relative to that of a larger container, to a point where, for example, dose content uniformity or particle size distribution or both would be outside of the acceptance criteria. Therefore, smaller containers may have shorter expiration dating periods than larger containers of the same drug product when the same seals are used.

o. Pressure Testing

This test is recommended for MDI products that are formulated using a cosolvent and/or more than one propellant. The test verifies the internal pressure of the container and ensures the use of proper propellants or propellant mixture ratio. A reasonable and achievable acceptance criteria may be 5 percent variation around the target pressure at specified conditions. An appropriate sampling plan should be used that selects a representative number of canisters from the batch (e.g., beginning, middle, and end of a fill run).

p. Valve Delivery (Shot Weight)

This test is directly related to the metering ability of the valve, and it evaluates valve-to-valve reproducibility of the drug product. The proper performance of a metering valve should be ensured primarily by the valve manufacturer, who should assemble the valve with parts of precise dimensions. Valve delivery should be verified by the applicant for each drug product. In general, metered dose valves should have a valve delivery acceptance criteria of NMT $|\pm 15|$ percent for individual actuations and NMT $|\pm 10|$ percent for the mean of the actuations relative to the target.

q. Leachable

The drug product should be evaluated for compounds that leach from elastomeric, plastic components or coatings of the container and closure system, such as polynuclear aromatics (PNAs), nitrosamines, monomers, plasticizers, accelerators, antioxidants, and vulcanizing agents, The development of appropriate analytical methods to identify, monitor, and quantify the leached compounds in the drug product should be done during investigational studies. These validated methods can, in turn, be used for testing of the drug product throughout the expiration dating period. Appropriate acceptance criteria for the levels of leached compounds in the formulation should be established. For additional discussion, refer to the container and closure section of this guidance (section 111. G).

2. DPIs

The following test parameters are recommended for DPI drug products. Appropriate acceptance criteria and validated test methods should be established for each test parameter.

a. Appearance and Color

The appearance of the content of the container (formulation contained in dose unit for pre-metered and reservoir for device-metered) and the appearance of the device components should conform to their respective descriptions as an indication of the drug product integrity. If there is any color associated with the formulation (either present initially or from degradative processes occurring during shelf life), then a quantitative acceptance criterion should be established for the drug product formulation.

b. Identification

See MDIs, section III.F. 1.b.

c. Microbial Limits

See MDIs, section III.F. 1.c.

d. Water or Moisture Content

Water in the drug product should be strictly limited since it may have a significant effect on characteristics such as aerosolization of the particles, particle size

distribution, crystallinity, dose content uniformity, microbial content, and stability.

e. Net Content (Fill) Weight (Device-metered)

DPIs that have a reservoir containing the bulk formulation to be metered should have a test and acceptance criteria for the weight of the contents. See MDIs, section III.F. 1.f.

f. Drug Content (Assay)

This test determines the amount of the drug substance in each individual dosage unit for pre-metered DPIs and in the reservoir for device-metered DPIs. The assay should be determined analytically with a stability indicating method. The acceptance criteria should be tight enough to ensure conformance in other related attributes (e.g., dose content uniformity).

g. Impurities and Degradation Products

See MDIs, section III.F. 1.h.

h. Dose Content Uniformity

The recommendations for acceptance criteria and tests for emitted dose content uniformity from the mouthpiece of DPIs under defined optimum test conditions are the same as for MDIs (refer to section III.F.1.i .). Both air flow rate and total volume of air drawn through the device should be thoroughly evaluated to obtain optimum test conditions. It is recommended that the volume of air drawn through the device be limited to two liters. Acceptance criteria and tests would apply to both device-metered DPIs and pre-metered DPIs (e.g., blisters, capsules). In the case of device-metered DPIs, the dose content uniformity should be established and monitored at the beginning, middle, and end of the labeled number of doses. In addition, the content uniformity of the pre-metered dose units should be controlled by a separate test and acceptance criteria, for example USP <905> Uniformity of Dosage Units by assay.

i. Dose Content Uniformity Through Container Life (device-metered)

Refer to MDIs (section III.F. 1.j) and the discussion of the Dose Content Uniformity tests and acceptance criteria above (section HI. F.2.h).

j. Particle Size Distribution of Emitted Dose

Refer to MDIs (section III.F. 1 k). The emitted particle size distribution under defined test conditions should be determined by multistage cascade impaction to profile the aerodynamic diameters of the drug substance particles. The equipment and accessories should be selected so that the majority of the dose is introduced into the cascade impactor for fractionation. A complete profile of the dose including the finer particles (e.g., less than or equal to 2 pm) should be determined.

Additional testing parameters should be considered for DPIs, as compared with MDIs, to maximize reproducibility and limit the variability to that inherent to the DPI. This is important because of intrinsic differences between formulations, devices, and methods of dose delivery of DPIs and MDIs. For example, since DPI formulations are necessarily dry, selection of and specifications for the impaction surface may be more critical in terms of re-entrainment of impacted particles. Because powders are not typically propelled from the device, more consideration may need to be given to flow rate selection and duration. For routine testing, the same flow rate and duration should be used as for dose content uniformity testing.

In general, DPI formulations maybe more sensitive to varying humidity conditions during particle size distribution determinations, necessitating tighter control of this condition. In the case of device-metered DPIs, the particle size distribution of the drug substance within the formulation should be established and monitored at the initial dose and the last dose of the labeled number of doses.

k. Microscopic Evaluation

Appropriate acceptance criteria should be instituted for the appearance of the drug product formulation using a microscopic test approach. This testis useful for detection of large particles and agglomerates of the drug substance, can define morphology of drug substance and carrier particles, and can detect foreign particulate matter. The type, origin, and profile of foreign particulate, including fine particulate, should be controlled. Refer to the section on microscopic evaluation of MDIs (section III.F. 1.1).

G. Container and Closure Systems

1. MDIs

One significant difference between MDI drug products and other, more conventional drug products is that the clinical efficacy of MDIs may be directly dependent on the design, reproducibility, and performance characteristics of the container and closure system. In MDIs, the container and closure system consists of the container, the actuator, the valve and its components, and any additional accessories (e.g., spacer), as well as protective packaging if applicable. For MDIs, the use of some type of dose counting mechanism should be considered.

Since inhalation aerosol formulations include organic liquids as the propellant or the vehicle (e.g., chlorofluorocarbons, hydrofluorocarbons, alcohols), potential leaching of compounds from the elastomeric and plastic components of the container and closure system into the formulation is a serious concern that should be addressed. Therefore, the composition and quality of the materials used in the manufacture of the container and closure system components should be carefully selected. For safety considerations, materials should be chosen that minimize or eliminate leachable without compromising the integrity or the performance of the drug product.

Identity and concentration profiles of the leachables in the drug product or placebo formulation (i.e., drug product formulation without drug substance) should be determined through the end of the drug product's shelf life and correlated, if possible, with the extractable profile(s) of the container and closure components determined under the various control extraction study conditions. Such a correlation may obviate the need to evaluate leachable in the drug product formulation in future routine stability studies. Note that for ANDAs, the applicant may compare the extraction profiles of the container and closure components with the leachable profile(s) of the drug product (or placebo) after storage under accelerated stability conditions for three months, as long as a commitment is provided to confirm the results for the drug product (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 methods, and sampling plans used for each component of the container and closure system to ensure its suitability for

G. Container and Closure Systems

1. MDIs

closure systems, refer to FDA's guidance *Submitting Documentation for Packaging for Human Drugs and Biologics* (February 1987).'

a. Container

Concerning the container (canister), the following information should be included in the drug application:

- Source(s) and fabricator(s)
- Item number
- Composition and quality of materials (including coating, if appropriate)
- Schematic drawing
- Precise dimensional measurements
- Quality of the inside surface
- Description of the cleaning procedures
- Control extraction studies (when coated)
- Examination for residual contaminants and residue from canister washing
- Toxicological evaluation, where appropriate, of the extracted materials and residues
- Acceptance criteria, test methods, and sampling plans including:
  - Physiochemical parameters and dimensional measurements
  - Quality of inside surface
  - Qualitative and quantitative extractable profile(s)

Additional information on select topics is provided below.

i. Source, Composition, and Physical Dimensions

The source, composition, and physical dimensions of the components should be specified. The composition of the container and coating material (if applicable) should be provided in the application and/or an appropriately referenced DMF. Specific citations to the food additive regulations for the materials used in fabrication and treatment of the container, where applicable, should be provided. A toxicological appraisal of the extractable and residual materials should be submitted in the application. For guidance on such safety data, applicants are encouraged to contact the responsible review division.

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[2] 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.

ii. Control Extraction Studies

The purpose of the control extraction study is to define an acceptable quantitative extractable profile(s) under specified test conditions, and establish acceptance criteria for each of the extracts from the components used for the submitted batches (e.g., clinical, preclinical, biobatch, primary stability, production). The extractable profile(s) of the specified container should be established and documented both qualitatively and quantitatively under defined experimental conditions. The documentation should include the sampling plan, component tested, type and amount of solvent, temperature, duration, extraction method, methods of analysis, and data. Solvents of various polarities should be used for initial determination of the profiles. Use of different solvents to maximize the extraction of different extractable may be necessary. Typically, the extraction solvent(s) would include the propellant(s) and formulation cosolvent(s), but a more effective extraction solvent could be used instead.

For coated containers, control extraction studies should be performed and the profile of each extract should be evaluated both analytically and toxicologically. The toxicological evaluation should include appropriate in vitro and in vivo tests. A rationale, based on available toxicological information, should be provided to support acceptance criteria for components in terms of the extractable profile(s). A toxicological appraisal of the extractable should be provided and the results of USP Biological Reactivity Tests (USP <87> and <88>) should also be submitted.

iii. Residue Studies

A profile of residues from manufacture or cleaning of the component should be developed. A rationale, based on available toxicological information, should be provided to support acceptance criteria for components in terms of the residual contaminants profile(s). A toxicological appraisal of the residues from manufacture or canister cleaning should be provided and the results of USP Biological Reactivity Tests (USP <87> and <88>) should be submitted.

iv. Routine Extraction and Residue Tests

Based on the analytical and toxicological evaluation of the extractable from both the control extraction and residue studies, the applicant should establish discriminatory test methods and set appropriate acceptance criteria for the extractable profile and the residues for routine testing of incoming containers. Test methods and sampling plans should be provided. The accuracy, precision,

specificity, sensitivity, and ruggedness of each method should be documented with proper standards during validation in the control extraction studies.

v. Acceptance Criteria

Acceptance criteria should be established for dimensional measurements, particularly for critical parts of the container. Acceptance criteria should also be established for the quality of the inside surface, profile(s) of the extractable (when coated), and residual contaminants.

For the extractable and residual contaminants 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 containers.

b. Valves

A properly performing valve of an inhalation aerosol drug product should ensure leak-proof sealing of the container, while in use and during storage. The valve should repeatedly dispense the aerosolized drug in discrete, accurate, small doses in the desired physical form. The performance of the valve and its compatibility with other drug product components should be thoroughly investigated before initiating critical clinical and/or bioequivalence studies. The specific valve used in each MDI drug product should be carefully selected considering the type and critical dimensions of the container, the formulation, stem diameter, stem groove dimensions, if applicable, the stem and body orifices of the valve, and so on. The information submitted in support of the valve in a drug application should include the following:

- Source(s) and fabricator(s) of the assembled valve
- Source(s) and fabricator(s) for each part of the valve
- Item numbers of different parts of the valve
- Item number of the assembled valve
- Schematic engineering drawings of valve components
- Precise dimensional measurements of valve components
- Composition and quality of materials of the valve components
- Treatment procedures of elastomeric components (e.g., cleaning, pre-extraction, washing, drying) before valve assembly
- Control extraction studies for elastomeric and plastic components
- Toxicological evaluation of extractable
- Acceptance criteria, test methods, and sampling plans

- Physiochemical parameters and dimensional measurements
- Qualitative and quantitative extractable profile(s)
- Performance characteristics of the valve

Additional information on select topics is provided below.

i. Source, Composition, and Physical Dimensions

The source, composition, and physical dimensions of the components should be specified. The dimensional measurements of metering valve components should be held to very tight tolerances through precision measurements. The composition of the valve should be provided in the application and/or an appropriately referenced DMF. Specific citations to food additive regulations for materials used in fabricating the valve, where applicable, should be included. A toxicological appraisal of the extractable, which may consist of supportive citations and additional safety data, should also be submitted in the application. For guidance on such safety data, applicants are encouraged to contact the responsible review division.

The compatibility of the selected valve component materials with the formulation should be investigated to avoid problems. For plastic components, the potential of drug sorption, swelling of the plastic, and leaching of contaminants from the plastics into the drug product (e.g., monomers, plasticizer, accelerators, release agents) should be investigated. Special attention should be paid to elastomeric components such as the mounting cup gasket, o-ring, diaphragm (stem gasket), and tank seal (metering) gasket. The elastomers may adsorb and/or absorb drug substance, release additional leachable into the formulation (e.g., PNAs, nitrosamines, vulcanization accelerators, retarders, lubricants, plasticizers, antioxidants), and swell to various degrees, which may alter the performance and/or toxicological profile of the drug product.

ii. Pre-extraction

Since inhalation aerosol formulations include organic liquids as the propellant or the vehicle (e.g., chlorofluorocarbons, hydrofluorocarbons, alcohols), potential leaching of compounds from the elastomeric and plastic components of the device into the formulation is a serious concern. To ensure potential leachable in the drug product are minimized, each production batch of elastomeric components used in the valve should be pre-extracted prior to assembly, unless data obviate such an approach. The extraction procedure should be optimized to remove the maximum amount of potentially toxic leachable without compromising the

integrity or performance of the elastomeric valve components. A detailed description of the pre-extraction procedure should include information such as the quantities of elastomeric valve component(s) and selected solvent(s), method and duration of extraction procedure, temperature, as well as additional cleaning, washing, and drying procedures. Each of the pre-extraction processing parameters may have an effect on the quality and purity of valve components and, ultimately, the amount of leachables that may enter into the final drug product formulation upon storage.

iii. Control Extraction Studies

See section III.G.1.a.ii for general information on control extraction studies. To verify the efficiency of the pre-extraction procedure for the elastomeric components and the quality and purity of other valve components, the components should be subjected to control extraction studies using selected representative samples and appropriate solvent(s). 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 methods (e.g., chromatography with mass spectroscopy), to identify and quantify each extractable and establish appropriate acceptance criteria. The toxicological evaluation should include appropriate in vitro and in vivo tests. The results of USP Biological Reactivity Tests (USP <87> and <88>) should be submitted. A rationale, based on the available toxicological information, should be provided to support the limits specified for major components of the extractable profile. Because some extractable components from rubber 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.

iv. Routine Extraction Tests

Based on the analytical and toxicological evaluation of the extractable from the control extraction study, the applicant should establish discriminatory test methods and set appropriate acceptance criteria for the extractable profile(s) for routine testing of the incoming individual valve components. This testing will verify the efficiency of the pre-extraction procedure for the elastomeric components and provide continued assurance of the batch-to-batch consistency of the quality and purity of the valve components. Test methods and sampling plans should be provided. The accuracy, precision, specificity, sensitivity, and ruggedness of each method should be documented with proper standards during validation in the control extraction studies.

v. Acceptance Criteria

The application should include specifications for each component of the valve and the assembled valve itself. The specification should be comprised of dimensional measurements, physiochemical parameters, and individual and total extractable for the different valve components as outlined above under the discussion of the control extraction studies. In addition, the specifications should include performance characteristics of the assembled valve (e.g., valve function, valve delivery, valve leakage). All proposed acceptance criteria should reflect the test results of valves used in submitted drug product batches (e.g., clinical, primary stability, biobatch, and production batches, all using identical valves). If the information outlined above is generated by the valve manufacturer through authorized DMFs, applicants should also develop or have access to the necessary analytical and other methods that will allow them to verify the reliability of the supplier's test results at appropriate intervals.

For the extractable profiles, a reduced acceptance testing schedule maybe considered once the applicant establishes the reliability of the supplier's test results. The applicant should confirm the results by testing individual valve components from multiple batches of incoming valves.

c. Actuator/Mouthpiece and Additional Accessories

For inhalation aerosols, the actuator and additional accessories, if applicable, have important roles in generating aerosol particles, directing the dose, influencing the velocity of the aerosol particles, and controlling the amount of available medication to the patient. If accessories (e.g., spacer, holding chamber) are attached to the actuator, the pertinent information and controls outlined below for the actuator should also be provided for these parts.

Information submitted in support of the actuator should include the following:

- Source(s) and fabricator(s)
- Item number
- Schematic drawings
- Precise critical dimensional measurements
- Composition and quality of materials
- Control extraction studies
- Toxicological evaluation of the extractable
- Acceptance criteria, test methods, and sampling plans including:

- Physiochemical parameters and dimensional measurements
- Qualitative and quantitative extractable profile(s)
- Performance characteristics

Additional information on select topics is provided below.

i. Source, Composition, and Physical Dimensions

The source, composition, and physical dimensions of the components should be specified. The composition of the materials used in the fabrication of the actuator should be provided in the application and/or in an appropriately referenced DMF(s). Specific citations to food additive regulations for materials used in fabricating the actuator, where applicable, should be included. If the materials are not recognized as safe for food contact under appropriate regulations, additional safety data may be needed. For guidance on such safety data, applicants are encouraged to contact the responsible review division.

The size, shape, tolerances, and design of the actuator, actuator orifice, and the valve stem holder are critical to the function of the actuator. Dimensional acceptance criteria for these components should be precisely defined.

ii. Control Extraction Studies

See section III.G. 1.a.ii for general information on control extraction studies. For actuators, the profile of each specified extract should be established and documented both qualitatively and quantitatively under defined experimental conditions. Each extract should be evaluated both analytically and toxicologically. The toxicological evaluation should include appropriate in vitro and in vivo tests. A rationale, based on available toxicological information, should be provided to support acceptance criteria for components in terms of the extractable profile(s). The toxicological information should include the results of appropriate in vitro and in vivo tests. Safety concerns will usually be satisfied if the materials in the components meet food additive regulations and the actuator meets the USP Biological Reactivity Tests (USP <87> and <88>).

iii. Routine Extraction Tests

Based on the analytical and toxicological evaluations of the extractable from the control extraction study, the applicant should establish discriminatory test methods and set appropriate acceptance criteria for the extractable profile(s) for routine testing of incoming actuator component(s). This will ensure batch-to-

batch consistency of the components using appropriate, validated analytical methods. Test methods and sampling plans should be provided. The accuracy, precision, specificity, sensitivity, and ruggedness of each method should be documented with proper standards during validation in the control extraction studies.

iv. Acceptance Criteria

Appropriate acceptance criteria, test methods, and sampling plans should be provided for the dimensional measurements, physiochemical parameters, qualitative and quantitative profiles for extractable, and performance characteristics (e.g., plume geometry, spray pattern, velocity).

In terms of the extractable profiles, a reduced acceptance testing schedule maybe considered once the applicant establishes the reliability of the supplier's test results. The applicant should confirm the results by testing multiple batches of incoming actuator component(s) and, if applicable, accessories.

2. DPIs

As w-ith MDIs, the clinical efficacy of a DPI drug product may be directly dependent on the design, reproducibility, and performance of the container and closure system. The container and closure system consists of the overall device with all primary and protective packaging (e. g., overwrap). The design, composition, and quality control of the individual components of the container and the closure are key to maintaining the chemical and physical stability of the formulation and ensuring that the performance characteristics of the drug product (e.g., dosing and particle size distribution) are reproducible and in accord with label claim. During development and before initiating critical clinical studies, the performance characteristics of the device and its compatibility with the formulation should be thoroughly investigated. A properly performing DPI should deliver accurate, small doses of the drug substance in the desired physical form through the life of the device. Additionally, for device-metered DPIs, some type of dose counting mechanism is recommended. From a clinical perspective, it is also recommended that a mechanism that would prevent unintentional multiple dosing be included. If used, these mechanisms should be described in the application. For additional information on container and closure systems, refer to FDA's *Guideline for Submitting Documentation for Packaging for Human Drugs and Biologics* (February 1987).3

[3] Ibid.

Whereas MDIs usually consist of three basic components, i.e., the container, the valve and the actuator/mouthpiece, there is wide diversity of DPI designs with differing characteristics. Nevertheless, the drug application should include the following specific information for device components:

- Source(s) and fabricator(s) of the overall device
- Source(s) and fabricator(s) for each part of the container and closure system
- Item number(s) for each component
- Schematic engineering drawings
- Dimensional measurements
- Composition and quality of materials
- Control extraction studies
- Toxicological evaluation of the extractable
- Device flow resistance
- Acceptance criteria, test methods and sampling plans including:
  - Physicochemical parameters and dimensional measurements
  - Extractable profile(s) of the critical components
  - Performance characteristics

Additional information on select topics is provided below.

a. Source, Composition, and Physical Dimensions

A complete description of the source and composition of all device components should be provided, and each should be identified by number and in schematic drawings with dimensional measurements. Reference to an authorized DMF may be made for this information.

The composition (e.g., resin and additives, colorants) and the quality of materials of each individual device and packaging component for the container and closure system should be carefully selected, and the supporting information provided in the application. The components should be compatible with the formulation, and their functionality should be well established to ensure ruggedness of the assembled device or container and closure system. Specific citations to the food additive regulations for the materials used in the fabrication of critical components of the DPI, where applicable, should be included. If the materials are not recognized as safe for food contact under appropriate regulations, additional safety data may be needed. For guidance on such safety data, applicants are encouraged to contact the responsible review division. The information to support

a component's compatibility with the formulation should be provided in the application or by reference to authorized DMFs.

Additionally, dimensional measurements of the critical components of the device should be held to very tight tolerances through precision measurements. Critical components of the DPI are defined as those that contact either the patient (i.e., the mouthpiece) or the formulation, components that affect the mechanics of the overall performance of the device, or any necessary protective packaging. Submission of a sample of the assembled device as well as disassembled components of the device is recommended to facilitate the application review process.

b. Control Extraction Studies

Control extraction studies should be performed on the critical components, except protective packaging, under defined experimental conditions to determine the qualitative and quantitative extractable profiles. Full documentation of these studies and the resulting profiles should be provided. See section III.G. 1.a.ii for additional information on control extraction studies.

The profile of each critical component extract should be evaluated both analytically and toxicologically. The toxicological evaluation should include appropriate in vitro and in vivo tests. A rationale, based on available toxicological information, should be provided to support acceptance criteria for components in terms of the extractable profile(s). Safety concerns will usually be satisfied if the components that contact either the patient or the formulation meet food additive regulations and the mouthpiece meets the USP Biological Reactivity Test criteria (USP <87> and <88>). If the components are not recognized as safe for food contact under appropriate regulations, additional safety data may be needed. For guidance on such safety data, applicants are encouraged to contact the responsible review division,

c. Routine Extraction Tests

Based on the analytical and toxicological evaluation of the extractable from the control extraction study, the applicant should establish discriminatory test methods and set appropriate acceptance criteria for the extractable profile(s) for routine testing of incoming individual critical device components. Test methods and sampling plans should be provided. The accuracy, precision, specificity, sensitivity, and ruggedness of each method should be documented with proper standards during validation in the control extraction studies.

d. Flow Resistance

The total flow resistance of the device and, preferably, the flow resistance of each of the individual components involved in the flow paths within the inhaler should be characterized and established, Supportive information should be included in the application.

e. Acceptance Criteria

To ensure batch-to-batch reproducibility of the drug product, appropriate acceptance criteria and validated test methods with adequate sampling should be established for incoming critical components of the DPI container and closure system. Specifications should include physiochemical parameters, dimensional measurements, qualitative and quantitative extractable profile(s) of each individual component for indirect control of composition, and performance characteristics of the assembled device (e.g., dose content uniformity, medication retention, metering accuracy where appropriate, device flow resistance).

For the extractable profiles for the critical device components, 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 batches of incoming individual critical device components.

H. Drug Product Stability

Stability studies provide a means for checking acceptable performance of the inhalation unit, as well as the physical and chemical stability of the drug product, including the compatibility of the formulation with the components of the device. The application should contain (1) a complete, detailed stability protocol, (2) stability data, and (3) information regarding the suitability of the test methods 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 methods
- Test intervals
- Container storage orientations

- Test storage conditions
- Type, size, and source of container and closure components
- Quality, purity, and source 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)
- 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 *Submitting Documentation, for the Stability of Human Drugs and Biologics* (February 1987).4 The following additional discussion elaborates on specific aspects of information for MDIs and DPIs that should be included in the application.

a. Test Parameters, Acceptance Criteria, and Methods

The stability test parameters, with appropriate acceptance criteria, should include those tests identified in the release specification of the drug product (refer to section III.F) with the following exceptions: for MDIs, identity of the drug substance, spray pattern, container pressure, and net content weight; for DPIs, identity, fill weight (pre-metered and device-metered), and net content (device-metered). Test methods should be stability indicating where applicable.

b. Test Intervals

The stability test intervals should be indicated in the application. Long-term test intervals of O, 3, 6, 9, 12, 18, 24 months, accelerated test intervals of a minimum of four test time-points for 6 months (e.g., O, 1, 3, 6 months), and intermediate test intervals (e. g., O, 3, 6, 9, 12 months) should be included. For ANDAs, the same long-term and intermediate test intervals should be used, but intervals of O, 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.

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[4]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.

c. Container Storage Orientations

The stability of MDIs and, potentially, of some DPIs (depending on design) can be affected by storage under differing orientations. For example, leachable levels, valve appearance, leak rate, and dose content uniformity 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 DPI's 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. 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. If moisture-protective packaging was deemed necessary, additional storage under conditions of 25*2 °C/75±5%RH for one-third of the proposed expiration dating period (or to the scheduled test-interval closest to one-third of the proposed expiration dating period) should be incorporated in the stability protocol for routine testing (refer to Drug Product Characterization Studies, sections IV.A. 1 and IV.B. 1). Stability studies under the various storage conditions may be initiated concurrently. Due to the complexity of these types of drug products, accelerated stability studies (i.e., 40±2 °C/75±5%RH) alone may not be predictive of the product performance throughout the extrapolated expiration dating period.

For NDAs, the first three production batches manufactured post-approval should be placed in the accelerated, intermediate (if applicable), and long-term stability testing program. In addition, these three batches should be placed in the stability testing program under conditions of 25±2 °C/75±5%RH, if applicable, for one-third of the proposed expiration dating period. The approved stability protocol should be used for the above studies. 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 post-approval to be placed on stability.

For ANDAs, refer to *Submitting Documentation for the Stability of Human Drugs and Biologics* (February 1987).[5]

e. Batches, Manufacturing Process, Facilities, Components, and Container and 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 and closure system or device intended for marketing, which should be the same as those used in submitted batches (e.g., clinical, biobatch, primary stability, production). Stability batches identified in the application should be described in terms of the size, manufacturing method, manufacturing site, testing methods and acceptance criteria, and packaging. Applications both for MDIs and DPIs should indicate the type, size, and source of various container and closure components that were used in generating stability data on 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 batches 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 may not be limited to the synthetic method, synthesis site, micronization site, micronization procedure, and testing. This information should also be provided for most excipients, in particular, major excipients (e.g., propellants, carriers) and noncompendial excipients (see section 111. C.2).

g. Sampling Plans

The design of a stability study for complex dosage forms such as MDIs and DPIs should include any special sampling plans. A special sampling plan (e.g., a predetermined number of MDI or DPI units may be randomly or otherwise sampled) may increase assurance that the resulting data for each batch are truly representative of the batch as a whole. In addition, the number of samples to be tested should be increased, if possible, near the end of the study, to better establish the various parameters and confidence levels at either side of the curve for determining the expiration dating period.

[5] Ibid,

For ANDAs, refer to *Submitting Documentation, for the Stability of Human Drugs and Biologics* (February 1987).[5]

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Data should be provided to demonstrate the quality and purity of drug substance batches 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 may not be limited to the synthetic method, synthesis site, rnicronization site, micronization procedure, and testing. This information should also be provided for most excipients, in particular, major excipients (e.g., propellants, carriers) and noncompendial excipients (see section 111. C.2).

g. Sampling Plans

The design of a stability study for complex dosage forms such as MDIs and DPIs should include any special sampling plans. A special sampling plan (e.g., a predetermined number of MDI or DPI units may be randomly or otherwise sampled) may increase assurance that the resulting data for each batch are truly representative of the batch as a whole. In addition, the number of samples to be tested should be increased, if possible, near the end of the study, to better establish the various parameters and confidence levels at either side of the curve for determining the expiration dating period.

[5] Ibid.

h. Statistical Analysis Approaches and Evaluation

Refer to *Submitting Documentation for the Stability of Human Drugs and Biologics* (February 1987).[6]

i. 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 a statement in the stability protocol committing to conduct and/or complete prescribed studies on production batches of a drug after approval,

j. 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.

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 composition) of device and device components; or source or grade of excipient may affect the stability of the drug product. Under such scenarios, additional stability data should be generated for the drug product prepared under the various conditions (as discussed above) so that comparability can be assessed and necessary linkages established between the various batches.

If multiple manufacturing facilities, manufacturing processes, or sources for the components (device or formulation) are intended to be used in the manufacturing of an MDI or DPI, adequate stability data should be generated from each different facility, process, or source. Stability studies should be performed on all sizes of the inhalation drug products (e.g., trade and sample sizes).

In general, the use of bracketing and matrixing protocols may not be appropriate for MDIs and DPIs. If applicants believe that a bracketing or matrixing protocol

[6] Ibid.

is justified, then they are encouraged to contact the responsible 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*.[7]

IV. DRUG PRODUCT CHARACTERIZATION STUDIES

For MDI and DPI drug products, certain studies should be performed to determine appropriate stability test storage conditions. Additional studies should be performed to characterize the optimum performance properties of the drug product and to support appropriate labeling statements. Devices may vary in both design and mode of operation, and these characteristics may be unique to a particular drug product. Drug product-specific information will help define the appropriate storage conditions, facilitate correct use and maintenance of the inhaler, and contribute to patient compliance. For the most part, these are one-time studies, usually performed on a minimum of three batches of drug 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.

A. MDIs

The following additional types of drug product characterization studies should be performed for MDI products. Data should be collected on the product that uses the formulation, container, valve, actuator, and protective packaging (unless otherwise specified below) intended for marketing. The studies should be documented and the results submitted in the application.

1. Determination of Appropriate Storage Conditions

Studies described below and displayed in figure 1 are recommended to determine the appropriate stability test storage conditions (refer to test storage conditions in section III.H. 1.d) for the drug product intended for marketing. Moreover, in terms of stability, these studies assess formulation and container and closure system, and the necessity for secondary or additional protective packaging. The testing scheme in figure 1 is based on assessing whether a significant change occurs. The studies in figure 1 apply equal 1 y for DPIs. The following changes would generally be considered significant:

[7] Ibid.

- A 5 percent change from the initial drug content assay value of a batch;

- A failure to meet established stability acceptance criteria except for dose content uniformity and particle size distribution criteria;

- For dose content uniformity, a 10 percent change in the mass of the mean dose (beginning, middle, and end means determined separately) at any test interval relative to the initial time-point value or failure to meet the established acceptance criteria for the first tier of testing (refer to sections III.F.1.i and 111. F.2.h);

- For particle size distribution, generally a greater than 10 percent change in the total mass of relevant fine particles (e.g., particles less than 5 micrometers) within the particle size distribution or a shift in the profile for these particles. Note: Due to the complexity of interpreting a shift in the particle size distribution, the magnitude of the shift should be discussed with the responsible review team, e.g., End-of-Phase 2 Meeting.

Initially, the drug product without protective or secondary packaging (e.g., MDI canister, blister units, device-metered DPIs) and in some cases without primary packaging (e.g., capsules for DPIs) should be stored under accelerated conditions of 40±2 °C/75±5%RH (hereafter referred to as 40 °C/75%RH) and tested for all stability parameters at the test intervals described above in section III.H.1.b.

a. No significant change for all parameters after storage at 40 °C/75%RH

If no significant change has occurred after storage at 40 °C/75%RH at the end of test period, for example, six months for NDAs, testing for all parameters should proceed for stability samples stored under long-term conditions of 25±2 °C/60±5%RH, hereafter referred to as 25 °C/60%RH (path A, figure 1).

b. Significant change for any parameter, except particle size distribution and dose content uniformity, after storage at 40 °C/75%RH

If there is any observed significant change (except for particle size distribution or dose content uniformity) after storage under conditions of 40 °C/75%RH for six months, stability studies should be completed for all parameters for the product stored for one year at the intermediate conditions of30+2°C/60+50/ORH, hereafter referred to as 30 °C/600/ORH (path B, figure 1). If no significant change is observed after storage for one year under intermediate conditions, then routine

testing should proceed for stability samples stored under long-term conditions of 25 °C/60%RH (path C, figure 1).

If a significant change occurs under intermediate storage test conditions of 30 °C/60%RH, there maybe several options, for example, reformulation of the drug product, modification of the manufacturing procedure, use of a modified or more protective container and closure system, and/or shortening of the proposed expiration dating period (path D, figure 1). If the product is reformulated, the manufacturing procedure is changed, or the container and closure system is changed or modified, the assessment in figure 1 should be repeated to obtain the necessary stability data (accelerated, intermediate, and long-term) to establish the appropriate expiration dating period, test storage conditions, and stability characteristics of the product (path E, figure 1). If such changes are introduced after preparation of the submitted batches (e.g., clinical, biobatch, primary stability, production), contact the responsible review division for guidance.

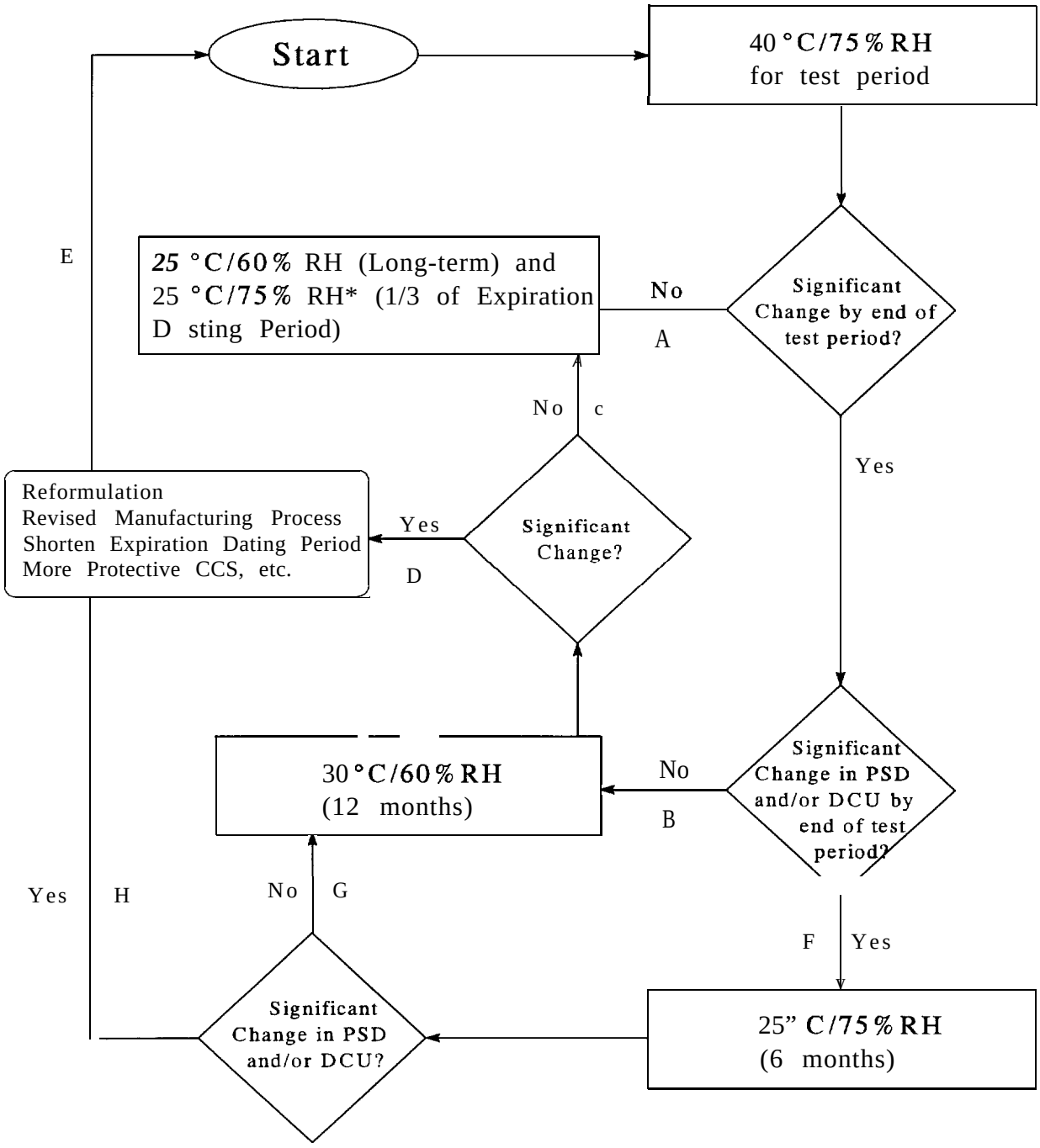
c. Significant change in the particle size distribution or dose content uniformity after storage at 40 °C/75%RH

If a significant change was noted in the particle size distribution or in dose content uniformity for product stored at 40 °C/75%RH, additional testing for the affected parameter should be performed for the drug product stored for 6 months at 25 °C/75%RH (path F, figure 1).

If a significant change was noted in the particle size distribution or in dose content uniformity for product stored at 40 °C/75%RH but not after storage for six months storage at 250C/750/ORH, testing for all stability parameters should proceed under intermediate conditions of 30 °C/600/ORH (path G, figure 1). The results obtained under the intermediate conditions should determine, as described above, the path(s) (C or D and E) that should be followed.

On the other hand, if a significant change is observed in the particle size distribution or dose content uniformity for product stored under 40 °C/75%RH and 25 °C/75%RH conditions for a minimum of six months, this would indicate that protective packaging or other modification is needed (path H, figure 1), After modifications, the assessment outlined in figure 1 should be repeated (path E) to determine the appropriateness of the protective packaging or other modifications under the various stability storage conditions.

Figure 1: Stability Test Storage Conditions



*If protective /secondary packaging is used.

Moreover, if moisture-protective packaging is needed, the routine stability test storage conditions for the product in the presentation intended for marketing should include both long-term storage at 25°C/60%RH **and** testing through to one-third of the proposed expiration dating period for product stored at 25°C/75%RH (or to the scheduled test-interval closest to one-third of the proposed expiration dating period).

2. Stability of Primary (Unprotected) Package

If secondary or additional protective packaging (e.g., foil overwrap) was deemed necessary for the drug product, adequate stability data from a study conducted at a minimum of 25°C and 75%RH should be generated on these units without the protective package to establish the maximum length of time for patient 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 if possible. Periodic reassessment of this time period should be performed post-approval to ensure continued integrity of the primary packaging.

3. Temperature Cycling

For MDI inhalation aerosols, a stress temperature cyclic study should evaluate the effects of temperature and associated humidity changes on the quality and performance of the drug product, under extremes of high and low temperatures, that may be encountered during shipping and handling. Such a study may consist of three or four six-hour cycles per day, between subfreezing temperature and 40°C for a period of up to six weeks. At the end of predetermined cycles, the samples should be analyzed for appropriate parameters and compared with the control drug product. At a minimum, test parameters for MDIs after cycling studies should include particle size distribution, microscopic evaluation, physical appearance of the content, valve component integrity, dose content uniformity, water content, and leak rate. With regard to the appearance of the MDI drug product, one should consider the discoloration of the contents, microscopic evaluation, distortion or elongation of valve components, valve clogging, canister corrosion, and adherence of the drug to the walls of the container or valve components.

4. Effect of Resting Time

A study is recommended to determine the effect of increasing resting time on the first actuation of unprimed MDI units followed immediately by the second and the third actuations. MDI units are only primed prior to initiation of the study. After

resting for increasing periods of time (e.g., 6, 12, 24, 48 hours), content uniformity of the first, second, and third actuations (no priming) should be determined to define the medication profile per actuation. Testing should be performed on MDI containers which have been stored in different orientations (i.e., upright, inverted and/or horizontal). To shorten the length of the study, testing may be performed concurrently on separate samples with progressively longer resting periods.

5. Priming/Repriming

Studies should be performed to characterize the drug product in terms of initial priming and repriming requirements after various periods of non-use. The interval that may pass before the MDI needs to be reprimed to deliver the labeled amount of medication should be determined, as well as the number of actuations needed to prime or reprime the MDI. This information may also be derived from studies similar to the study described in section IV.A.4. Priming and repriming information will be used to support proposed labeling statements.

6. Effect of Storage on the Particle Size Distribution

During primary stability studies for suspension aerosols, the effect of storage on particle size distribution from the initial actuation to the labeled number of actuations should be evaluated to determine any trends (refer to section IV.A.1).

7. Drug Deposition on Mouthpiece and/or Accessories

The amount of drug deposited per actuation on the mouthpiece and any other drug product accessory should be established and documented in the application.

8. Cleaning Instructions

In-use studies should be performed to determine the frequency of cleaning and related instructions to be included in the labeling. For NDAs, it is recommended that MDIs used in clinical studies be sent for testing of pertinent parameters after use (dose content uniformity and the particle size distribution) and, if feasible, the same units be returned for continued patient use.

9. Profiling of Actuations Near Canister Exhaustion

A study should be conducted to determine the profiles of the delivered amount and the aerodynamic particle size distribution of the drug substance of each

individual actuation after the point at which the labeled number of actuations have been dispensed until no more actuations are available (i.e., the canister is empty). These studies help to determine if a proposed overfill of the containers is justified and give a profile of the dose delivery after the labeled number of actuations. A graphical representation of the findings is also recommended.

10. Plume Geometry

A study should be performed to characterize the plume geometry to help evaluate the performances of the valve and the actuator. As with the spray pattern (discussed above in section III.F. 1 m), various factors can affect the plume geometry, such as the size and shape of the actuator orifice, design of the actuator, size of the metering chamber, size of the stem orifice of the valve, vapor pressure in the container, and nature of the formulation.

Plume geometry may be evaluated by a variety of methods, (e.g., the time sequence sound-triggered flash photography method, video tape recording and taking pictures of different frames). The approaches used should allow for a detailed study of the aerosol and droplet development. The plume geometry does not distinguish between drug substance particles and propellant droplets in the plume nor indicate the drug substance density gradient in the aerosol plume, but determines the shape of the complete aerosol mist. For assessing the performance of the valve and actuator, the study of plume geometry is complementary to the spray pattern test, which may directly examine the drug substance particles from the plume. The resulting baseline may be used to compare similar drug products by different manufacturers or when introducing certain changes to an already approved drug product.

11. Microbial Challenge

A study should be performed to determine the viability of microorganisms in drug product formulation that has been inoculated intentionally .

12. In Vitro Dose Proportionality

For MDIs with multiple-strength doses, studies should include characterization of the in vitro dose proportionality in terms of the emitted dose content uniformity and the particle size distribution.

13. Effect of Varying Flow Rates

If the MDI is intended to be marketed with a spacer or similar accessory, a study should be performed to characterize the emitted dose and the particle size distribution as a function of different flow rates at constant volume (e.g., two liters). This important study assesses the sensitivity of the drug product to widely varying flow rates that will be generated by patients of different age and gender and with different severity of disease. A study to assess the effect of increasing waiting periods (e. g., O, 5, 10 seconds) between actuation and initiation of in-flow on the emitted dose and the particle size distribution is encouraged.

B. DPIs

The following additional types of drug product characterization studies should be performed for DPI products. Data should be collected on the product that uses the formulation and the device intended for marketing (protective packaging should be included unless otherwise specified below). The studies should be well documented and the results submitted in the application.

1. Determination of Appropriate Storage Conditions

Studies similar to those for MDIs should be undertaken to determine the appropriate stability test storage conditions (i.e., temperature, humidity) and the necessity for any moisture-protective packaging. For details on these studies, refer to section IV. A. 1 for MDIs.

2. Stability of Primary (Unprotected) Package

If protective packaging (e.g., foil overwrap) was deemed necessary for the drug product device or unit-dose container, adequate stability data conducted at a minimum of 25°C and 75%RH need to be generated for these units, without the protective packaging, to establish or confirm the maximum length of time for use after the protective packaging is compromised. As discussed for MDIs in section IV. A.2., these studies should consider both new and aged drug product. Additionally, a periodic reassessment of the determined period should be performed postapproval to ensure continued integrity of the primary packaging.

3. Effect of Varying Flow Rates

A study should be undertaken to determine the emitted dose and the particle size distribution as a function of different flow rates at constant volume. The total volume should be limited to two liters. This important study assesses the sensitivity of the device to widely varying flow rates that will be generated by

patients of different age and gender and with different severity of disease. For NDAs, to relate these in vitro tests to in vivo performance for DPIs (which are dependent on patient effort for deaggregation and dose delivery), studies should also be conducted to determine what flow characteristics are obtained through the device by adult and pediatric subjects w-ith normal lung function and by adult and pediatric patients with varying degrees of obstructed lung function. To examine the effects of severe limitations of a patient's forced expiatory volume in one second (FEV,) on inspiratory flow rates that can be generated through the device, the use of stable, severe COPD subjects is acceptable.

4. Effect of Storage on the Particle Size Distribution

During primary stability studies for device-metered DPIs, the effect of storage on the particle size distribution from the initial dose to the labeled number of doses should be evaluated to determine any trends (refer to section IV.B. 1).

5. Dose Buildup and Flow Resistance

Studies should be conducted to determine the characteristics of the DPI in terms of dose build-up issues and flow resistance. For further discussion on device flow resistance, refer to section III.G.2.

6. Effect of Orientation

Studies should be undertaken to determine the performance of the device in terms of metered and emitted dose content uniformity, and the particle size distribution at various dosing orientations to demonstrate the ruggedness of the DPI. This study should also include testing the device under different handling situations (e.g., dropping, shaking).

7. In Vitro Dose Proportionality

For DPIs with multiple strength doses, studies should be included for characterization of the in vitro dose proportionality in terms of the emitted dose content uniformity and the particle size distribution.

8. Effect of Patient Use

Studies should be carried out for all types of DPIs to identify the effects of patient use on the characteristics of the drug product. For NDAs, it is recommended that devices used in clinical studies be sent for testing of pertinent performance

parameters and physical attributes after use (e.g., emitted dose, particle size distribution, moisture content, microbial limits) and, if feasible, the same device be returned for continued patient use.

9. Effect of Moisture

A study should be conducted to determine the effect of moisture equilibration of the DPI at various high and low humidity conditions on pertinent parameters (e.g., emitted dose content uniformity, particle size distribution, microscopic evaluation, water content). The purpose of such a study is to assess the effect of different environmental conditions on various interactive forces within the device, which together are responsible for the fluidization and aerosolization behavior of the formulation and, hence, performance.

10. Photostability

Photostability studies for DPIs should be performed using appropriate test conditions, if warranted by the immediate container. For example, if capsules or clear blisters are used for pre-metered DPIs or if the reservoir containing the formulation in a device-metered DPI can receive light exposure, photostability studies should be conducted. 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 *QIB Photostability Testing of New Drug Substances and Products* (November 1996).[8]

11. Profiling of Doses Near Device Exhaustion

For device-metered DPIs that do not incorporate any type of locking mechanism to prevent use after the labeled number of actuations, a study should be conducted to determine the metered dose and emitted dose and particle size distribution profiles from the labeled number of doses until no more formulation can be obtained. For ease of review, the resulting profile data should also be presented in a graphical format.

12. Priming

For device-metered DPIs, consideration should be given to priming the device, in terms of the effect of various orientations or particular handling (e.g., tapping) that

[8] 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.

is necessary to ensure reproducible dose content uniformity and particle size distribution.

13. Fill Weight

For device-metered DPIs, the optimum and minimum fill weight for a given reservoir size and geometry should be investigated and documented to justify the proposed overfill and to ensure consistent dose content uniformity and particle size distribution through the labeled number of doses from the device under use conditions.

14. Device Ruggedness

For pre-metered DPIs that maybe reused repeatedly, a study should be conducted to establish the DPI's performance characteristics (emitted dose and particle size distribution) throughout the life of the device. This study may also address, where applicable, limits of use related to failure of critical device mechanisms (ruggedness). The results of this study would be useful for determining necessary replacement intervals for the pre-metered DPI device.

15. Cleaning Instructions

In-use studies should be performed, if necessary, to determine the frequency of cleaning and related instructions to be included in the labeling.

V. LABELING CONSIDERATIONS

A. MDIs

To achieve consistency and uniformity in the content, product title, and format of MDI labeling, the following information pertinent to MDIs is recommended in the labeling. These comments are not all inclusive, and they are directed mainly at labeling issues unique to NDAs for prescription MDI drug products. See 21 CFR part 201 for additional information regarding the labeling of drug products. In general, labeling for ANDAs should be the same as the reference listed drug.

1. Product Title

To standardize the nomenclature for oral MDIs, the established name of all such drug products should include the designation *(Drug Substance) Inhalation*

Aerosol. For nasal MDIs, the drug product would include the name *(Drug Substance) Nasal Aerosol.* 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 mouthpiece and the valve
- Number of medication actuations per container
- Net content (fill) weight
- Usual dosage
- Excipients (established names)
- Route of administration
- Recommended storage conditions including any warning statements regarding temperature and humidity
- 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
- A statement that the drug product canister should only be used with the mouthpiece provided (e.g., *For oral inhalation with (Drug Product Name) actuator only).*
- Warning statements required under 21 CFR 369.21 (e.g., *storage above 120 'F may cause bursting, keep out of reach of children, do not puncture, do not use or store near heat or open flame, never throw container into fire or incinerator, do not spray into eyes)*
- Warning statements required under 21 CFR 20 1.320(b), if applicable

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 MDI drug products:

- The medication dose delivered to the patient should be expressed by a statement in this section, such as: *Each actuation meters 'x' mcg of drug substance in 'w' mg of suspension (solution) from the valve and delivers 'y' mcg of drug substance, equivalent to 'z' mcg of drug substance base (if applicable) from the actuator (i. e., mouthpiece or* ***nasal adapter).*** The term *approximately* should not be used to modify the medication dose delivered.
- If the drug substance forms solvates or clathrates with the propellants, 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 actuations per container should be included.
- The number of priming actuations needed before using the MDI for the first time and in cases where the aerosol 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 MDI drug product labeling:

- The net content (fill) weight of the container should be stated.
- The number of medication doses expected throughout the shelf life of the drug product should be indicated for each canister fill weight. Qualifying terms such as *at least* and *approximately* should not be used.
- Identification of the actuator and protective cap to be used with the container and valve, including the color and appearance, should be included.
- A statement should be included that the drug inhalation canister should only be used with the drug inhalation aerosol mouthpiece and that the mouthpiece should not be used with any other inhalation drug product.
- A statement should be provided that the correct amount of medication in each inhalation cannot be ensured after the labeled number of actuations from the canister even though the canister may not be completely empty.

Additionally, a statement should be included that the canister should be discarded when the labeled number of actuations has been dispensed.

- Storage conditions should be clearly stated including any warning statements regarding temperature and humidity.
- Any preferred storage orientation should be indicated.
- If protective packaging (e.g., foil overwrap) was deemed necessary and is used for the MDI 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 upon which the package was compromised. The length of time specified should be supported by data in the application (refer to section IV. A.2).
- A statement should be included regarding the appropriate temperature of the MDI before use as well as any requirements for shaking, if necessary (i.e., for suspension products).
- For products that contain chlorofluorocarbons or use chlorofluorocarbons during manufacturing, this section should include the warning statement required under the Clean Air Act (42 U. S .C. 7671 j) and Environmental Protection Agency regulations (40 CFR part 82). Note: The patient instructions should include a similar warning and a statement that the patient should consult his or her physician if there are questions about alternative drug products. Refer to 21 CFR 201.320.
- 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 statement instructing the patient to confirm that the canister is fully seated in the actuator (i.e., mouthpiece or nasal adapter).
  - A statement instructing the patient to confirm the absence of foreign objects in the mouthpiece before using the MDI and after removing the protective mouthpiece cap.
  - A figure that displays the various elements of the MDI (e.g., mouthpiece, cap, canister, sleeve).
  - Instructions for initial priming and repriming of the MDI unit.
  - A statement cautioning against spraying the eyes with the formulation.

- Storage conditions should be clearly stated, including any warning statements regarding temperature and humidity. A statement should be included regarding the appropriate temperature of the MDI at the time of use as well as 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 MDI drug product device, 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 package was removed.
- A statement should be included that the drug inhalation canister should only be used with the drug inhalation aerosol mouthpiece and that the mouthpiece should not be used with any other inhalation drug product.
- Appropriate cleaning instructions should be included (refer to section IV. A.8).
- A statement should be included that the correct amount of medication in each inhalation cannot be ensured after the labeled number of actuations even though the canister may not be completely empty. A statement instructing the patient to keep track of the number of actuations used from the canister should also be included.
- Warning statements required under 21 CFR 369.21 (e.g., *storage above 120°F may cause bursting, keep out of reach of children, do not puncture, do not use or store near heat or open flame, never throw container into fire or incinerator, do not spray into eyes).*
- The warning statement required under 21 CFR 201.320 should be included.

B. DPIs

To achieve consistency and uniformity in the content, product title, and format of DPI labeling, the following information pertinent to DPIs is recommended in the labeling. These comments are not all inclusive, and they are directed mainly at labeling specific for DPI inhalation drug products. See 21 CFR part201 for additional information regarding the labeling of drug products.

1. Product Title

To standardize the nomenclature for oral DPIs, the established name of all such drug products should include the designation *(Drug Substance) Inhalation Powder,* and the metered dose. The name and strength 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
- Metered-dose
- Number of medication actuations per container or device
- Net content (fill) weight (device-metered)
- Usual dosage
- Excipients (established names)
- Route of administration
- Recommended storage conditions including any warning statements regarding temperature, humidity, and light
- Manufacturer's and/or distributor's name and address
- "Rx Only" or "℞ Only" statement
- Lot number
- Expiration date
- Use period once the unit is removed from protective packaging (if applicable)
- NDC number(s)
- Dispensing instructions for pharmacist and additional statements for physician, if applicable.
- Reference to the Patient's Instructions for Use and additional instructional statements (e, g., loading instructions for pre-metered DPIs, inhalation instructions, instructions pertaining to protective caps, etc.)

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 Title 21 for the description of the drug substance and formulation, the package insert should include the following information that is specific for DPI drug products:

- Metered-dose
- Emitted dose delivered from the mouthpiece under specified in vitro conditions should be stated.

- All excipients used in the formulation should be identified by their established names.
- A statement should be included that the amount of drug delivered to the lung will depend on patient factors such as inspiratory flow and peak inspiratory flow (PIF) through the device, which may vary for different asthma and COPD patient populations. The labeling should include typical PIF values for patients within a range of pulmonary function. The details provided on these values should relate the findings of in vivo flow rate studies and describe the relationship of these flow rates to demographics (i.e., adult vs. pediatric and any gender effect) and to the degree of airflow obstruction (i.e., the PIF obtained in subjects with a particular level of FEV_1 decrement). The flow rates given should include the mean rate for any given group and, in parentheses following the mean, the range found in that group.

4. HOW SUPPLIED Section of the Package Insert

- The net content weight of the container should be stated for device-metered DPIs.
- The number of medication doses expected throughout the shelf life of the drug product should be indicated. Qualifying terms such as *at least* and *approximately* should not be used.
- If protective packaging (e.g., foil overwrap) was deemed necessary and is used for the drug product device or unit dose container, this should be clearly stated. In addition, appropriate statements should be included that the content of the protective packaging (e.g., device-metered DPIs, pre-metered multi-dose DPIs, or pre-metered single dose units) should not be used after a specified number of days (e. g., 2 weeks, 30 days) from the date the protective package was removed. The length of time specified should be supported by data presented in the application (refer to section IV. B.2).
- For device-metered DPIs without a locking mechanism, a statement should be provided that the correct amount of medication in each inhalation cannot be ensured after the labeled number of actuations from the unit even though the unit may not be completely empty. Additionally, a statement should be included that the DPI unit should be discarded when the labeled number of actuations has been used.
- Storage conditions should be clearly stated including any warning statements regarding temperature, humidity, and light.

- A brief description of the appearance and color of the body, cap, and other markers of the device should be provided, particularly for ease of identification of different strengths of drugs delivered by the same device.
- Different strengths and special identification markings should be stated.

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.
- Storage conditions should be clearly stated, including any warning statements regarding temperature, humidity, and light.
- If protective packaging (e.g., foil overwrap) was deemed necessary and is used for the drug product device or unit dose container, this should be clearly stated. Appropriate statements should be included that the content of the protective packaging (e.g., device-metered DPIs, pre-metered multi-dose DPIs, or pre-metered single dose units) should not be used after a specified number of days (e.g., 2 weeks, 30 days) from the date the protective packaging was removed.
- For device-metered DPIs, a warning should be included stating that the correct amount of medication in each inhalation cannot be ensured after the labeled number of doses even though the device may not be completely empty. A statement recommending that the device-metered DPI be discarded after the labeled number of doses has been delivered can be included as well.
- Cleaning instructions should be included if appropriate (refer to section IV. B.15).

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 2 10.3(b)(2)).

Container and Closure System: For MDIs, the container, the valve, the actuator, and any associated accessories (e.g., spacers) or protective packaging collectively constitute the container and closure system. For DPIs, the device and all its parts including any protective packaging (e.g., overwrap) constitute the container and closure system.

Drug Product: For MDIs, the formulation, container, the valve, the actuator, and any associated accessories (e.g., spacers) or protective packaging collectively constitute the drug product. For DPIs, the formulation, and the device with all of its parts including any protective packaging (e.g., overwrap) 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)).

Dry Powder **Inhalers/DPIs/Inhalation** Powders: Drug products designed to dispense powders for inhalation. DPIs contain active ingredient(s) alone or with a suitable excipient(s). A DPI product may discharge up to several hundred metered doses of drug substance(s). Current designs include pre-metered and device-metered **DPIs**, both of which can be driven by patient inspiration alone or with power-assistance of some type. Pre-metered DPIs contain previously measured doses or dose fractions in some type of units (e. g., single or multiple presentations in blisters, capsules, or other cavities) that are subsequently inserted into the device during manufacture or by the patient before use. Device-metered DPIs typically have an internal reservoir containing sufficient formulation for multiple doses which are metered by the device itself during actuation by the patient.

Excipient: Formulation component(s) other than the drug substance.

Extractable: For both MDI and DPI drug products, compounds that can be extracted from elastomeric, plastic components or coatings of the container and closure system when in the presence of an appropriate 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.

Leachable: Compounds that leach from elastomeric, plastic components or coatings of the container and closure system as a result of direct contact with the formulation of the MDI.

Metered-Dose **Inhalers/MDIs/Inhalation** Aerosols: Drug products that contain active ingredient(s) dissolved or suspended in a propellant, a mixture of propellants, or a mixture of solvent(s), propellant(s), and/or other excipients in compact pressurized aerosol dispensers. An MDI product may discharge up to several hundred metered doses of drug substance(s).

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

Random Sample: A selection of units chosen from a larger population of such units so that the probability of inclusion of any given unit in the sample is defined. In a simple random sample, each unit has equal chance of being included. Random samples are usually chosen with the aid of tables of random numbers found in many statistical texts.

Specification: A list of tests, references to analytical methods, 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. Acceptance criteria are numerical limits, ranges, or other criteria for the tests described.

ABBREVIATIONS

CCS: container and closure system
CFN: central file number
CFR: Code of Federal Regulations
COPD: chronic obstructive pulmonary disease
DCU: dose content uniformity
DPI: dry powder inhaler
FEV,: forced expiatory volume in one second
GSD: geometric standard deviation
mcg: microgram(s)
MDI: metered dose inhalation aerosol also known as metered dose inhaler
mg: milligram(s)
MMAD: mass median aerodynamic diameter
NF: National Formulary
NMT: not more than
PIF: peak inspiratory flow
PNA: polynuclear aromatic
PSD: Particle Size Distribution
USP: United States Pharmacopeia