Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products - Quality Considerations

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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Revision 1

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Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products – Quality Considerations Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to provide recommendations to industry on the development and manufacture of inhalation aerosols (also known as metered dose inhalers (or MDIs)) and inhalation powders (also known as dry powder inhalers (or DPIs)). The recommendations in this guidance can apply to MDI and DPI products intended for local or systemic effect.

This guidance describes points to consider to ensure product quality and performance for MDIs and DPIs. It describes chemistry, manufacturing, and controls (CMC) information recommended for inclusion in new drug applications (NDAs) and abbreviated new drug applications (ANDAs); however, the principles are applicable to products used during clinical trials, and over the product lifecycle as well. It also provides recommendations on certain aspects of labeling for NDA and ANDA MDI and DPI products.

This guidance does not discuss aqueous-based nasal spray drug products and inhalation solution, suspension, and spray drug products, or the manufacture of drug substances. However, some of the principles of this guidance may be applicable to nasal delivery products. Also, this guidance does not discuss considerations for when an MDI or DPI includes electronic components, software, or novel inhaler components that might affect the performance or reliability of the product. The applicant should refer to the applicable requirements and recommendations outlined in the appropriate regulations and guidances, respectively, from the Center for Devices and Radiological Health (CDRH).

FDA previously published a draft guidance on this topic on November 13, 1998.[2] The present guidance is a revision of the previous draft, updated to reflect current standards and requirements

[1] This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research, in collaboration with the Center for Devices and Radiological Health, at the Food and Drug Administration.

[2] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

to enhance understanding of appropriate development approaches for these products consistent with the quality by design (QbD) paradigm.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. General

MDIs and DPIs are products that deliver one or more drug substances to the site of action through the inhalation route. Both types of products are used to treat lung diseases characterized by obstruction of airflow and shortness of breath, including asthma and chronic obstructive pulmonary disease (COPD), as well as respiratory infections and cystic fibrosis. The inhalation route offers further potential for systemic drug delivery.

MDI products consist of a drug formulation (the drug constituent part) and a container closure system. An MDI drug formulation contains the drug substance(s), either dissolved or suspended, in a (1) propellant, (2) mixture of propellants, or (3) mixture of solvents, propellants, and/or other excipients. An MDI container closure system consists of the device constituent part (i.e., the canister, the actuator, the metering valve), and any additional features (e.g., integrated spacer, integrated dose counter), as well as protective secondary packaging (e.g., an overwrap). MDI products use energy stored in a liquefied gas propellant under pressure for generating aerosols suitable for pulmonary drug delivery.

DPI products also consist of a drug formulation (the drug constituent part) and a container closure system. However, the designs of DPI products differ considerably from those for MDI products. A DPI drug formulation contains the drug substance and excipients including a drug carrier (e.g., lactose). A DPI container closure system consists of the device constituent part and any protective secondary packaging (e.g., an overwrap). Current designs of DPI products include pre-metered and device-metered DPIs, either of which can be driven by a patient's inspiration alone (passive) or with power-assistance of some type (active) for production of drug particles intended for inhalation.

> *Pre-metered DPIs* contain previously measured amounts of drug formulation in individual containers (e.g., capsules, blisters, cartridges, dosing discs) that are inserted into the device constituent part during manufacturing or by the patient before use. The pre-metered dose can be inhaled directly or it can be transferred to a chamber before being inhaled by the patient.

Device-metered DPIs have an internal reservoir containing sufficient quantity of formulation for multiple doses that are metered by the device constituent part during use by the patient.

The performance of MDI and DPI products depends on many key aspects of the drug formulation, container closure system (including the device constituent part), manufacturing, and patient handling. Product and process understanding is therefore critical to: (1) the development and manufacture of these products, (2) the maintenance of product quality and performance through the expiration date under patient use conditions, and (3) the maintenance of product quality and performance over the product life cycle, including continual improvement.

B. Regulatory Status

MDIs and DPIs are combination products (see 21 CFR 3.2(e)).[3] As drug-device combination products, they are subject to the current good manufacturing practice (CGMP) requirements for drugs and devices (see 21 CFR part 4).[4] Further information about the CGMP requirements for combination products is available in the FDA guidance for industry and FDA staff *Current Good Manufacturing Practice Requirements for Combination Products*, including an explanation of a streamlined approach for demonstrating compliance with both drug and device CGMP requirements.

In particular, design controls (21 CFR 820.30) apply to any combination product that includes a device constituent part that is subject to them, including all MDIs and DPIs.[5] Essentially, design control activities confirm that there are no negative interactions between constituent parts, and assure that their combined use results in a combination product that is safe and effective and performs as expected. Guidance for industry on pharmaceutical development addresses product design and development procedures, reflecting quality by design principles.[6] While quality by design and design controls share similar characteristics and goals, the device Quality System regulation (21 CFR 820) includes specific requirements for design development that manufacturers must satisfy.[7]

It may be possible to leverage many aspects of pharmaceutical development as described in ICH Q8(R2) to achieve compliance with design controls. For example, the Quality Target Product

[3] A combination product is composed of two or more of the three types of medical products (i.e., drug, device, and biological product), that are either physically, chemically, or otherwise combined into a "single-entity;" "co-packaged" together; or under certain circumstances distributed separately to be used together as a "cross-labeled" combination product. See 21 CFR 3.2(e).

[4] See 21 CFR part 4 available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=4.

[5] For single-entity and co-packaged combination products, design control requirements apply to the development of the combination product as a whole. For cross-labeled combination product, design control requirements apply only to the device constituent part but should ensure the safety and effectiveness of the device when used with the other constituent part(s) of the combination product.

[6] See FDA guidance for industry *Q8(R2) Pharmaceutical Development*, ICH.

[7] For example, requirements under 21 CFR 820 for design control, purchasing controls, management responsibility and corrective and preventive action must be met. See Current Good Manufacturing Requirements for Combination Products at: https://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm for additional information regarding options for complying with the requirements of 21 CFR 820 for a combination product.

Profile (QTPP) (see section III.A. below) is similar to "design inputs" (21 CFR 820.30(c)), which ensure that design requirements are appropriate to address the intended use of the product. Further, studies conducted to verify that the critical quality attributes (CQAs) are met in the finished product may also address requirements for design "verification" and "validation" (21 CFR 820.30(f), (g)), which ensure that the product's "design outputs" (21 CFR 820.30(d)) result in a product that safely and effectively meets user needs and achieves its intended effects.[8]

MDI and DPI applicants must ensure that their development and manufacturing procedures and documentation satisfy all regulatory requirements applicable to their combination product, including for design control (some of which may be satisfied by following Q8(R2) as previously noted). This guidance offers recommendations for how to pursue product development and manufacture in a compliant manner, generally using concepts and terminology familiar to drug sponsors and manufacturers to do so.

III. MDI and DPI PRODUCT DEVELOPMENT

A. Quality Target Product Profile (QTPP)

Prior to the development of an MDI or DPI, the applicant should establish the desired quality target product profile (QTPP). The QTPP is a prospective summary of the quality characteristics of a drug product, and in this case, the combination product, that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the MDI or DPI (ICH Q8(R2)).[9] Examples of QTPP elements for MDIs and DPIs include: proposed dosage form and delivery system, strength (e.g., targeted metered dose for DPIs, targeted delivered dose for MDIs), purity, stability, and aerodynamic performance.

B. Critical Quality Attributes (CQAs)

1. *MDI and DPI Products*

Early in the development process of an MDI or DPI, the applicant should develop a list of potential CQAs for the combination product. A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality (ICH Q8(R2)). Those aspects of the design of the combination product that are essential for proper functioning of the product are also considered part of the required design output (21 CFR 820.30(d)). Knowledge of the QTPP for the product, in combination with information from prior knowledge, risk assessments, and/or experimentation, can be used to develop the list of product CQAs. The list of product CQAs can be modified as product development progresses and new knowledge is gained. CQAs for the

[8] Additional requirements for design control include preparation of a design plan (21 CFR 820.30(b)) and holding review meetings with specified personnel in attendance (21 CFR 820.30(e)). See Current Good Manufacturing Requirements for Combination Products for additional information regarding design control requirements for combination products and other CGMP requirements for combination products that include a device constituent part.

[9] See FDA guidance for industry *Q8(R2) Pharmaceutical Development*, ICH.

drug substance(s), excipients, and container closure system (including the device constituent part) should also be developed (see below).

For MDIs, potential product CQAs typically include assay, impurities and degradants, delivered dose, aerodynamic particle size distribution (APSD), spray pattern, leachables, alcohol/excipient content, foreign particulate matter, moisture content, net content (drug substance and excipients), microbial load and device constituent part characteristics such as component dimensions and valve delivery (shot weight). The force and distance necessary to advance the dose counter[10] and the product actuation force (force to deliver the drug from the device constituent part) are CQAs. If the MDI product is actuated by the patient's inhalation, the air flow necessary to actuate the device for drug release can be considered a CQA.

For DPIs, potential product CQAs typically include assay, impurities and degradants, delivered dose, APSD, volatile/semi-volatile leachables content, foreign particulate matter, moisture content, net content, microbial load, and device constituent part characteristics such as specific resistance to air flow.

Each CQA, either alone or in concert with other CQAs, should relate to one or more elements of the product QTPP. Some of the elements of the QTPP can be related to CQAs of the device constituent part as well as to CQAs of the product formulation. For example:

- Delivered drug purity is usually related to the following CQAs: impurities and degradants of the drug substance and excipients, foreign particulate matter, and amount of leachables (e.g., from the device constituent part, container components, or manufacturing environment).

- Targeted delivered dose (product strength) for MDIs is usually related to the following CQAs: assay, metered dose, and net content.

- Aerodynamic performance for MDIs is usually related to the following CQAs: delivered dose, APSD, spray pattern, moisture content, net content, device constituent part CQAs, and drug substance CQAs.

- Targeted metered dose in a device-metered DPI is usually related to the following CQAs: the device constituent part CQAs (e.g., dimensions of metering components) and the physicochemical properties of the formulation.

Additional relationships between QTPP elements and CQAs for MDIs and DPIs are shown in Table A, Table B, and Table C in the Appendix, section V.A.

2. *Drug Substance*

The physical, chemical, and microbiological properties of the drug substance that should be within an appropriate limit, range, or distribution to ensure the desired product quality are

[10] See FDA guidance for industry *Integration of Dose-Counting Mechanisms into MDI Drug Products*.

considered CQAs of the drug substance. These should be identified and characterized early in development. Additional characterization can take place throughout the development and life cycle of the product.

For drug substances used in MDIs or DPIs, potential CQAs can include assay, particle size distribution (PSD), moisture content, bulk density, flow properties, morphic form (e.g., amorphous, crystalline, hydrate), morphology of drug particles (e.g., shape, crystal habit, texture, surface area, rugosity), residual solvent content, and impurities.

3. *Excipients*

The physical, chemical, and microbiological properties of the excipients that should be within an appropriate limit, range, or distribution to ensure the desired product quality are considered CQAs of the excipients. These should be identified and characterized early in development. Prior knowledge can be particularly useful in identifying the CQAs of excipients since many excipients are already used in similar products.

The potential impact of an excipient on product quality can depend on the intrinsic characteristics and properties of the excipient chosen, and the amount of the excipient used in the formulation. Examples of potential CQAs for excipients used in MDIs or DPIs can include: assay, boiling point and vapor pressure, moisture content, density, impurity profile, particle morphology (e.g., shape, crystal habit, texture, surface area, rugosity), flow properties, amorphous content, microbial limits, pyrogens or bacterial endotoxins, and PSD.

4. *Container Closure System (Including the Device Constituent Part) for MDIs*

The container closure system for an MDI consists of the device constituent part (i.e., canister, the actuator, the metering valve), including any additional features (e.g., integrated spacer, integrated dose counter). It can also include protective secondary packaging. Critical device constituent part components are those that may come into contact with the formulation or the patient, or are necessary for device function.

The materials used to fabricate the MDI device constituent part may come into direct contact with either the formulation or the patient, thereby potentially affecting product safety and performance. For example, due to the presence of organic propellant/vehicle in MDI formulations, leaching of compounds from the valve and/or canister components of the container closure system into the formulation can occur, which is a potential safety or effectiveness concern. Device constituent part materials also have the potential to affect the aerodynamic performance of the MDI product. For example, delivered dose and APSD of the MDI product can be affected by the surface properties of the device constituent part and/or its components. Therefore, the properties of materials used in the fabrication of the device constituent part and the quantitative compositions after fabrication should be considered CQAs.

The device constituent part (e.g., actuator orifice, mouthpiece, metering chamber) has an important role in generating aerosol particles, determining the aerosol characteristics, and controlling the amount of medication available to the patient. For instance, the actuator orifice

size can affect the APSD, spray velocity, plume geometry, and spray pattern. Thus, the dimensions of the device constituent part can be considered CQAs.

The secondary packaging (e.g., foil pouch) for MDIs can provide additional protection to the product from humidity. Therefore, when such additional protection is important, the material properties of the secondary packaging can be considered CQAs.

5. *Container Closure System (Including the Device Constituent Part) for DPIs*

The container closure system for a DPI consists of the device constituent part and protective secondary packaging (e.g., overwrap, carton).

As with MDIs, the materials used to fabricate the DPI device constituent part may come in direct contact with either the formulation or the patient, thereby potentially affecting product safety and performance. For instance, drug particle-surface interactions, such as adhesion of drug onto mouthpiece surfaces, can affect the delivered dose and APSD. Therefore, the properties of materials used in the critical device constituent part components are important and the quantitative compositions of the critical device constituent part components after molding should be considered CQAs. Critical device constituent part components are those that may come into contact with the formulation or the patient or are necessary for device function.

A DPI device constituent part acts as the delivery system of the drug. The design, geometry, and dimensions of the device constituent part can influence the device resistance, air flow, shear, and turbulence generated within the device constituent part, and thus the drug delivery of a DPI product. Therefore, these device constituent part attributes can be considered CQAs.

The secondary packaging (e.g., foil pouch) for DPIs can provide additional protection to the product from humidity. Therefore, when such additional protection is important, the material properties of the secondary packaging can be considered CQAs.

C. Product and Process Development

Development of an MDI or DPI product should involve consideration of aspects such as aerosol delivery characteristics, portability, ease of use, device constituent part robustness, inclusion of a dose counter, appropriateness of a lockout, cleaning needs, and suitability to the patient population.

The Agency recommends that applicants use prior knowledge specific to their formulation, manufacturing process, and device constituent part design to identify QTPP, CQAs, and potential risks to the product, and then initiate product and process development to define a control strategy that eliminates or mitigates the risks. Applicants should consider using risk assessment tools such as those listed in ICH Q9[11] or ISO 14971 *Risk Management – Medical Devices*[12] (e.g., Failure Modes and Effects Analysis (FMEA), Failure Modes, Effects, and Criticality Analysis

[11] See FDA guidance for industry *Q9 Quality Risk Management,* ICH.

[12] For additional information on risk management for combination products, see Current Good Manufacturing Requirements for Combination Products. See also ISO 14971 Risk Management – Medical Devices.

(FEMCA), Fault Tree Analysis (FTA), Ishikawa diagram) starting from early product development to identify factors (e.g., material attributes, process parameters) which have the potential to impact product quality. The identified factors can be further studied (e.g., experimentally, by modeling) to define an appropriate control strategy that assures that the manufacturing process consistently produces product of the desired quality.

Examples of some of the factors the applicant should consider, to understand potential impacts on MDI or DPI product CQAs, include the following:

- Physiochemical properties of the drug substance(s) and excipients and their interactions (e.g., densities, amorphous or crystalline forms, flow properties, adhesive and cohesive properties).

- Lot-to-lot variability of drug substance and excipient properties (e.g., PSD, moisture content, impurity profiles, surface morphology) and device constituent part composition and properties (e.g., surface contamination, leachables content).

- Interaction of two or more drug substances when co-formulated.

- Potential for microbial growth.

Risk assessment and process development experiments can lead to an understanding of univariate and multivariate relationships between material attributes and process parameters and how they affect MDI or DPI CQAs. Experimentation and modeling can also help identify appropriate ranges for these variables, within which consistent product quality can be achieved. Identification of appropriate ranges can facilitate scale-up and technology transfer. Multivariate combinations of appropriate ranges for material attributes and process parameters also can be included in a design space.

Another factor to consider concerns the stage of development when pivotal clinical trials (i.e., phase 2b, phase 3) are conducted. Dose-ranging studies are considered pivotal trials, and the to-be-marketed MDI should be used during dose-ranging studies to avoid potential therapeutic differences. If an applicant completes optimization of the MDI or DPI product and manufacturing process only after the pivotal clinical trials have been completed, the applicant should consider establishing a relationship between the in vitro characterization of the product and its in vivo performance. In the absence of such a relationship, additional in vivo studies (e.g., clinical studies) might be warranted to determine whether the product manufactured for clinical trials and the product proposed for commercial distribution have the same therapeutic effect.

1. *Product Development*

    a. MDIs

The following are examples of potential design and development issues that should typically be considered during the development of an MDI:

- The selection or design of the device constituent part (canister, valve components, actuator, and dose counter) is generally informed by prior knowledge or experience, and can be optimized during development as early as feasible and should be completed prior to phase III study of the combination product if possible.

- The target fill volume of an MDI is usually established based on the number of actuations required from the product, delivered dose, concentration of the drug substance in the formulation, and metered volume. Unavoidable leakage of the propellant over the shelf-life and the number of actuations required for priming during testing and use should also be factored into the fill volume. Fill volume, formulation homogeneity (for suspensions) and concentration, and fill weight are likely to have a significant impact on the delivered dose of the product throughout the life of the unit. The internal pressure of the device constituent part and vaporization rate of the aerosol produced upon actuation are determined primarily by the properties and amount of propellant(s) and cosolvent(s), because these constitute the majority of the MDI formulation.

- For suspension based MDIs, the potential for settling, creaming, or aggregation of the drug substance can be minimized if the drug substance and the propellants have similar densities.

- A non-uniform dispersion of drug substance can also result from adhesion of the suspended drug particles to various components of the device constituent part (e.g., valves, canister). This adhesion can contribute to changes in delivered dose and APSD.

- Solution-based MDIs generally have better delivered dose uniformity (DDU) compared to suspension based MDIs, but they may have more degradants, since the drug substance is completely dissolved and is more susceptible to degradation reactions.

- Organic cosolvents, which are often used to enhance the solubility of the drug substance, may have the potential to solubilize the components of the device constituent part. Thus, it is prudent to employ materials of construction in the device constituent part that reduce the possibility of leachables in the product (e.g., plastics and coatings less likely to be solubilized in the liquid phase of the formulation, pre-extracted elastomers).

b. DPIs

The following are examples of potential design and development issues that should typically be considered during the selection and development of a DPI:

- Carriers such as lactose can promote uniformity and flowability of a blend during manufacturing. Carriers can also enhance the reproducibility of the metered,

delivered, and fine particle dose of the DPI product (by reducing agglomeration of the drug substance).

- Properties that can be important to consider for selection of carriers during product development include: ratio of drug substance to excipient, physical and chemical compatibility, and PSD. Interparticulate interactions between the drug substance and excipients and with the container closure/device constituent part at a microscopic level (e.g., cohesive and adhesive properties, surface activity, specific surface area, static charge properties of the formulation) can also be important. These properties and interactions can affect, for example, blend uniformity, powder flow, and delivered dose.

- The stability of the formulation can be affected by ambient humidity. For example, exposing hygroscopic excipients to moisture can result in a decrease in the fine particle dose of the drug substance. If moisture ingress into the device constituent part affects product performance, additional protective container closure components (e.g., desiccants, foil overwraps) can be used.

2. *Process Development*

Process development should include the following:

- Selection of an appropriate manufacturing process (including manufacturing equipment).

- Identification of factors or process variables that have a potential to impact MDI or DPI product CQAs.

- Process optimization (which includes determination of appropriate ranges for the process variables).

- Determination of in-process controls.

- Identification of an approach for scale-up (if applicable).

The crystallinity of the drug substance in MDIs and DPIs can be affected by mechanical processing, including micronization. This can lead to the generation of amorphous particles that are thermodynamically unstable, with a tendency to convert to a more stable crystalline state with time. This recrystallization of micronized material could lead to uncontrolled particle growth, thereby affecting the MDI or DPI product CQAs (e.g., APSD, DDU). Therefore, a conditioning step should be considered following micronization to allow conversion of amorphous to crystalline form under controlled conditions of temperature and humidity.

Evaluation of process monitoring data during the development of the manufacturing process can enhance process understanding and support continual process development over the product life cycle.

a. MDIs

Typical manufacturing operations for an MDI are sequential mixing of the drug substance(s), propellants and cosolvents, filling, device constituent part assembly, and packaging.

- For a suspension formulation, adequate mixing and circulation within the formulation tank, filling tank, and filling heads is necessary during the filling process to achieve uniformity of product fill into individual units.

- Filling processes are usually pressure fill, cold fill, or a combination of these depending on the formulation characteristics, type of equipment available, and manufacturing expertise and experience. MDI canisters can be filled with a pre-specified calibrated amount of formulation in single or multiple steps.

- A better understanding of the filling process can be obtained by designing experiments to study the impact of deliberate variations in the process parameters on the MDI product assay, consistency of filling of both the drug substance and the propellant, valve crimp measurements, weight checking, spray testing, etc. These experiments could be used to optimize the filling operation and define an appropriate design space for the MDI filling operation. For example, the filling operation of an MDI can be optimized by evaluating the change in concentration of the drug substance in the formulation tank during the filling process (due to the volatility of the propellants) and determining the amount of propellant to be added to maintain the concentration of the drug substance.

- Results from testing of product from trial runs can form the basis for further optimization of the formulation or manufacturing process.

b. DPIs

Typical manufacturing operations for a DPI are dry powder blending or spray drying of the drug substance(s) and excipients (carrier), blister or capsule filling (reservoir filling for device-metered DPIs), device constituent part assembly, and packaging.

- The physical properties of the drug substance(s) and/or excipient(s) are usually modified before they are used in the formulation. Particle generation or modification processes can include spheronization, spray drying, and micronization.

- Increased drug substance particle cohesiveness resulting from the presence of very small particles can adversely affect flowability, fillability, and dispersibility. Because the concentration of the drug substance in the formulation is usually low, it can be difficult to achieve a uniform distribution of the drug substance by direct blending. These problems are typically minimized by blending drug particles with larger carrier particles (e.g., lactose).

- Blend uniformity can be measured using traditional methods such as High Performance Liquid Chromatography (HPLC), where samples are obtained at the end of blending using a sampling thief. Also, online technologies such as near infrared-based procedures can be used to monitor blending in real time and ensure a homogenous blend. The equipment (e.g., blender type), process parameters associated with blending (e.g., blending time, blender speed, blender fill level), and environmental conditions can impact blend uniformity and therefore the dose content uniformity of the drug product. Final blend properties (e.g., bulk density, particle size, flowability) can impact the process parameters for filling capsules, blisters, and reservoirs.

- Other approaches to achieving a uniform distribution of the drug substance in the formulation can include the use of spray drying or supercritical fluid technology.

- Typical filling methods for DPIs include dosator or tamp filling. Process parameters can include blister/capsule filling speed, powder bed height in auger, and encapsulator speed (for capsules). The capsules, blisters, reservoirs, or disks are normally sealed to protect the formulation from environmental factors (e.g., humidity) which can affect product performance. Process parameters for sealing can include the sealing temperature, dwell time, and machine speed. The effect of the sealing process parameters on DPI product CQAs (e.g., impurities and degradants, delivered dose, and APSD) should be investigated since the sealing process normally involves heating.

D. Development of Control Strategy

As defined in ICH Q10,[13] a control strategy is a "planned set of controls, derived from current product and process understanding that assures process performance and product quality." For MDIs and DPIs, the overall purpose of the control strategy is to ensure that the CQAs are within the appropriate range, limit, or distribution to assure drug substance and product quality.

The control strategy can include controls for incoming materials, in-process controls, and release testing.

1. *Controls for Incoming Materials*

Appropriate controls for the drug substance(s), excipients, device constituent part(s), and packaging materials should be established.[14] If more than one drug substance is used in the product formulation, controls should be in place for each of them, irrespective of the amount present. If PSD of the drug substance or an excipient can affect the CQAs (e.g., APSD) of the product, the PSD should be controlled. Similarly, other CQAs such as polymorphic form or moisture content should be controlled if they can affect the quality of the product. If PSD of the drug substance or an excipient is further modified by the product manufacturer as part of the

[13] See FDA guidance for industry *Q10 Pharmaceutical Quality System*, ICH.

[14] These controls must satisfy purchasing control requirements as described at 21 CFR 820.50. See Current Good Manufacturing Requirements for Combination Products for additional information regarding this requirement.

product manufacturing process, appropriate in-process controls and monitoring should be established (see next section on in-process measurements and monitoring).

Excipients used in MDIs and DPIs are typically referenced to Drug Master Files (DMFs) and have compendial monographs. For excipient CQAs that can impact the performance of the finished MDI or DPI product, but are not included in a compendial monograph, appropriate controls should be established.

Performance testing of the device constituent part (e.g., dimensions, valve functionality, dose counter, actuator-orifice, extractables) is typically done by the vendors or fabricators of the device constituent part and verified initially and on an annual basis by the applicant under their internal quality system. The appropriateness of these tests and acceptance criteria should be evaluated. For device constituent part components that will be in contact with the formulation or the patient's mouth, appropriate testing for extractables can be used as a substitute for leachables testing in the product if a valid extractables-leachables correlation is established. Suitability of the materials used for the device constituent part components can be addressed by their compliance to biocompatibility testing standards (e.g., United States Pharmacopoeia (USP) <87>, USP <88>, ISO 10993).

2. *In-process Measurements and Monitoring*

The in-process controls typically used for the manufacturing processes of MDIs can include: formulation homogeneity, valve performance testing, heat stress testing, and weight checking. Similarly, in-process controls for the manufacturing processes of DPIs can include: blend uniformity, moisture content, fill weight, and sealing integrity, where applicable. Additional monitoring of content uniformity using a stratified sampling approach during manufacturing[15] should be used for pre-metered DPIs with low drug loading.

Typically, drug substance or excipient manufacturers control the PSD of these materials before they are provided for further manufacture. Alternatively, the manufacturer producing the formulation for inclusion in the MDI or DPI can choose to adjust the PSD of these materials to an appropriate range or distribution prior to using them. If micronization is used to adjust the PSD, the in-process controls can include: total duration of micronization, PSD of the incoming materials, feed rate, inlet air flow rate, air pressure, physical and mechanical properties of input materials, number of times a lot is micronized, and re-introduction of carry-overs from previous micronized lots. If a spray drying process is used, the in-process controls can include: solution or suspension feed rate, inlet air and product temperatures, and air flow rate. If supercritical fluid extraction is used, the in-process controls can include: concentration of solution, pressure, temperature, and flow rates of carbon dioxide and drug solutions. For any of these three technologies, it may be possible to develop mathematical models to predict PSD as a function of process parameters or material attributes. In such cases, predictions from these models can be used in lieu of actual measurement of PSD. Such models should be verified and updated.[16]

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[15] The Use of Stratified Sampling of Blend and Dosage Units to Demonstrate Adequacy of Mix for Powder Blends, *PDA J Pharm Sci and Tech*, 57, 64-74 (2003).

[16] See FDA guidance for industry *Q8, Q9, & Q10: Questions and Answers: Appendix: Q&As from Training Sessions; (Q8, Q9, & Q10 Points to Consider)*, ICH.

In situations where PSD cannot be directly measured (e.g., samples may not be accessible from the formulation tank of an MDI until the canisters are filled), controls should be established to ensure consistent manufacture of product with the desired PSD (e.g., monitoring and trending of manufacturing process parameters that impact PSD).

When blister units or protective secondary packaging are used, controls should be established to ensure that the seal area functions properly in terms of adhesion (e.g., heat seal, adhesive) and mechanical seal. Appropriate integrity testing and acceptance criteria for seal completeness (e.g., vacuum leak test) and seal strength (e.g., peel strength test) should be established to ensure acceptable sealing properties within a batch and between batches.

3. *Release Testing of the MDI and DPI Product*

Release testing is performed on each batch of MDI or DPI product as part of the overall control strategy. Each of the product attributes listed on the MDI or DPI product specification, most of which are related to product CQAs, are normally tested at release. In some cases, if upstream controls can be used to confirm that a batch of product meets a CQA related to an attribute on the specification, that attribute does not need to be tested at release for every batch.

DDU and APSD should be included on the specifications for all MDIs and DPIs. Testing of these attributes is performed on the assembled product using appropriate analytical procedures (e.g., USP <601>). For DDU, the Agency also supports alternative statistical approaches using parametric tolerance interval testing (PTIT),[17,18] because these approaches are more relevant for assuring the overall quality of the entire batch of an MDI or DPI.

APSD testing for an MDI or DPI confirms that the APSD profile of the product remains consistent from the beginning of device constituent part use to the end. APSD testing is also used to confirm that the product used in the clinical trials has similar drug delivery characteristics to the to-be-marketed product. APSD is typically tested using an appropriate cascade impactor and is dependent on both the formulation and the container closure system. The measurement of the APSD is influenced by the characteristics of the MDI or DPI product aerosol and is not solely determined by the size of the individual drug substance particles present in the formulation. The impactor should have enough sizing stages to measure the total distribution. The Agency recommends that all of the cascade impactors used to test the MDI or DPI product throughout development should have the same design (e.g., Andersen Cascade Impactor or Next Generation Impactor) and configuration. DPIs with low flow resistance require high flow rates to achieve optimal pressure drop across the device constituent part. These device constituent parts should be tested using impactors with alternative validated stage configurations. It can be appropriate to refer to the current USP chapter for APSD procedures.

[17] Presentation on "Parametric Tolerance Interval Test for Dose Content Uniformity (PTIT)" to the Advisory Committee for Pharmaceutical Science (ACPS) on October 25, 2005. See http://www.fda.gov/ohrms/dockets/ac/05/slides/2005-4187s1_Slide%20Index%20Day%201.htm.

[18] Parametric Two-Tier Sequential Quality Assurance Test of Delivery Dose Uniformity of Multiple-Dose Inhaler and Dry Powder Inhaler Drug Products, *Journal of Biopharmaceutical Statistics*, 18: 976-984, 2008.

During development, the formulation and device constituent part components should be examined microscopically. If the results indicate the formation of agglomerates, crystal growth, the presence of large particles or foreign particulates, or changes in morphology of the drug substance, appropriate controls for release and stability should be developed. In addition, if the formulation supports microbial growth, appropriate controls for release and stability should be considered.

IV. INFORMATION TO BE SUBMITTED IN AN APPLICATION

An applicant must provide technical data and information in sufficient detail to permit the Agency to make a knowledgeable judgment about whether to approve the application or whether grounds exist under section 505(d) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) to refuse to approve the application.[19] This includes information about the drug substance[20] and information about the MDI or DPI product.[21, 22]

The recommendations below are particularly relevant to MDIs and DPIs developed by following traditional developmental approaches and are based on Agency experience with these products. Information for more enhanced development could be different, although an applicant would be expected to demonstrate enhanced knowledge and understanding. For example, alternative control strategies to ensure product quality could be proposed. Applicants are encouraged to discuss such proposals and their justification with the appropriate review division during development.

The focus of this section is on aspects of MDIs and DPIs that are unique to these products. The format of the submitted information should be based along the lines described in ICH M4Q.[23]

A. Information on the Drug Substance

As described in section 3.2.S of ICH M4Q, the information submitted about the drug substance should include information on General Properties, Manufacturer, Description of the Manufacturing Process and Process Controls, Control of Materials, Controls of Critical Steps and Intermediates, Manufacturing Process Development, Characterization, Control of Drug Substance, Reference Standards, Container Closure System, and Stability.

Attributes typically included on the specifications for drug substances used in MDIs and DPIs are listed in Table 1, below. Additional recommendations can be found in ICH Q6A,[24] and other applicable guidances.

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[19] See 21 CFR 314.50(d).

[20] See 21 CFR 314.50(d)(1)(i).

[21] See 21 CFR 314.50(d)(1)(ii).

[22] For additional assistance on where to provide device constituent information using the eCTD format see eCTD Technical Conformance Guide: Technical Specifications Document: guidance for industry *Providing Regulatory Submissions in Electronic Format —Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications.*

[23] See FDA guidance for industry *M4Q: The CTD — Quality*, ICH.

[24] See FDA guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products*, ICH.

Table 1. Attributes Usually Tested at Release and on Stability for Drug Substances Used in MDIs and DPIs

Attribute	Release	Stability
Color	X	
Appearance (visual and microscopic)	X	X
Identity	X	
Moisture Content	X	X
Residue on Ignition	X	
Specific Rotation	X	
Assay	X	X
Impurities	X	X
Microbial Limits	X	X
Melting Range	X	X
PSD	X	X
Morphology*	X	X
Amorphous Content	X	X
Individual Residual Solvents	X	
Heavy Metals**	X	

* Examples include shape, crystal habit, texture, surface area, and rugosity.

** Can be replaced with elemental impurities.[25]

B. Description and Composition (P1)

As described in ICH M4Q, section 3.2.P.1 of the application should include a list of all components (i.e., ingredients) used in the manufacture of the MDI or DPI drug constituent part.

1. *MDIs*

The amount of each component in the final formulation should be expressed in terms of concentration (i.e., amount per unit volume or weight), as well as amount per container and amount delivered from the valve per actuation. The amount of drug delivered from the mouthpiece and any associated features (e.g., integrated spacers) per actuation should be provided. The mass of drug delivered from the mouthpiece per actuation is the specified target delivered dose (TDD) and is used to denote the strength. In addition, for suspension formulations, the density of the individual formulation components should be included. The reported densities should be measured at the product storage temperature.

[25] See FDA guidance for industry *Q3D Elemental Impurities*, ICH, USP General Chapter <232> *Elemental Impurities-Limits,* USP General Chapter <233> *Elemental Impurities-Procedures,* and FDA guidance for industry *Elemental Impurities in Drug Products.* When final, this guidance will represent the FDA's current thinking on this topic.

2. *DPIs*

The amount of each drug should be expressed in terms of concentration (i.e., amount per unit weight (e.g., micrograms per gram)) and as net content (in micrograms) per capsule or blister. The metered amount and the mass of the drug delivered from the mouthpiece under defined test conditions (i.e., flow rate, duration) should both be provided. The mass of drug delivered from the mouthpiece is the specified target delivered dose (TDD). The metered amount of the drug from a DPI is used to denote its strength, not the specified TDD.

For device-metered DPIs, the TDD, metered dose, and net formulation content should be provided.

C. Pharmaceutical Development (P2)

As described in ICH M4Q, section 3.2.P.2 of the application should contain information on studies conducted to establish that the dosage form, formulation, manufacturing process, container closure system, microbiological attributes, and usage instructions specified in the application are appropriate for the intended use of the MDI or DPI product. Because an MDI or DPI is a combination product, this section should address the developmental process for the entire product including the device constituent part. The applicant should consider including the following:

- A description of the QTPP.

- A list of the CQAs of the MDI or DPI product, along with the limit, range, or distribution associated with each CQA and appropriate justification.

- Identification of those aspects of drug substances, excipients, container closure system (including the device constituent part), and manufacturing processes important to attaining product quality.

- Rationale for the selection or design of the proposed container closure system (including the device constituent part) and storage conditions, including a summary of the changes in container closure components used throughout the development (e.g., in tabular form).

- Pilot scale or larger scale process development studies used to support the proposed commercial scale control strategy. This could include:

    - Summary of prior knowledge and risk assessment methodologies used to identify the process parameters and material attributes that have the potential to impact product CQAs.

    - Summary of experimental studies used to identify operating ranges or design space. If design of experiments (DOE) was used, a summary table should be provided that includes input factors, ranges studied, results, and conclusions.

- Appropriate scale-up correlations should be provided to justify proposed ranges at commercial scale.

- Rationale for the selection of input materials and their proposed acceptance criteria.

- Rationale for the selection of the manufacturing process, including in-process controls.

- Justification for the formulation overfill per unit, needed to maintain the performance of the MDI or DPI product throughout the labeled number of actuations, as applicable.

- Summary data from MDI or DPI product characterization studies. These are used to demonstrate the robustness and performance of the product and support labeling. Studies recommended for MDIs and DPIs are listed in Table 2, below. The applicability of each of the characterization studies outlined below for a given product can be discussed with the responsible review division. Additional information on the purpose and design of these characterization studies can be found in the Appendix, section V.B.2.

Table 2. Characterization Studies

Studies	**MDI**	**DPI**
In-Use Period	X	X
Temperature Cycling	X	X
Priming and Repriming	X	
Effect of Patient Use	X	X
Effect of Storage and Shaking (suspension formulated MDIs only)	X	
Effect of Orientation of the Device on Delivered Dose		X
Drug Deposition on Mouthpiece and/or Accessories	X	X
Cleaning Instructions	X	X
Profiling of Actuations Near Device Exhaustion	X	X
Effect of Varying Flow Rate on DPI Performance		X
Effect of Flow Rate and Inhalation Delay on MDIs with Spacers	X	
Robustness	X	X

D. Manufacture (P3)

As described in ICH M4Q, section 3.2.P.3 of the application should contain information about where and how the MDI or DPI product will be manufactured. This should include information on the drug and device constituent parts and the final combination product assembly. In addition, the application should contain information necessary to demonstrate compliance with

21 CFR part 4. See the FDA guidance for industry and staff *Current Good Manufacturing Practice Requirements for Combination Products* for more information on these requirements. In addition, the FDA guidance for industry and staff *Quality System Information for Certain Premarket Application Reviews* provides information regarding the quality system information that should be included in a regulatory submission.

The complete street address and contact information (e.g., email, phone and fax numbers) should be listed in the application form 356h for each facility involved in the manufacturing or testing of the MDI or DPI product, including the testing of components of the product. If manufacturing information is provided in a DMF, all sites that are described in the DMF should also be listed in the application form 356h.

The batch formula and a description of the manufacturing process and process controls should be provided. A detailed schematic diagram of the proposed production process, including descriptions of the equipment, operating conditions, and process controls, should also be provided.[26]

If a drug substance or excipient is micronized after being received from a supplier, the process parameters for micronization should be described as part of the product manufacturing process. If a conditioning step follows micronization, the conditioning parameters and process controls should also be described.

If the MDI manufacturing process involves filling a suspension into a canister, either by pressure fill or cold fill, appropriate process parameters and in-process controls to assure the formulation homogeneity should be provided in the application.

If the manufacturing process involves blending of drug or excipient particles, the process parameters associated with blending (e.g., blender size, blending time, blender speed, blender loading configurations, environmental conditions) and in-process controls for assuring blend uniformity should be described.

Filling and packaging procedures (primary and protective secondary packaging) for the MDI or DPI product should be described in the application, including relevant process controls for these operations.

E. Control of Excipients (P4)

As described in ICH M4Q, section 3.2.P.4 of the application should provide the following information on control of excipients:

- Manufacturer, supplier, characterization studies, certificate of analysis and other specific information should be provided as appropriate, for all excipients.

- Specifications for excipients.

[26] See 21 CFR 314.50(d)(1)(ii)(c).

- Analytical procedures used for testing the excipients, when appropriate.

- Analytical validation information, when appropriate.

DMFs can also be referenced in the application for quality and toxicological information. For additional guidance on pharmacological and toxicological considerations, the applicant should consult available CDER guidance,[27] or contact the responsible review division.

For certain compendial excipients, the specifications should include tests in addition to those stated in the monograph. Typical examples are shown in Table 3, below.

Table 3. Examples of Tests in Addition to Compendial Excipient Tests

Dosage Form	Excipient	Function	Tests
MDI	Dehydrated Alcohol, USP	Cosolvent	• Water content (e.g., Karl Fischer) • Impurity profile
	Lecithin, NF	Surfactant	• Tests that define the compositional profile in detail
	Oleic Acid, NF	Surfactant	• Impurity profile in detail
DPI	Lactose Monohydrate, NF	Carrier	• Quantitative color and clarity • Anomeric purity • Elemental impurities • Amorphous content • Microbial limits • Organic volatile impurities • Related impurities • Particle size distribution • pH • Assay • Particle size and morphology • Pyrogens and bacterial endotoxins
	Anhydrous Lactose, NF	Carrier	• Quantitative color and clarity • Anomeric purity • Elemental impurities • Amorphous content • Microbial limits • Organic volatile impurities • Related impurities

[27] See FDA guidance for industry *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*.

Dosage Form	Excipient	Function	Tests
			• Particle size distribution • pH • Assay • Monohydrate lactose content • Particle size and morphology • Pyrogens and bacterial endotoxins

For propellants (e.g., HFA-134a, HFA-227) specifications should include the following tests: identity, appearance, assay, acidity, total residue, moisture content, related impurities, and unrelated impurities (e.g., CO, N_2, O_2 gases). Generally, the assay acceptance criterion should not be less than 99.99 percent for propellants. The related impurities acceptance criteria for HFA-134a and HFA-227, shown in Table 4 and Table 5, are typical of the limits that are considered acceptable.

Table 4. Examples of Acceptance Criteria for Impurities in HFA-134a

Impurity	Acceptance Criteria (ppm)	Impurity	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	20	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-1318my-T	5
HCFC-22	50	FC-1318my-C	5
HCFC-31	5	Total unsaturates (including HCFC-1122)	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

Table 5. Examples of Acceptance Criteria for Impurities in HFA-227

Impurity	Acceptance Criteria (ppm)
P124	3
P227 ca (Saturated)	3
Unsaturated related impurities	
P1216 hexafluoropropene	3
P1225ye 1,1,1,2,3, pentafluoropropene	3
P1225zc 1,1,1,3,3,pentafluoropropene	3
P245cb 1,1,1,2,2-Pentafluoropropene	
Hexafluorocyclopropane	2
1 chloro-1,2,2,2,tetrafluoroethane	10
Octafluoropropane	2
Chloropentafluoroethane	2
4-methylperfluoropentene-2 (isomer 1)	2
2-methylperfluoropentene-2 (isomer 2)	2
2-chloroheptafluoropropane	2
Hexafluoropropane	2
Heptafluorobutene	2
2-H-2-methyperfluoropentane	2
Water content	10
Acidity as Hydrogen Chloride	0.1
Non-volatile residue	20
Total unsaturated	5
Individual unidentified impurities	3
Other organic impurities	50
Any other identified saturated impurity	5
Total impurities	20
Purity by GC Assay	>99.99

F. Control of MDI and DPI Product (P5)

As described in ICH M4Q, section 3.2.P.5 of the application should contain the following information on control of MDI or DPI product:

- Specification.
- Analytical procedures.
- Validation of analytical procedures.
- Characterization of impurities.

- Batch analyses.
- Justification for the proposed specification.

Typical release tests for MDIs and DPIs are provided in Table 6, below.

Table 6. Attributes Typically Included on Specifications for MDIs and DPIs

Attribute	MDI	DPI
Description	X	X
Identification	X	X
Assay	X	X
Impurities and Degradation Products	X	X
Valve Delivery (Shot Weight)	X	
Delivered Dose Uniformity (DDU)	X	X
Uniformity of Dosage Units		X
Aerodynamic Particle Size Distribution (APSD)	X	X
Spray Pattern	X	
Foreign Particulate Matter	X	X
Microbial Limits	X	X
Water or Moisture Content	X	X
Alcohol/Antioxidants/Preservatives Content*	X	
Net Content (Fill) Weight	X	X
Leachables (Stability)	X	X

* When present

The proposed analytical procedures should be documented in sufficient detail[28] that they can be reviewed and reproduced in FDA laboratories. If any attribute is tested in-process during manufacturing in lieu of release testing, it should be indicated as such on the specification.

The following information for specific attributes and criteria should be provided:

1. *Description*

MDIs and DPIs: The appearance of the contents of the container (i.e., formulation) and the appearance of components of the container closure system should conform to their respective descriptions as an indication of product integrity. For example, there should be no visible evidence of drug substance surface deposition or corrosion of container closure system components of an MDI, such as pitting or discoloration. If any color is associated with the formulation (either present initially or from a known degradative process occurring during shelf life), a quantitative color test with appropriate acceptance criteria should be established, unless the impurity causing the color has been identified and its concentration will be monitored by another analytical procedure.

[28] See USP General Chapter <5> *Inhalational and Nasal Drug Products-General Information and Product Quality Tests,* and USP General Chapter <601> *Aerosols, Nasal Sprays, Metered-Dose Inhalers, and Dry Powder Inhalers*, for additional information, including analytical procedures for some of the attributes.

2. *Valve Delivery*

MDIs: Valve delivery (amount of formulation released per actuation, shot weight) should be measured for 10 units. The acceptance criteria should be not more than (NMT) ±15 percent for individual actuations and NMT ±10 percent for the mean of the actuations relative to the target. Acceptance testing for valve delivery on incoming valve lots can be substituted for the release testing of valve delivery for the MDI product, if justified. However, the acceptance criteria for valve delivery should be included in the MDI product specification.

3. *Delivered Dosage Uniformity (DDU)*

MDIs and DPIs: The test for DDU measures the amount of drug discharged from the mouthpiece of the MDI or DPI and compares that measurement to the TDD.

Not more than two actuations per determination should be used for DDU. Where the number of actuations per minimum dose specified in the product labeling is one, the number of actuations per determination should be limited to one. The amount of drug substance discharged should be expressed both as the actual weight and as a percent of the label claim from the actuator. The USP Unit Spray <601> sampling apparatus can be used and containers should be primed according to the instructions in the labeling (as appropriate). Testing should be carried out under optimized conditions of air flow rate and total air volume (drawn through the device during the test). For DPIs, inhalation aerosols, and inhalation aerosols with integrated spacers or similar accessories, the volume of collection should not exceed 2 L at a constant flow rate.

Testing for each batch should be conducted on an appropriate number of representative units (at least 10). For MDIs and device-metered DPIs, each MDI or device-metered DPI is considered a unit and both the initial dose and the last of the labeled number of doses should be tested. For pre-metered DPIs, each container (capsule, single blister, or single cartridge) is considered a unit. The sampling approach (including the number of samples tested and the number of replicate analyses performed per sample) should be included as part of the analytical procedure and acceptance criteria.

The Agency recommends that applicants adopt a PTIT approach to measuring DDU. However, alternative approaches can be used if appropriately justified. The Appendix (section V.C.) includes two examples of approaches to measuring DDU, including the PTIT approach. MDIs and DPIs: The test for DDU measures the amount of drug discharged from the mouthpiece of the MDI or DPI and compares that measurement to the TDD.

4. *Uniformity of Dosage Units*

Pre-metered DPIs (i.e., each dose is separately packaged or segregated within a package): The DPI product specification should include a test and acceptance criteria for the content uniformity of pre-metered dosage units (e.g., as described in USP General Chapter <905> Uniformity of Dosage Units).

5. *Aerodynamic Particle Size Distribution (APSD)*

MDIs and DPIs: The equipment (e.g., multistage cascade impactor, vacuum source, valve, timing system) used to characterize the APSD of the MDI or DPI product should be described. Any accessories or modifications to the equipment (e.g., stage substitution, expansion chamber, inlet stem, adaptors, collection plate surface coating) should be included in the description. The qualification criteria for the equipment should be included in the description of the analytical procedure.

Testing should be carried out under the same optimized conditions of air flow rate as is used in the DDU test. Other important test parameters (e.g., air flow duration, relative humidity, temperature) and information (e.g., cleaning of the equipment between runs, frequency of mensuration) should be specified in the procedure. For DPIs, the volume per measurement should not exceed 4 L.

APSD should be determined separately for each MDI or DPI. An appropriate minimum number of MDI or DPI products (e.g., 5) should be tested individually and the determination for each unit should be performed with the minimum number of actuations justified by the sensitivity of the analytical procedure used to quantitate the deposited drug. The amount of drug 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 variability. For MDIs, device-metered DPIs, and pre-metered DPIs that contain enclosed ordered assemblies of individual dose units, the APSD should usually be measured for the initial dose and also for the last of the labeled number of doses. However, if there is no discernible APSD trend from beginning- to end-of-unit life in the data from submission batches, routine testing for post-approval batches can be performed only at the beginning-of-unit life.

It is not considered adequate to characterize the APSD in terms of the mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) alone, or to limit the characterization only to fine particle mass or fine particle fraction. Acceptance criteria should be proposed based on the amount of drug deposited on various stages of the equipment. Applicants should propose acceptance criteria for groupings of consecutive stages rather than proposing an acceptance criterion for each individual stage. In most cases, three or four groupings should be sufficient to characterize the APSD adequately.

The mass balance (i.e., the amount of drug substance deposited on all surfaces from the valve to the equipment filter) should be measured for each run. If the mass balance is not between 85 and 115 percent of TDD, the test result should be investigated under the applicant's quality system. The investigation should include evaluation of the suitability of the analytical procedure and dose delivery testing of the units that failed APSD mass balance.

6. *Spray Pattern*

MDIs: The test procedure for spray pattern of the MDI product should include the following information: collection distances between the mouthpiece and the measurement plane (preferably at least two), number of actuations per spray pattern (preferably n = 1), position and

orientation of the measurement plane relative to the mouthpiece, and visualization method. The collection distances should provide adequate discriminatory capability. The acceptance criteria at different distances should include the shape and size of the spray pattern with the ratio of the longest to the shortest axes stated (e.g., 1.00 – 1.20).

Acceptance testing for spray pattern on incoming actuator lots with the specified valve can substitute for the release testing of spray pattern for the MDI product, if justified. However, the acceptance criteria for the spray pattern should be included in the MDI product specification.

7. *Foreign Particulates*

MDIs and DPIs: The MDI or DPI product specification should include tests and acceptance criteria for foreign particulates. The acceptance criteria should include limits for less than 10 micrometers, 10 to 25 micrometers, and greater than 25 micrometers.

8. *Microbial Limits*

MDIs and DPIs: The MDI or DPI product specification should include tests and acceptance criteria for total microbial count and specified indicator organisms. USP compendial methods and criteria in General Chapters <610> Alternative Microbiological Sampling Methods for Nonsterile Inhaled and Nasal Products and <1111> Microbiological Examination of Nonsterile Products Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use can be referenced.

9. *Leachables*

MDIs and DPIs: Additional information related to leachables and extractables can be found in the following documents: USP Chapters <1663>, <1664>, and <1664.1>, and PQRI Recommendations to FDA.[29]

G. Reference Standards or Materials (P6)

As described in ICH M4Q, section 3.2.P.6 of the application should contain information on reference standards or reference materials used for testing of the MDI or DPI product, if not previously provided in 3.2.S.5, Reference Standards or Materials.

H. Container and Closure System (P7)

As described in ICH M4Q, section 3.2.P.7 of the application should contain the information for the container closure system (which includes the device constituent part and the primary and secondary packaging). The application for MDIs and DPIs should also include the following information, as provided in Table 7, below.

[29] See http://pqri.org/wp-content/uploads/2015/08/pdf/LE_Recommendations_to_FDA_09-29-06.pdf.

978 **Table 7. Information to be Submitted in Support of an**
979 **Application for an MDI or DPI Container Closure System**
980 **(Including the Device Constituent Part)**

	MDI			MDI and DPI	DPI
	Canister	Valves and Components	Actuator/Mouthpiece and Additional Accessories	Protective Packaging	Device Constituent Part and Components
Fabricator(s) of Device Constituent Part and Components	•	•	•	•	•
Unique Identifier(s)	•	•	•	•	•
Composition and Control of Materials for Critical Components	•	•	•	•	•
Engineering Drawings with Precise Dimensions and Tolerances	•	•	•		•
Cleaning procedures and reagents used	•				
Control Extraction Procedures and Data	•	•			
Control Procedures for Residues[1]	•				
Qualitative and Quantitative Extractable Profile(s)	•	•			
Toxicological Evaluation of Extracted Materials (and Residues[1])	•	•			
Specification and Analytical Sampling Plans [2]	•	•	•	•	•
CoA or Representative Test Data	•	•	•	•	•
Functional and Performance Characteristics[3]		•			
Identity, Composition, and Treatment Procedures of Elastomeric Components		•			
Flow Resistance[4]					•
USP Biological Reactivity Testing <87> and <88> and Food Additive Regulation[5]			•		•

981 [1] Process contaminants (where appropriate)
982 [2] Can include for example, dimensions, qualitative and quantitative extractables and residues, physicochemical
983 parameters, compositional controls, and/or performance characteristics
984 [3] For example: valve actuation force, stroke length, valve delivery, and valve leakage of the assembled
985 valve/canister combination containing placebo formulation
986 [4] Supportive information and data should be provided to characterize any dependence of the drug delivery and
987 formulation deagglomeration on the flow resistance of the device constituent part
988 [5] If the components are not recognized as safe for food contact under appropriate regulations, extractables (e.g.,
989 organic solvent(s), water), obtained under defined experimental conditions, should be established analytically both
990 qualitatively and quantitatively. In addition to in vitro and in vivo tests and other safety data for these components

not recognized as safe for food contact, extractables profiles with multiple solvents should be assessed toxicologically and a rationale provided to support limits for extractables that can be applied on a routine basis.

Identity and concentration profiles of the leachables in the MDI or DPI product or placebo formulation (i.e., MDI or DPI product formulation without drug substance) should be determined for the primary stability batches and should include testing at multiple time-points to the end of the proposed shelf life. These data should be correlated, if possible, with the extractables profile(s) of the container closure system determined under the various control extraction study conditions.

For ANDAs, the applicant can compare the extraction profiles of the container closure system with the leachables profile(s) of the MDI or DPI product (or placebo) after storage under accelerated stability conditions as long as the applicant confirms that post-approval verification activities will include an assessment of initial production stability batches to confirm the results for the MDI or DPI product (or placebo) through the expiration dating period. If equilibrium is not reached by six months, real-time long-term data should be used to establish an appropriate expiration dating period. 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.

For additional information on container closure systems, refer to appropriate Agency guidance and available standards.

I. Stability (P8)

Stability studies should be conducted as recommended in ICH Q1A(R2), Q1C, Q1D, and Q1E.[30,31] The MDI or DPI product should be packaged as intended for commercialization, including secondary packaging. Stability data collected during the clinical investigations phase on the MDI or DPI product packaged in a different container closure system configuration can be provided as supporting data, with appropriate justification.

If protective secondary packaging is used, the routine stability test storage conditions for the product in the presentation intended for distribution should include both long-term storage at 25ºC/60 percent relative humidity (RH) and at 30ºC/65 percent RH for one-half of the proposed expiration dating period.

Table 8 below describes the attributes that should be tested during stability studies. During the conduct of stability studies, the MDI or DPI product should be stored in upright, horizontal, and inverted orientations. If sufficient data demonstrate that orientation does not affect the product quality, routine stability studies can be conducted on product stored in only one orientation. Alternatively, if data demonstrate a certain orientation is detrimental to product stability, that

[30] See FDA guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products*, ICH, FDA guidance for industry *Q1C Stability Testing for New Dosage Forms*, ICH, FDA guidance for industry *Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products*, ICH, and FDA guidance for industry *Q1E Evaluation of Stability Data*, ICH.

[31] See FDA guidance for industry *ANDAs: Stability Testing of Drug Substances and Products* and FDA guidance for industry *ANDAs: Stability Testing of Drug Substances and Products: Questions and Answers*.

orientation should be used in routine stability studies. However, shipping and storage of the marketed product should utilize the most favorable orientation.

Table 7. Attributes Normally Tested During Stability Studies

Attribute	MDI	DPI
Description	X	X
Assay	X	X
Impurities and Degradation Products	X	X
Valve Delivery (Shot Weight)	X	
Delivered Dose Uniformity (DDU)	X	X
Aerodynamic Particle Size Distribution (APSD)*	X	X
Spray Pattern	X	
Particulate Matter	X	X
Microbial Limits	X	X
Leachables	X	
Alcohol Content**	X	
Water or Moisture Content***	X	X
Leak Rate	X	

* For suspension-based MDIs, device-metered DPIs, and multi-dose DPIs that contain enclosed ordered assemblies of individual pre-metered dose units, the stability studies on the primary stability batches should determine the effect of storage time and conditions on the APSD through unit life (determinations from the initial actuations and also for the last of the labeled number of actuations). If APSD changes through unit life, the proposed stability protocol should include APSD testing at the beginning and end of unit life.

** When present

*** In addition to moisture present in the excipient

J. Labeling

The following information is recommended for the labeling of MDIs and DPIs, to help achieve consistency and uniformity in the content, product title, and format.[32] In this section, the term "drug product" refers to the combination product (i.e., the MDI or DPI product) and is used for clarity because pertinent labeling regulations and requirements use the term "drug product." These comments are directed mainly at labeling issues unique to prescription MDI and DPI products. Additional information regarding the labeling of drug products can be found in 21 CFR part 201. See also FDA guidance for industry on *Naming of Drug Products Containing Salt Drug Substances.*[33]

[32] As a general matter, ANDAs are required to include information to show that the labeling proposed for the generic drug is the "same" as the RLD, with certain limited exceptions, such as for changes required because of differences approved under a suitability petition (see section 505(j)(2)(c) of the FD & C Act and 21 CFR 314.93), or because the generic drug and the RLD are produced or distributed by different manufacturers the (see section 505(j)(2)(A)(v) of the FD & C Act). Applicants intending to submit an ANDA covering an MDI or DPI may also refer to FDA's draft guidance entitled *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* for additional information. When final, this guidance will reflect FDA's current thinking on this topic.

[33] In addition, see USP General Chapter <1121> *Nomenclature* for the *Monograph Naming Policy for Salt Drug Substances in Drug Products and Compounded Preparations.*

1. *MDIs*

The labeling of oral MDIs should state the established name of the product as *(Drug) Inhalation Aerosol* and provide the strength as the amount delivered per actuation under defined in vitro conditions. For nasal MDIs, the product labeling should state the established name of the product as *(Drug) Nasal Aerosol* and provide the strength as the amount delivered per actuation. The established name and strength should be followed by a phrase such as "For oral inhalation only" or "For nasal inhalation only," as appropriate.

In addition to the information typically required under Title 21 for the description of the drug substance and formulation (21 CFR part 201), the product labeling should include the following information specific to MDI products:

a. DESCRIPTION Section of the Prescribing Information

- A description of the appearance of the actuator and cap.

- The specified TDD from the mouthpiece per actuation should be expressed:

  - For example: "Each actuation meters 'x' mcg of drug in 'w' mg of suspension (solution) from the valve and delivers 'y' mcg of drug, equivalent to 'z' mcg of drug substance (if applicable) from the actuator (i.e., mouthpiece or nasal adapter)."

  - The term "approximately" should not be used to modify the medication amount delivered. If special circumstances warrant additional statements regarding the metered amount, this should be discussed with the appropriate review division.

- A statement should be included that the amount of drug delivered to the lung will depend on patient coordination of device actuation with the inhalation maneuver, as well as on patient factors such as inspiratory flow and peak inspiratory flow (PIF) through the delivery system, which may vary for asthma, COPD, and other patient populations.

- A list of all excipients should be included. Substances should be identified by their established names.

- If the drug substance that exits the mouthpiece is a hydrate, solvate, or complex, this information should be clearly specified with proper strength conversion for the active moiety.

- The number of usable actuations per container.

- A statement should be included that the canister should be discarded when the labeled number of actuations has been used.

b. HOW SUPPLIED/STORAGE AND HANDLING Section of the Prescribing Information

- The net content (fill) weight of the container should be stated.

- The medication amount delivered (TDD) from the actuator.

- The number of actuations for each canister fill weight should be included. Qualifying terms such as "at least" and "approximately" should not be used.

- A description 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 provided that the canister should only be used with the accompanying actuator and that the actuator 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 has been used, 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 used.

- Storage conditions should be clearly stated, including any warning statements regarding temperature and humidity.

- Any preferred storage orientation should be indicated.

- A statement should be included regarding the appropriate temperature of the MDI before use, as well as any requirements for shaking, if necessary. In addition, the impact of the cooling effect from multiple successive actuations on product performance should be described, if applicable.

- If protective secondary packaging (e.g., foil overwrap) is used, this should be clearly stated. In addition, appropriate statements should be included that the contents enclosed in the protective secondary packaging should not be used after a specified number of days (e.g., 2 weeks, 30 days) from the date the protective package was compromised (in-use period).

- Any warning statements required under 21 CFR 369.21 (e.g., storage above 120ºF 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).

- Information about shaking, priming, and repriming should be provided, and should be supported by data in the pharmaceutical development section of the application.

c. Instructions for Use[34,]

- Detailed, step-by-step, appropriately illustrated instructions for patient use should be included. FDA recommends that the following information be incorporated into the instructions:

  - A figure that displays the various elements of the MDI (e.g., actuator, cap, canister, sleeve, counter).

  - A statement should be included that the canister should only be used with the specified accompanying actuator and that the actuator should not be used with any other inhalation drug product.

  - 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.

  - Instructions for initial priming and repriming of the MDI units.

  - Instructions to provide assurance of coordination of device actuation with patient inhalation.

  - A statement cautioning against spraying the eyes with the formulation.

- Storage conditions should be 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 secondary packaging was used for the MDI product, appropriate statements should be included that the content of the protective secondary

[34] Instructions for Use: Typically these are developed as part of the Human Factors Engineering Design and Risk Mitigation analysis. For additional information, see: FDA guidance for industry and staff, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design*, and FDA draft guidance for industry, *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development*. When final, this guidance will represent the FDA's current thinking on this topic.

packaging should not be used after a specified number of days (e.g., 2 weeks, 30 days) from the date the protective package was opened (in-use period).

- Cleaning instructions should be included, if appropriate.

- A statement should be included that the canister should be discarded when the labeled number of actuations has been used.[35] Also, 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.

- Warning statements required under 21 CFR 369.21 (e.g., storage above 120ºF 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).

d. Container Labels and Carton Labeling

In addition to the information typically required to be included on the container label and/or carton labeling under Title 21, the container label should include the following information specific to MDI products:

- Amount of the drug delivered per actuation from the mouthpiece/nosepiece and the valve.

- Number of usable actuations per container.

- Recommended storage conditions including any warning statements regarding temperature and humidity.

- Use period once the MDI product is removed from protective packaging (if applicable).

- The instruction “Shake well before using” for suspension formulations.

- A statement that the MDI product should only be used with the mouthpiece provided (e.g., “For oral inhalation with *(Drug Product Name)* actuator only”).

- Reference to the patient’s Instructions for Use and additional instructional statements (e.g., instructions for initial priming and repriming the MDI unit, inhalation instructions, instructions pertaining to protective caps, etc.).

[35] See FDA guidance for industry *Integration of Dose-Counting Mechanisms into MDI Drug Products*.

- 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).

In the case of small labels, only some of the information listed above must be included on the label (21 CFR 201.10(i)). However, all labeling information required by the FD&C 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.

2. *DPIs*

The labeling of oral DPIs should state the established name of the product as *(Drug) Inhalation Powder* and provide the strength as the amount per metered dose unit. For nasal DPIs, the product labeling should state the established name of the product as *(Drug) Nasal Powder* and provide the strength as the metered dose. The established name and strength should be followed by a phrase such as "For oral inhalation only" or "For nasal inhalation only," as appropriate.

In addition to the information typically required under Title 21 for the description of the drug substance and formulation (21 CFR part 201), the product labeling should include the following information specific to DPI products:

a. DESCRIPTION Section of the Prescribing Information

- A description of the appearance of the actuator and cap.

- The metered amount of medication to be delivered to the patient should be expressed:

  - For example: "Each metered amount of 'x' mg of formulation contains 'y' mcg of drug equivalent to 'w' mcg of drug substance (if applicable) and 'z' mg of carrier excipient(s)."

  - If special circumstances require additional statements regarding the metered amount, this should be discussed with the appropriate review division.

- Specified TDD from the mouthpiece under defined *in vitro* conditions should be stated:

  - For example: "The drug product delivers 'y' mcg of drug with an *in vitro* flow rate of 60 L/min for a collection time of 2 seconds (2 L total volume)."

- A statement should be included that the amount of drug delivered to the lungs will depend on patient factors, such as inspiratory flow and PIF through the

delivery system, which may vary for asthma, COPD, and other patient populations.

- A list of all excipients should be included. Substances should be identified by their established names.

- If the drug substance that exits the mouthpiece is a hydrate, solvate, or complex, this information should be clearly specified with proper strength conversion for the active moiety.

- For DPIs that contain lactose, a statement should be included that the formulation may contain residual amounts of milk-related proteins.

- The number of usable actuations per container if appropriate.

b. HOW SUPPLIED Section of the Prescribing Information

- The net weight of the container contents should be stated for device-metered DPIs.

- The number of medication actuations expected throughout the shelf life of the drug product should be indicated. Qualifying terms such as “at least” and “approximately” should not be used.

- Protective secondary packaging (e.g., foil overwrap) should be described. In addition, appropriate statements should be included that the content of the secondary 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 compromised (in-use period).

- Storage conditions should be 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 constituent part should be provided, particularly for ease of identification of different strengths of drugs delivered by the same device constituent part.

- A statement should be included that the DPI unit should be discarded when the labeled number of actuations has been used, if appropriate.

c. Instructions for Use[36]

- Detailed, step-by-step, appropriately illustrated instructions for patient use should be included. Important elements of the DPI (e.g., body, cap, other instructive markings such as arrows depicting direction or alignment, etc.) should be clearly identified with illustrations.

- Storage conditions should be stated, including any warning statements regarding temperature, humidity, and light.

- If secondary protective packaging (e.g., foil overwrap) is used for the DPI product, device constituent part, or unit dose container, this should be stated. Appropriate statements should be included that the content of the secondary protective packaging (e.g., device-metered DPIs, pre-metered DPIs) should not be used after a specified number of days (e.g., 2 weeks, 30 days) from the date the secondary protective packaging was opened (in-use period).

- For device-metered DPIs without a locking mechanism, a statement 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-metered DPI may not be completely empty. A statement recommending that the device-metered DPI be discarded after the labeled number of doses has been delivered should be included as well.

- Cleaning instructions should be included, if appropriate.

d. Container Labels and Carton Labeling

In addition to the information typically required to be included on the container label and/or carton labeling under Title 21, the container label should include the following information specific to DPI products:

- Amount of the drug per metered unit.

- Number of usable actuations per container or device-metered DPI or for the device constituent part (if re-used), as appropriate.

- Recommended storage conditions including any warning statements regarding temperature, humidity, or light.

- Use period once the DPI product is removed from protective packaging, if applicable.

[36] Ibid

- A statement that the DPI product should only be used with the device constituent part provided, where applicable (e.g., "For oral inhalation with *(Drug Product Name)* actuator only").

- Any special dispensing instructions for the pharmacist and additional statements for the 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 on the label (21 CFR 201.10(i)). However, all labeling information required by the FD&C 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.

V. APPENDIX

A. Tables

Table A. General Relationship Between QTPP Elements and CQAs for MDIs

CQA	QTPP Elements			
	Strength (Emitted Dose)	**Purity**	**Aerodynamic Performance**	**Stability**
Assay	X		X	X
Purity Profile		X		X
Delivered Dose	X	X	X	X
Aerodynamic Particle Size Distribution (APSD)			X	X
Spray Pattern/Plume Geometry				X
Leachables		X		X
Amount of Excipients/Formulation			X	X
Foreign Particulate Matter		X		X
Moisture Content			X	X
Net Contents	X		X	X
Device Constituent Part (dimensions, etc.)			X	X

Table B. General Relationship Between QTPP Elements and CQAs for DPIs

CQA	QTPP Elements			
	Strength (Metered Dose)	**Purity**	**Aerodynamic Performance**	**Stability**
Assay	X		X	X
Purity Profile		X		X
Delivered Dose	X	X	X	X
Aerodynamic Particle Size Distribution (APSD)			X	X
Spray Pattern/Plume Geometry				X
Volatile/Semi-volatile Leachables		X		X
Amount of Excipients/Formulation			X	X

CQA	QTPP Elements			
	Strength (Metered Dose)	**Purity**	**Aerodynamic Performance**	**Stability**
Foreign Particulate Matter		X		X
Moisture Content			X	X
Net Contents	X		X	X
Device Constituent Part (dimensions, etc.)			X	X

Table C. Typical MDI and DPI Product Specifications, CQAs and Stability Attributes.

Attribute	MDI	CQA for MDIs	DPI	CQAs for DPIs	Stability
Description	X		X		X
Identification	X		X		X
Assay	X	X	X	X	X
Impurities and Degradation Products	X	X	X	X	X
Valve Delivery (Shot Weight)	X				X
Delivered Dose Uniformity (DDU)	X	X	X	X	X
Aerodynamic Particle Size Distribution (APSD)	X	X	X	X	X
Spray Pattern	X	X			X
Particulate Matter	X	X	X		X
Microbial Limits	X	X	X	X	X
Leachables (Stability)	X	X			X
Water or Moisture Content	X	X	X	X	X
Alcohol Content*	X	X			X
Net Content (Fill) Weight	X	X	X	X	X

* When present

B. MDI and DPI Product Characterization Studies (P2)

As stated in section IV.C. (Pharmaceutical Development (P2)), summary data from various MDI or DPI product characterization studies should be provided in the application. Table 2. Characterization Studies lists the recommended studies. Some detail for each of these studies is provided below in section B.2. Unless otherwise indicated, the studies should be conducted on the to-be-marketed configurations and versions of MDI and DPI products. A minimum of three batches using the formulation and device constituent part of the to-be-marketed configuration and version should be studied to support the reliability of the manufacturing processes and the reproducibility of product performance.

1. *General Considerations for Significant Change*

For any of the characterization studies described in this section that involve stability testing, significant change should be considered:

- In general, failure to meet the acceptance criteria for any attribute normally tested during stability studies.
- For assay, a change from the initial value of five percent or more.
- For DDU, a change in the mass of the mean dose of 10 percent or more (determined separately on samples taken from the beginning and end of product life), or a failure to meet the acceptance criteria for first tier testing.
- For APSD, a change in the total mass of fine particles (e.g., particles less than five micrometers) more than 10 percent.
- For the description, changes such as: discoloration or other changes in the appearance of the contents, distortion of valve components, valve clogging or malfunction, canister corrosion, and adherence of the drug to the walls of the container or valve components.

2. *Recommendations for Specific Characterization Studies*

a. In-Use Period

The purpose of these studies is to demonstrate, for MDI or DPI products marketed in protective secondary packaging, that the product will perform in accordance with its specification for the entire length of the proposed in-use period after the protective secondary packaging is opened.

Study Design: Conduct stability studies under intermediate conditions (e.g., 30°C/65 percent RH) on samples of the MDI or DPI product with the protective secondary packaging opened. Measure appropriate parameters (e.g., DDU, APSD, water content). Include samples of product at the beginning and near the end of its proposed shelf life. It is recommended that the study duration period be twice the proposed in-use period.

b. Temperature Cycling

The purpose of these studies is to demonstrate that fluctuating changes in temperature and humidity (such as those encountered during shipping and handling) will not have an adverse effect on the quality and performance of the MDI or DPI product. This information, in conjunction with stability data, should support the proposed storage conditions in the product labeling.

Study Design: Conduct cycling studies for 3-4 weeks using two different storage conditions, one subzero (–10 to –20°C) and the other above room temperature (40ºC). Cycle between these

conditions every 12 hours. (Alternative conditions and durations can be used, if they can be justified.) Compare test results to results from control samples (stored under the proposed long-term storage conditions as opposed to the temperature cycling conditions) tested at the same intervals.

c. Priming and Repriming

The purpose of these studies is to support the instructions in the product labeling for priming (how many times a patient should actuate a unit before initial use) and repriming (how many times a patient should actuate a unit before using it again after defined periods of rest).

Study Design: Measure the delivered amount of drug substance from consecutive actuations of individual units after defined resting intervals (e.g., 0, 6, 12, 24, 48 hours, 3 days). After each resting interval, repeat actuations until the delivered amount of drug substance per actuation consistently meets the acceptance criteria for DDU. Test units at the beginning and near the end of the proposed shelf life. If resting orientation affects the results, test units in various resting orientations (upright and inverted, or upright and horizontal). Testing can be performed concurrently on separate samples with progressively longer resting periods.

d. Effect of Patient Use

The purpose of these studies is to confirm that the MDI or DPI product functions properly after repeated patient uses of the product.

Study Design: Collect a number (e.g., 50-100) of partially used product units (including units near the labeled number of actuations) from clinical studies and measure appropriate parameters (e.g., DDU and APSD) and dose counter function. Also collect and investigate any MDI or DPI products that were reported as malfunctioning.

e. Effect of Storage and Shaking (suspension formulated MDIs only)

The purpose of these studies is to confirm that shaking instructions in the product labeling for suspension formulated MDIs are adequate to assure satisfactory dose delivery performance.

Study Design: Measure appropriate parameters (e.g., DDU and APSD) on the MDI product stored for increasing periods of time subsequent to shaking. From the results, determine the maximum allowable use time after shaking. Include the effects of shaking duration and storage orientation if these factors affect the results.

f. Effect of Orientation of the DPI Product on Delivered Dose

The purpose of these studies is to support any statements made in the product labeling about the DPI product orientation during use.

Study Design: Measure appropriate parameters (e.g., DDU and APSD) for DPI products actuated while oriented at various angles.

g. Drug Deposition on Mouthpiece and/or Accessories

The purpose of these studies is to determine the amount of drug deposited within the device constituent part during use, which can relate to cleaning requirements.

Study Design: Measure the mean amount of drug deposited per actuation on the mouthpiece or other device constituent part components (e.g., spacers or valved holding chambers).

h. Cleaning Instructions

The purpose of these studies is to confirm that any cleaning instructions (method and frequency) included in the product labeling for the device constituent part components (e.g., actuator or mouthpiece) will assure that the product maintains its ability to deliver the labeled dose of drug upon use.

Study Design: Measure appropriate parameters (e.g., DDU and APSD) for product actuated according to a schedule that simulates patient use, including cleaning (if required). Include units both at the beginning and near the end of shelf life.

i. Profiling of Actuations Near Device Exhaustion

The purpose of these studies is to confirm that the product delivers the labeled number of doses, and to characterize delivery performance if the product is used beyond the labeled number of actuations (for MDIs and device-metered DPIs that do not lock after the labeled number of actuations).

Study Design: Measure appropriate parameters (e.g., DDU and APSD) for product units that have already delivered the number of doses listed on the product labeling until no more drug is delivered upon actuation. Include units at both the beginning and end of shelf life. Include a graphical presentation of the findings as part of the study results.

j. Effect of Varying Flow Rate on DPI Performance

The purpose of these studies is to characterize the sensitivity of the delivery performance of DPIs to variation in inspirational flow rates that can be achieved by the patient population that is to use the product. This information is used to confirm the chosen design of the device constituent part.

Study Design: Using a flow rate range and volume consistent with the intended patient population, measure appropriate parameters (e.g., DDU and APSD) as a function of flow rate at the recommended constant volumes.

k. Effect of Flow Rate and Inhalation Delay on MDIs with Spacers

The purpose of these studies is to characterize the sensitivity of the delivery performance to variation in inspirational flow rates and inhalation delay on MDI products used with a spacer or holding chamber.

Study Design: Using a flow rate range and volume consistent with the intended patient population, measure appropriate parameters (e.g., DDU and APSD) as a function of flow rate at the recommended constant volumes. Also assess the effect of increasing waiting periods (e.g., 0, 5, 10 seconds) between actuation and initiation of in-flow. For breath-activated MDI products, determine the ranges of flow rates that generate actuations containing the label claim amount of delivered dose and the corresponding acceptable APSD.

l. Robustness

The purpose of these studies is to confirm that the MDI or DPI product is of sufficiently robust design to withstand shipping conditions and typical patient usage.

Study Design: Subject a number of units to actions (e.g., dropping, agitation, shipping) that will simulate conditions the product could be exposed to after it is released, including during patient use. Determine the effect of these actions on MDI or DPI product performance by measuring DDU, APSD, and dose counter function.

C. Approaches to Evaluating Delivered Dose Uniformity (DDU)

1. *Parametric Tolerance Interval Testing (PTIT)*

FDA recommends that applicants establish test parameters (e.g., sample size, tolerance interval factor (k factor)) and acceptance criteria that will ensure, to a confidence level of 95 percent, that at least 90 percent of the units in a batch (i.e., the coverage) will meet the established upper and lower limits (i.e., 80-120 percent of TDD).

FDA recommends the use of a two one-sided tolerance interval (TOSTI) test and a two-tiered approach to setting acceptance criteria:

First tier acceptance criteria:

- For pre-metered DPIs, measure the amount of drug substance discharged from the mouthpiece as a percentage of TDD (X) from n units and calculate the mean ($\bar{X}$) and standard deviation(s). For MDIs and device-metered DPIs, measure the initial dose and the last of the labeled doses for each of the n units for a total of 2*n measurements. The batch passes if:

$\bar{X} + (k_1 \cdot s) \leq 120$ and $\bar{X} - (k_1 \cdot s) \geq 80$ — where k_1 is the one-sided tolerance interval factor, which depends on the sample size (n for pre-metered DPIs and 2*n for MDIs and device-metered DPIs), coverage, and confidence level.

Second tier acceptance criteria:

- If the batch does not pass tier one testing, measure the amount of drug substance discharged from the mouthpiece as a percentage of TDD (*X*) from an additional *m* units for pre-metered DPIs (or the initial dose and the last of the labeled doses for each of the additional *m* units for MDIs and device-metered DPIs), combine the results with those from the first tier, and calculate the mean ($\bar{X}$) and standard deviation(s). The batch passes if:

  $\bar{X} + (k_1 \cdot s) \leq 120$ and $\bar{X} - (k_1 \cdot s) \geq 80$ — where k_1 is the one-sided tolerance interval factor, which depends on the sample size (n+m for pre-metered DPIs and 2*(n+m) for MDIs and device-metered DPIs), coverage, and confidence level.

Table D below shows k_1 factors specific to a confidence level of 95 percent and 90 percent coverage for a range of sample sizes.

Table D. One-sided Tolerance Interval Factors (k_1) for 95 Percent Confidence Level and 90 Percent Coverage[37]

Sample Size	k_1 Factor
10	2.911
15	2.566
20	2.396
25	2.292
30	2.220
35	2.167
40	2.125
50	2.065
60	2.022
90	1.940
120	1.899
240	1.819
480	1.766

FDA recommends that applicants adopt a 1:3 ratio for the change in sample size from tier 1 to tier 2 testing (i.e., if $n = 10$, then $n+m = 30$). Furthermore, FDA recommends that the tier 1 sample size should not be smaller than ten units. Applicants can set sample sizes much larger than $n = 10$ and $n+m = 30$, but should consider the cost/benefit ratio before setting sample sizes

[37] For example, see Hahn and Meeker, *Statistical Intervals – A Guide for Practitioners*, John Wiley and Sons, Inc. 1991.

that are very large. FDA believes that tier 2 sample sizes larger than about 90 (i.e., $n+m = 90$) will provide very little additional benefit.

2. *Counting Test*

The application of a counting test for evaluating DDU was in use before other approaches such as PTIT were developed. If an applicant chooses to evaluate DDU using a counting test, the Agency recommends a two-tiered approach to acceptance criteria, as described below:

First tier acceptance criteria:

- For pre-metered DPIs, the amount of drug substance measured by the test is not outside 80-120 percent of TDD for more than 1 determination (out of 10). For MDIs and device-metered DPIs, for each of 10 units, the initial dose and the last of the labeled doses are measured. The amount of drug substance is not outside 80-120 percent of TDD for more than 2 determinations (out of 20).

- The amount of drug substance measured by the test is not outside 75-125 percent of TDD for any determination.

- For pre-metered DPIs, the mean is not outside 85-115 percent of TDD.

- For MDIs and device-metered DPIs, the mean of separate determinations made for the initial dose from each unit and the mean of separate determinations made for the last of the labeled number of doses for each unit are not outside 85-115 percent of TDD.

If the above acceptance criteria are met, the batch passes the test for DDU.

If the amount of drug substance is outside 80-120 percent of TDD in more determinations than are permitted by the first criterion, testing can be performed on 20 additional units to determine if the batch meets second tier acceptance criteria, provided that the other two criteria described above are met.

Second tier acceptance criteria:

- The amount of drug substance measured by the test is not outside 80-120 percent of TDD for more than 3 of 30 determinations for pre-metered DPIs or for more than 6 of 60 determinations for MDIs and device-metered DPIs (30 for the initial dose from each unit and 30 for the last of the labeled number of doses for each unit).

- The amount of drug substance measured by the test is not outside 75-125 percent of TDD for any determination.

- For pre-metered DPIs, the mean is not outside 85-115 percent of TDD.

- For MDIs and device-metered DPIs, the mean of separate determinations made for the initial dose from each unit and the mean of separate determinations made for the last of the labeled number of doses for each unit are not outside 85-115 percent of TDD.