

---

# Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products - Quality Considerations Guidance for Industry

## ***DRAFT GUIDANCE***

**This guidance document is being distributed for comment purposes only.**

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Division of Dockets Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Richard Lostritto 301-796-1697.

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

**April 2018  
Pharmaceutical Quality/CMC**

**Revision 1**

---

# Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products - Quality Considerations Guidance for Industry

*Additional copies are available from:  
Office of Communications, Division of Drug Information  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10001 New Hampshire Ave., Hillandale Bldg., 4<sup>th</sup> Floor  
Silver Spring, MD 20993-0002  
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353  
Email: [druginfo@fda.hhs.gov](mailto:druginfo@fda.hhs.gov)  
<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>*

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

**April 2018  
Pharmaceutical Quality/CMC**

**Revision 1**

---

***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

**TABLE OF CONTENTS**

<b>I.</b>	<b>INTRODUCTION.....</b>	<b>1</b>
<b>II.</b>	<b>BACKGROUND .....</b>	<b>2</b>
	<b>A. General .....</b>	<b>2</b>
	<b>B. Regulatory Status.....</b>	<b>3</b>
<b>III.</b>	<b>MDI AND DPI PRODUCT DEVELOPMENT.....</b>	<b>4</b>
	<b>A. Quality Target Product Profile (QTPP).....</b>	<b>4</b>
	<b>B. Critical Quality Attributes (CQAs).....</b>	<b>4</b>
	1. <i>MDI and DPI Products</i> .....	4
	2. <i>Drug Substance</i> .....	5
	3. <i>Excipients</i> .....	6
	4. <i>Container Closure System (Including the Device Constituent Part) for MDIs</i> .....	6
	5. <i>Container Closure System (Including the Device Constituent Part) for DPIs</i> .....	7
	<b>C. Product and Process Development.....</b>	<b>7</b>
	1. <i>Product Development</i> .....	8
	2. <i>Process Development</i> .....	10
	<b>D. Development of Control Strategy .....</b>	<b>12</b>
	1. <i>Controls for Incoming Materials</i> .....	12
	2. <i>In-process Measurements and Monitoring</i> .....	13
	3. <i>Release Testing of the MDI and DPI Product</i> .....	14
<b>IV.</b>	<b>INFORMATION TO BE SUBMITTED IN AN APPLICATION .....</b>	<b>15</b>
	<b>A. Information on the Drug Substance.....</b>	<b>15</b>
	<b>B. Description and Composition (P1) .....</b>	<b>16</b>
	1. <i>MDIs</i> .....	16
	2. <i>DPIs</i> .....	17
	<b>C. Pharmaceutical Development (P2) .....</b>	<b>17</b>
	<b>D. Manufacture (P3).....</b>	<b>18</b>
	<b>E. Control of Excipients (P4).....</b>	<b>19</b>
	<b>F. Control of MDI and DPI Product (P5) .....</b>	<b>22</b>
	1. <i>Description</i> .....	23
	2. <i>Valve Delivery</i> .....	24
	3. <i>Delivered Dosage Uniformity (DDU)</i> .....	24
	4. <i>Uniformity of Dosage Units</i> .....	24
	5. <i>Aerodynamic Particle Size Distribution (APSD)</i> .....	25
	6. <i>Spray Pattern</i> .....	25
	7. <i>Foreign Particulates</i> .....	26
	8. <i>Microbial Limits</i> .....	26
	<b>G. Reference Standards or Materials (P6).....</b>	<b>26</b>
	<b>H. Container and Closure System (P7) .....</b>	<b>26</b>

---

***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

<b>I.</b>	<b>Stability (P8)</b> .....	<b>28</b>
<b>J.</b>	<b>Labeling</b> .....	<b>29</b>
	1. <i>MDIs</i> .....	30
	2. <i>DPIs</i> .....	34
<b>V.</b>	<b>APPENDIX</b> .....	<b>38</b>
	<b>A. Tables</b> .....	<b>38</b>
	<b>B. MDI and DPI Product Characterization Studies (P2)</b> .....	<b>39</b>
	1. <i>General Considerations for Significant Change</i> .....	40
	2. <i>Recommendations for Specific Characterization Studies</i> .....	40
	<b>C. Approaches to Evaluating Delivered Dose Uniformity (DDU)</b> .....	<b>43</b>
	1. <i>Parametric Tolerance Interval Testing (PTIT)</i> .....	43
	2. <i>Counting Test</i> .....	45



*Contains Nonbinding Recommendations*

*Draft — Not for Implementation*

1 **Metered Dose Inhaler (MDI) and Dry Powder**  
2 **Inhaler (DPI) Products – Quality Considerations**  
3 **Guidance for Industry<sup>1</sup>**  
4

5  
6 This draft guidance, when finalized, will represent the current thinking of the Food and Drug  
7 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not  
8 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the  
9 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible  
10 for this guidance as listed on the title page.  
11

12  
13  
14 **I. INTRODUCTION**  
15

16 The purpose of this guidance is to provide recommendations to industry on the development and  
17 manufacture of inhalation aerosols (also known as metered dose inhalers (or MDIs)) and  
18 inhalation powders (also known as dry powder inhalers (or DPIs)). The recommendations in this  
19 guidance can apply to MDI and DPI products intended for local or systemic effect.  
20

21 This guidance describes points to consider to ensure product quality and performance for MDIs  
22 and DPIs. It describes chemistry, manufacturing, and controls (CMC) information recommended  
23 for inclusion in new drug applications (NDAs) and abbreviated new drug applications (ANDAs);  
24 however, the principles are applicable to products used during clinical trials, and over the  
25 product lifecycle as well. It also provides recommendations on certain aspects of labeling for  
26 NDA and ANDA MDI and DPI products.  
27

28 This guidance does not discuss aqueous-based nasal spray drug products and inhalation solution,  
29 suspension, and spray drug products, or the manufacture of drug substances. However, some of  
30 the principles of this guidance may be applicable to nasal delivery products. Also, this guidance  
31 does not discuss considerations for when an MDI or DPI includes electronic components,  
32 software, or novel inhaler components that might affect the performance or reliability of the  
33 product. The applicant should refer to the applicable requirements and recommendations outlined  
34 in the appropriate regulations and guidances, respectively, from the Center for Devices and  
35 Radiological Health (CDRH).  
36

37 FDA previously published a draft guidance on this topic on November 13, 1998.<sup>2</sup> The present  
38 guidance is a revision of the previous draft, updated to reflect current standards and requirements

---

<sup>1</sup> 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.

<sup>2</sup> 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>.

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

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

41  
42 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.  
43 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only  
44 as recommendations, unless specific regulatory or statutory requirements are cited. The use of  
45 the word *should* in Agency guidances means that something is suggested or recommended, but  
46 not required.

47  
48

## **II. BACKGROUND**

49  
50

### **A. General**

51  
52

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

58

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

67

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

76

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

82

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

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

86  
87 The performance of MDI and DPI products depends on many key aspects of the drug  
88 formulation, container closure system (including the device constituent part), manufacturing, and  
89 patient handling. Product and process understanding is therefore critical to: (1) the development  
90 and manufacture of these products, (2) the maintenance of product quality and performance  
91 through the expiration date under patient use conditions, and (3) the maintenance of product  
92 quality and performance over the product life cycle, including continual improvement.

### **B. Regulatory Status**

94  
95  
96 MDIs and DPIs are combination products (see 21 CFR 3.2(e)).<sup>3</sup> As drug-device combination  
97 products, they are subject to the current good manufacturing practice (CGMP) requirements for  
98 drugs and devices (see 21 CFR part 4).<sup>4</sup> Further information about the CGMP requirements for  
99 combination products is available in the FDA guidance for industry and FDA staff *Current Good*  
100 *Manufacturing Practice Requirements for Combination Products*, including an explanation of a  
101 streamlined approach for demonstrating compliance with both drug and device CGMP  
102 requirements.

103  
104 In particular, design controls (21 CFR 820.30) apply to any combination product that includes a  
105 device constituent part that is subject to them, including all MDIs and DPIs.<sup>5</sup> Essentially, design  
106 control activities confirm that there are no negative interactions between constituent parts, and  
107 assure that their combined use results in a combination product that is safe and effective and  
108 performs as expected. Guidance for industry on pharmaceutical development addresses product  
109 design and development procedures, reflecting quality by design principles.<sup>6</sup> While quality by  
110 design and design controls share similar characteristics and goals, the device Quality System  
111 regulation (21 CFR 820) includes specific requirements for design development that  
112 manufacturers must satisfy.<sup>7</sup>

113  
114 It may be possible to leverage many aspects of pharmaceutical development as described in ICH  
115 Q8(R2) to achieve compliance with design controls. For example, the Quality Target Product

---

<sup>3</sup> 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).

<sup>4</sup> See 21 CFR part 4 available at <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/cfrsearch.cfm?cfrpart=4>.

<sup>5</sup> 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.

<sup>6</sup> See FDA guidance for industry *Q8(R2) Pharmaceutical Development*, ICH.

<sup>7</sup> 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.

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

116 Profile (QTPP) (see section III.A. below) is similar to “design inputs” (21 CFR 820.30(c)),  
117 which ensure that design requirements are appropriate to address the intended use of the product.  
118 Further, studies conducted to verify that the critical quality attributes (CQAs) are met in the  
119 finished product may also address requirements for design “verification” and “validation” (21  
120 CFR 820.30(f), (g)), which ensure that the product’s “design outputs” (21 CFR 820.30(d)) result  
121 in a product that safely and effectively meets user needs and achieves its intended effects.<sup>8</sup>  
122

123 MDI and DPI applicants must ensure that their development and manufacturing procedures and  
124 documentation satisfy all regulatory requirements applicable to their combination product,  
125 including for design control (some of which may be satisfied by following Q8(R2) as previously  
126 noted). This guidance offers recommendations for how to pursue product development and  
127 manufacture in a compliant manner, generally using concepts and terminology familiar to drug  
128 sponsors and manufacturers to do so.  
129

130

### **III. MDI and DPI PRODUCT DEVELOPMENT**

132

#### **A. Quality Target Product Profile (QTPP)**

134

135 Prior to the development of an MDI or DPI, the applicant should establish the desired quality  
136 target product profile (QTPP). The QTPP is a prospective summary of the quality characteristics  
137 of a drug product, and in this case, the combination product, that ideally will be achieved to  
138 ensure the desired quality, taking into account safety and efficacy of the MDI or DPI (ICH  
139 Q8(R2)).<sup>9</sup> Examples of QTPP elements for MDIs and DPIs include: proposed dosage form and  
140 delivery system, strength (e.g., targeted metered dose for DPIs, targeted delivered dose for  
141 MDIs), purity, stability, and aerodynamic performance.  
142

143

#### **B. Critical Quality Attributes (CQAs)**

144

##### **1. MDI and DPI Products**

146

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

---

<sup>8</sup> 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.

<sup>9</sup> See FDA guidance for industry *Q8(R2) Pharmaceutical Development*, ICH.



## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

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

158  
159 For MDIs, potential product CQAs typically include assay, impurities and degradants, delivered  
160 dose, aerodynamic particle size distribution (APSD), spray pattern, leachables, alcohol/excipient  
161 content, foreign particulate matter, moisture content, net content (drug substance and excipients),  
162 microbial load and device constituent part characteristics such as component dimensions and  
163 valve delivery (shot weight). The force and distance necessary to advance the dose counter<sup>10</sup> and  
164 the product actuation force (force to deliver the drug from the device constituent part) are CQAs.  
165 If the MDI product is actuated by the patient's inhalation, the air flow necessary to actuate the  
166 device for drug release can be considered a CQA.

167  
168 For DPIs, potential product CQAs typically include assay, impurities and degradants, delivered  
169 dose, APSD, volatile/semi-volatile leachables content, foreign particulate matter, moisture  
170 content, net content, microbial load, and device constituent part characteristics such as specific  
171 resistance to air flow.

172  
173 Each CQA, either alone or in concert with other CQAs, should relate to one or more elements of  
174 the product QTPP. Some of the elements of the QTPP can be related to CQAs of the device  
175 constituent part as well as to CQAs of the product formulation. For example:

- 176
- 177 • Delivered drug purity is usually related to the following CQAs: impurities and  
178 degradants of the drug substance and excipients, foreign particulate matter, and  
179 amount of leachables (e.g., from the device constituent part, container components, or  
180 manufacturing environment).
  - 181
  - 182 • Targeted delivered dose (product strength) for MDIs is usually related to the  
183 following CQAs: assay, metered dose, and net content.
  - 184
  - 185 • Aerodynamic performance for MDIs is usually related to the following CQAs:  
186 delivered dose, APSD, spray pattern, moisture content, net content, device constituent  
187 part CQAs, and drug substance CQAs.
  - 188
  - 189 • Targeted metered dose in a device-metered DPI is usually related to the following  
190 CQAs: the device constituent part CQAs (e.g., dimensions of metering components)  
191 and the physicochemical properties of the formulation.
  - 192

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

### 195 196 2. *Drug Substance*

197  
198 The physical, chemical, and microbiological properties of the drug substance that should be  
199 within an appropriate limit, range, or distribution to ensure the desired product quality are

---

<sup>10</sup> See FDA guidance for industry *Integration of Dose-Counting Mechanisms into MDI Drug Products*.

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

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

203  
204 For drug substances used in MDIs or DPIs, potential CQAs can include assay, particle size  
205 distribution (PSD), moisture content, bulk density, flow properties, morphic form (e.g.,  
206 amorphous, crystalline, hydrate), morphology of drug particles (e.g., shape, crystal habit, texture,  
207 surface area, rugosity), residual solvent content, and impurities.

### 208 209 3. *Excipients*

210  
211 The physical, chemical, and microbiological properties of the excipients that should be within an  
212 appropriate limit, range, or distribution to ensure the desired product quality are considered  
213 CQAs of the excipients. These should be identified and characterized early in development.  
214 Prior knowledge can be particularly useful in identifying the CQAs of excipients since many  
215 excipients are already used in similar products.

216  
217 The potential impact of an excipient on product quality can depend on the intrinsic  
218 characteristics and properties of the excipient chosen, and the amount of the excipient used in the  
219 formulation. Examples of potential CQAs for excipients used in MDIs or DPIs can include:  
220 assay, boiling point and vapor pressure, moisture content, density, impurity profile, particle  
221 morphology (e.g., shape, crystal habit, texture, surface area, rugosity), flow properties,  
222 amorphous content, microbial limits, pyrogens or bacterial endotoxins, and PSD.

### 223 224 4. *Container Closure System (Including the Device Constituent Part) for MDIs*

225  
226 The container closure system for an MDI consists of the device constituent part (i.e., canister, the  
227 actuator, the metering valve), including any additional features (e.g., integrated spacer, integrated  
228 dose counter). It can also include protective secondary packaging. Critical device constituent  
229 part components are those that may come into contact with the formulation or the patient, or are  
230 necessary for device function.

231  
232 The materials used to fabricate the MDI device constituent part may come into direct contact  
233 with either the formulation or the patient, thereby potentially affecting product safety and  
234 performance. For example, due to the presence of organic propellant/vehicle in MDI  
235 formulations, leaching of compounds from the valve and/or canister components of the container  
236 closure system into the formulation can occur, which is a potential safety or effectiveness  
237 concern. Device constituent part materials also have the potential to affect the aerodynamic  
238 performance of the MDI product. For example, delivered dose and APSD of the MDI product  
239 can be affected by the surface properties of the device constituent part and/or its components.  
240 Therefore, the properties of materials used in the fabrication of the device constituent part and  
241 the quantitative compositions after fabrication should be considered CQAs.

242  
243 The device constituent part (e.g., actuator orifice, mouthpiece, metering chamber) has an  
244 important role in generating aerosol particles, determining the aerosol characteristics, and  
245 controlling the amount of medication available to the patient. For instance, the actuator orifice

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

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

248  
249 The secondary packaging (e.g., foil pouch) for MDIs can provide additional protection to the  
250 product from humidity. Therefore, when such additional protection is important, the material  
251 properties of the secondary packaging can be considered CQAs.

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

253  
254  
255 The container closure system for a DPI consists of the device constituent part and protective  
256 secondary packaging (e.g., overwrap, carton).

257  
258 As with MDIs, the materials used to fabricate the DPI device constituent part may come in direct  
259 contact with either the formulation or the patient, thereby potentially affecting product safety and  
260 performance. For instance, drug particle-surface interactions, such as adhesion of drug onto  
261 mouthpiece surfaces, can affect the delivered dose and APSD. Therefore, the properties of  
262 materials used in the critical device constituent part components are important and the  
263 quantitative compositions of the critical device constituent part components after molding should  
264 be considered CQAs. Critical device constituent part components are those that may come into  
265 contact with the formulation or the patient or are necessary for device function.

266  
267 A DPI device constituent part acts as the delivery system of the drug. The design, geometry, and  
268 dimensions of the device constituent part can influence the device resistance, air flow, shear, and  
269 turbulence generated within the device constituent part, and thus the drug delivery of a DPI  
270 product. Therefore, these device constituent part attributes can be considered CQAs.

271  
272 The secondary packaging (e.g., foil pouch) for DPIs can provide additional protection to the  
273 product from humidity. Therefore, when such additional protection is important, the material  
274 properties of the secondary packaging can be considered CQAs.

### 275 **C. Product and Process Development**

276  
277  
278 Development of an MDI or DPI product should involve consideration of aspects such as aerosol  
279 delivery characteristics, portability, ease of use, device constituent part robustness, inclusion of a  
280 dose counter, appropriateness of a lockout, cleaning needs, and suitability to the patient  
281 population.

282  
283 The Agency recommends that applicants use prior knowledge specific to their formulation,  
284 manufacturing process, and device constituent part design to identify QTPP, CQAs, and potential  
285 risks to the product, and then initiate product and process development to define a control  
286 strategy that eliminates or mitigates the risks. Applicants should consider using risk assessment  
287 tools such as those listed in ICH Q9<sup>11</sup> or ISO 14971 *Risk Management – Medical Devices*<sup>12</sup> (e.g.,  
288 Failure Modes and Effects Analysis (FMEA), Failure Modes, Effects, and Criticality Analysis

---

<sup>11</sup> See FDA guidance for industry *Q9 Quality Risk Management*, ICH.

<sup>12</sup> 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*.

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

289 (FEMCA), Fault Tree Analysis (FTA), Ishikawa diagram) starting from early product  
290 development to identify factors (e.g., material attributes, process parameters) which have the  
291 potential to impact product quality. The identified factors can be further studied (e.g.,  
292 experimentally, by modeling) to define an appropriate control strategy that assures that the  
293 manufacturing process consistently produces product of the desired quality.  
294

295 Examples of some of the factors the applicant should consider, to understand potential impacts  
296 on MDI or DPI product CQAs, include the following:  
297

- 298 • Physiochemical properties of the drug substance(s) and excipients and their  
299 interactions (e.g., densities, amorphous or crystalline forms, flow properties, adhesive  
300 and cohesive properties).  
301
- 302 • Lot-to-lot variability of drug substance and excipient properties (e.g., PSD, moisture  
303 content, impurity profiles, surface morphology) and device constituent part  
304 composition and properties (e.g., surface contamination, leachables content).  
305
- 306 • Interaction of two or more drug substances when co-formulated.  
307
- 308 • Potential for microbial growth.  
309

310 Risk assessment and process development experiments can lead to an understanding of  
311 univariate and multivariate relationships between material attributes and process parameters and  
312 how they affect MDI or DPI CQAs. Experimentation and modeling can also help identify  
313 appropriate ranges for these variables, within which consistent product quality can be achieved.  
314 Identification of appropriate ranges can facilitate scale-up and technology transfer. Multivariate  
315 combinations of appropriate ranges for material attributes and process parameters also can be  
316 included in a design space.  
317

318 Another factor to consider concerns the stage of development when pivotal clinical trials (i.e.,  
319 phase 2b, phase 3) are conducted. Dose-ranging studies are considered pivotal trials, and the to-  
320 be-marketed MDI should be used during dose-ranging studies to avoid potential therapeutic  
321 differences. If an applicant completes optimization of the MDI or DPI product and  
322 manufacturing process only after the pivotal clinical trials have been completed, the applicant  
323 should consider establishing a relationship between the in vitro characterization of the product  
324 and its in vivo performance. In the absence of such a relationship, additional in vivo studies  
325 (e.g., clinical studies) might be warranted to determine whether the product manufactured for  
326 clinical trials and the product proposed for commercial distribution have the same therapeutic  
327 effect.  
328

### 329 1. *Product Development*

#### 330 a. MDIs

331  
332  
333 The following are examples of potential design and development issues that should typically be  
334 considered during the development of an MDI:

## *Contains Nonbinding Recommendations*

*Draft — Not for Implementation*

335  
336  
337  
338  
339  
340  
341  
342  
343  
344  
345  
346  
347  
348  
349  
350  
351  
352  
353  
354  
355  
356  
357  
358  
359  
360  
361  
362  
363  
364  
365  
366  
367  
368  
369  
370  
371  
372  
373  
374  
375  
376  
377  
378  
379  
380

- 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,

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

381 delivered, and fine particle dose of the DPI product (by reducing agglomeration of the  
382 drug substance).  
383

- 384 • Properties that can be important to consider for selection of carriers during product  
385 development include: ratio of drug substance to excipient, physical and chemical  
386 compatibility, and PSD. Interparticulate interactions between the drug substance and  
387 excipients and with the container closure/device constituent part at a microscopic  
388 level (e.g., cohesive and adhesive properties, surface activity, specific surface area,  
389 static charge properties of the formulation) can also be important. These properties  
390 and interactions can affect, for example, blend uniformity, powder flow, and  
391 delivered dose.  
392
- 393 • The stability of the formulation can be affected by ambient humidity. For example,  
394 exposing hygroscopic excipients to moisture can result in a decrease in the fine  
395 particle dose of the drug substance. If moisture ingress into the device constituent  
396 part affects product performance, additional protective container closure components  
397 (e.g., desiccants, foil overwraps) can be used.  
398

### 399 2. *Process Development*

400  
401 Process development should include the following:  
402

- 403 • Selection of an appropriate manufacturing process (including manufacturing  
404 equipment).  
405
- 406 • Identification of factors or process variables that have a potential to impact MDI or  
407 DPI product CQAs.  
408
- 409 • Process optimization (which includes determination of appropriate ranges for the  
410 process variables).  
411
- 412 • Determination of in-process controls.  
413
- 414 • Identification of an approach for scale-up (if applicable).  
415

416 The crystallinity of the drug substance in MDIs and DPIs can be affected by mechanical  
417 processing, including micronization. This can lead to the generation of amorphous particles that  
418 are thermodynamically unstable, with a tendency to convert to a more stable crystalline state  
419 with time. This recrystallization of micronized material could lead to uncontrolled particle  
420 growth, thereby affecting the MDI or DPI product CQAs (e.g., APSD, DDU). Therefore, a  
421 conditioning step should be considered following micronization to allow conversion of  
422 amorphous to crystalline form under controlled conditions of temperature and humidity.  
423

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

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

427  
428  
429  
430  
431  
432  
433  
434  
435  
436  
437  
438  
439  
440  
441  
442  
443  
444  
445  
446  
447  
448  
449  
450  
451  
452  
453  
454  
455  
456  
457  
458  
459  
460  
461  
462  
463  
464  
465  
466  
467  
468  
469  
470  
471  
472

### **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).

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

- 473
- 474
- 475
- 476
- 477
- 478
- 479
- 480
- 481
- 482
- 483
- 484
- 485
- 486
- 487
- 488
- 489
- 490
- 491
- 492
- 493
- 494
- 495
- 496
- 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**

497

498

499 As defined in ICH Q10,<sup>13</sup> 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.

500

501

502

503

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

#### **1. Controls for Incoming Materials**

505

506

507

508

509 Appropriate controls for the drug substance(s), excipients, device constituent part(s), and packaging materials should be established.<sup>14</sup> 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

---

<sup>13</sup> See FDA guidance for industry *Q10 Pharmaceutical Quality System*, ICH.

<sup>14</sup> 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.



## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

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

518  
519 Excipients used in MDIs and DPIs are typically referenced to Drug Master Files (DMFs) and  
520 have compendial monographs. For excipient CQAs that can impact the performance of the  
521 finished MDI or DPI product, but are not included in a compendial monograph, appropriate  
522 controls should be established.

523  
524 Performance testing of the device constituent part (e.g., dimensions, valve functionality, dose  
525 counter, actuator-orifice, extractables) is typically done by the vendors or fabricators of the  
526 device constituent part and verified initially and on an annual basis by the applicant under their  
527 internal quality system. The appropriateness of these tests and acceptance criteria should be  
528 evaluated. For device constituent part components that will be in contact with the formulation or  
529 the patient's mouth, appropriate testing for extractables can be used as a substitute for leachables  
530 testing in the product if a valid extractables-leachables correlation is established. Suitability of  
531 the materials used for the device constituent part components can be addressed by their  
532 compliance to biocompatibility testing standards (e.g., United States Pharmacopoeia (USP)  
533 <87>, USP <88>, ISO 10993).

### 534 2. *In-process Measurements and Monitoring*

535  
536  
537 The in-process controls typically used for the manufacturing processes of MDIs can include:  
538 formulation homogeneity, valve performance testing, heat stress testing, and weight checking.  
539 Similarly, in-process controls for the manufacturing processes of DPIs can include: blend  
540 uniformity, moisture content, fill weight, and sealing integrity, where applicable. Additional  
541 monitoring of content uniformity using a stratified sampling approach during manufacturing<sup>15</sup>  
542 should be used for pre-metered DPIs with low drug loading.

543  
544 Typically, drug substance or excipient manufacturers control the PSD of these materials before  
545 they are provided for further manufacture. Alternatively, the manufacturer producing the  
546 formulation for inclusion in the MDI or DPI can choose to adjust the PSD of these materials to  
547 an appropriate range or distribution prior to using them. If micronization is used to adjust the  
548 PSD, the in-process controls can include: total duration of micronization, PSD of the incoming  
549 materials, feed rate, inlet air flow rate, air pressure, physical and mechanical properties of input  
550 materials, number of times a lot is micronized, and re-introduction of carry-overs from previous  
551 micronized lots. If a spray drying process is used, the in-process controls can include: solution  
552 or suspension feed rate, inlet air and product temperatures, and air flow rate. If supercritical  
553 fluid extraction is used, the in-process controls can include: concentration of solution, pressure,  
554 temperature, and flow rates of carbon dioxide and drug solutions. For any of these three  
555 technologies, it may be possible to develop mathematical models to predict PSD as a function of  
556 process parameters or material attributes. In such cases, predictions from these models can be  
557 used in lieu of actual measurement of PSD. Such models should be verified and updated.<sup>16</sup>

---

<sup>15</sup> 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).

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

## *Contains Nonbinding Recommendations*

*Draft — Not for Implementation*

558

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

563

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

569

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

570

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

576

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

582

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

597

598

---

<sup>17</sup> 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](http://www.fda.gov/ohrms/dockets/ac/05/slides/2005-4187s1_Slide%20Index%20Day%201.htm).

<sup>18</sup> 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.

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

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

605

606

### **607 IV. INFORMATION TO BE SUBMITTED IN AN APPLICATION**

608

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

614

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

622

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

625

#### **626 A. Information on the Drug Substance**

627

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

633

634 Attributes typically included on the specifications for drug substances used in MDIs and DPIs  
635 are listed in Table 1, below. Additional recommendations can be found in ICH Q6A,<sup>24</sup> and other  
636 applicable guidances.

---

<sup>19</sup> See 21 CFR 314.50(d).

<sup>20</sup> See 21 CFR 314.50(d)(1)(i).

<sup>21</sup> See 21 CFR 314.50(d)(1)(ii).

<sup>22</sup> 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*.

<sup>23</sup> See FDA guidance for industry *M4Q: The CTD — Quality*, ICH.

<sup>24</sup> See FDA guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products*, ICH.

## Contains Nonbinding Recommendations

Draft — Not for Implementation

637  
638  
639  
640

**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.<sup>25</sup>

641  
642  
643  
644  
645  
646  
647  
648  
649  
650  
651  
652  
653  
654  
655  
656  
657  
658  
659

### **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.

---

<sup>25</sup> 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.

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

### 660 2. *DPIs*

661  
662 The amount of each drug should be expressed in terms of concentration (i.e., amount per unit  
663 weight (e.g., micrograms per gram)) and as net content (in micrograms) per capsule or blister.  
664 The metered amount and the mass of the drug delivered from the mouthpiece under defined test  
665 conditions (i.e., flow rate, duration) should both be provided. The mass of drug delivered from  
666 the mouthpiece is the specified target delivered dose (TDD). The metered amount of the drug  
667 from a DPI is used to denote its strength, not the specified TDD.

668  
669 For device-metered DPIs, the TDD, metered dose, and net formulation content should be  
670 provided.

### 671 672 **C. Pharmaceutical Development (P2)**

673  
674 As described in ICH M4Q, section 3.2.P.2 of the application should contain information on  
675 studies conducted to establish that the dosage form, formulation, manufacturing process,  
676 container closure system, microbiological attributes, and usage instructions specified in the  
677 application are appropriate for the intended use of the MDI or DPI product. Because an MDI or  
678 DPI is a combination product, this section should address the developmental process for the  
679 entire product including the device constituent part. The applicant should consider including the  
680 following:

- 681 • A description of the QTPP.
- 682  
683 • A list of the CQAs of the MDI or DPI product, along with the limit, range, or  
684 distribution associated with each CQA and appropriate justification.
- 685  
686 • Identification of those aspects of drug substances, excipients, container closure  
687 system (including the device constituent part), and manufacturing processes important  
688 to attaining product quality.
- 689  
690 • Rationale for the selection or design of the proposed container closure system  
691 (including the device constituent part) and storage conditions, including a summary of  
692 the changes in container closure components used throughout the development (e.g.,  
693 in tabular form).
- 694  
695 • Pilot scale or larger scale process development studies used to support the proposed  
696 commercial scale control strategy. This could include:
  - 697 ○ Summary of prior knowledge and risk assessment methodologies used to identify  
698 the process parameters and material attributes that have the potential to impact  
699 product CQAs.
  - 700 ○ Summary of experimental studies used to identify operating ranges or design  
701 space. If design of experiments (DOE) was used, a summary table should be  
702 provided that includes input factors, ranges studied, results, and conclusions.

## Contains Nonbinding Recommendations

Draft — Not for Implementation

- 706
- 707 ○ Appropriate scale-up correlations should be provided to justify proposed ranges at
- 708 commercial scale.
- 709
- 710 ○ Rationale for the selection of input materials and their proposed acceptance
- 711 criteria.
- 712
- 713 ○ Rationale for the selection of the manufacturing process, including in-process
- 714 controls.
- 715
- 716 ○ Justification for the formulation overfill per unit, needed to maintain the
- 717 performance of the MDI or DPI product throughout the labeled number of
- 718 actuations, as applicable.
- 719
- 720 • Summary data from MDI or DPI product characterization studies. These are used to
- 721 demonstrate the robustness and performance of the product and support labeling.
- 722 Studies recommended for MDIs and DPIs are listed in Table 2, below. The
- 723 applicability of each of the characterization studies outlined below for a given product
- 724 can be discussed with the responsible review division. Additional information on the
- 725 purpose and design of these characterization studies can be found in the Appendix,
- 726 section V.B.2.

727 **Table 2. Characterization Studies**

728

<b>Studies</b>	<b>MDI</b>	<b>DPI</b>
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

- 729
- 730 **D. Manufacture (P3)**
- 731
- 732 As described in ICH M4Q, section 3.2.P.3 of the application should contain information about
- 733 where and how the MDI or DPI product will be manufactured. This should include information
- 734 on the drug and device constituent parts and the final combination product assembly. In
- 735 addition, the application should contain information necessary to demonstrate compliance with

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

736 21 CFR part 4. See the FDA guidance for industry and staff *Current Good Manufacturing*  
737 *Practice Requirements for Combination Products* for more information on these requirements.  
738 In addition, the FDA guidance for industry and staff *Quality System Information for Certain*  
739 *Premarket Application Reviews* provides information regarding the quality system information  
740 that should be included in a regulatory submission.

741  
742 The complete street address and contact information (e.g., email, phone and fax numbers) should  
743 be listed in the application form 356h for each facility involved in the manufacturing or testing of  
744 the MDI or DPI product, including the testing of components of the product. If manufacturing  
745 information is provided in a DMF, all sites that are described in the DMF should also be listed in  
746 the application form 356h.

747  
748 The batch formula and a description of the manufacturing process and process controls should be  
749 provided. A detailed schematic diagram of the proposed production process, including  
750 descriptions of the equipment, operating conditions, and process controls, should also be  
751 provided.<sup>26</sup>

752  
753 If a drug substance or excipient is micronized after being received from a supplier, the process  
754 parameters for micronization should be described as part of the product manufacturing process.  
755 If a conditioning step follows micronization, the conditioning parameters and process controls  
756 should also be described.

757  
758 If the MDI manufacturing process involves filling a suspension into a canister, either by pressure  
759 fill or cold fill, appropriate process parameters and in-process controls to assure the formulation  
760 homogeneity should be provided in the application.

761  
762 If the manufacturing process involves blending of drug or excipient particles, the process  
763 parameters associated with blending (e.g., blender size, blending time, blender speed, blender  
764 loading configurations, environmental conditions) and in-process controls for assuring blend  
765 uniformity should be described.

766  
767 Filling and packaging procedures (primary and protective secondary packaging) for the MDI or  
768 DPI product should be described in the application, including relevant process controls for these  
769 operations.

### 770 771 **E. Control of Excipients (P4)**

772  
773 As described in ICH M4Q, section 3.2.P.4 of the application should provide the following  
774 information on control of excipients:

- 775
- 776 • Manufacturer, supplier, characterization studies, certificate of analysis and other  
777 specific information should be provided as appropriate, for all excipients.
  - 778
  - 779 • Specifications for excipients.

---

<sup>26</sup> See 21 CFR 314.50(d)(1)(ii)(c).

## Contains Nonbinding Recommendations

Draft — Not for Implementation

780  
781  
782  
783  
784  
785  
786  
787  
788  
789  
790  
791  
792  
793

- 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,<sup>27</sup> 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	<ul style="list-style-type: none"><li>• Water content (e.g., Karl Fischer)</li><li>• Impurity profile</li></ul>
	Lecithin, NF	Surfactant	<ul style="list-style-type: none"><li>• Tests that define the compositional profile in detail</li></ul>
	Oleic Acid, NF	Surfactant	<ul style="list-style-type: none"><li>• Impurity profile in detail</li></ul>
DPI	Lactose Monohydrate, NF	Carrier	<ul style="list-style-type: none"><li>• Quantitative color and clarity</li><li>• Anomeric purity</li><li>• Elemental impurities</li><li>• Amorphous content</li><li>• Microbial limits</li><li>• Organic volatile impurities</li><li>• Related impurities</li><li>• Particle size distribution</li><li>• pH</li><li>• Assay</li><li>• Particle size and morphology</li><li>• Pyrogens and bacterial endotoxins</li></ul>
	Anhydrous Lactose, NF	Carrier	<ul style="list-style-type: none"><li>• Quantitative color and clarity</li><li>• Anomeric purity</li><li>• Elemental impurities</li><li>• Amorphous content</li><li>• Microbial limits</li><li>• Organic volatile impurities</li><li>• Related impurities</li></ul>

<sup>27</sup> See FDA guidance for industry *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*.



## *Contains Nonbinding Recommendations*

*Draft — Not for Implementation*

Dosage Form	Excipient	Function	Tests
			<ul style="list-style-type: none"> <li>• Particle size distribution</li> <li>• pH</li> <li>• Assay</li> <li>• Monohydrate lactose content</li> <li>• Particle size and morphology</li> <li>• Pyrogens and bacterial endotoxins</li> </ul>

794  
795 For propellants (e.g., HFA-134a, HFA-227) specifications should include the following tests:  
796 identity, appearance, assay, acidity, total residue, moisture content, related impurities, and  
797 unrelated impurities (e.g., CO, N<sub>2</sub>, O<sub>2</sub> gases). Generally, the assay acceptance criterion should  
798 not be less than 99.99 percent for propellants. The related impurities acceptance criteria for  
799 HFA-134a and HFA-227, shown in Table 4 and Table 5, are typical of the limits that are  
800 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

## Contains Nonbinding Recommendations

Draft — Not for Implementation

804  
805  
806

**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

807  
808  
809  
810  
811  
812  
813  
814  
815  
816

### 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.

## Contains Nonbinding Recommendations

Draft — Not for Implementation

- 817
- Batch analyses.
  - Justification for the proposed specification.
- 818
- 819

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

821

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

823

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

824

825

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

829

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

831

832 1. *Description*

833

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

---

<sup>28</sup> 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.

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

843  
844  
845  
846  
847  
848  
849  
850  
851  
852  
853  
854  
855  
856  
857  
858  
859  
860  
861  
862  
863  
864  
865  
866  
867  
868  
869  
870  
871  
872  
873  
874  
875  
876  
877  
878  
879  
880  
881  
882  
883  
884  
885  
886  
887  
888

### ***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)  $\pm 15$  percent for individual actuations and NMT  $\pm 10$  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).

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

### 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

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

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

939  
940 Acceptance testing for spray pattern on incoming actuator lots with the specified valve can  
941 substitute for the release testing of spray pattern for the MDI product, if justified. However, the  
942 acceptance criteria for the spray pattern should be included in the MDI product specification.

### 943 944 7. *Foreign Particulates*

945  
946 MDIs and DPIs: The MDI or DPI product specification should include tests and acceptance  
947 criteria for foreign particulates. The acceptance criteria should include limits for less than 10  
948 micrometers, 10 to 25 micrometers, and greater than 25 micrometers.

### 949 950 8. *Microbial Limits*

951  
952 MDIs and DPIs: The MDI or DPI product specification should include tests and acceptance  
953 criteria for total microbial count and specified indicator organisms. USP compendial methods  
954 and criteria in General Chapters <610> Alternative Microbiological Sampling Methods for  
955 Nonsterile Inhaled and Nasal Products and <1111> Microbiological Examination of Nonsterile  
956 Products Acceptance Criteria for Pharmaceutical Preparations and Substances for  
957 Pharmaceutical Use can be referenced.

### 958 959 9. *Leachables*

960  
961 MDIs and DPIs: Additional information related to leachables and extractables can be found in  
962 the following documents: USP Chapters <1663>, <1664>, and <1664.1>, and PQRI  
963 Recommendations to FDA.<sup>29</sup>

### 964 965 **G. Reference Standards or Materials (P6)**

966  
967 As described in ICH M4Q, section 3.2.P.6 of the application should contain information on  
968 reference standards or reference materials used for testing of the MDI or DPI product, if not  
969 previously provided in 3.2.S.5, Reference Standards or Materials.

### 970 971 **H. Container and Closure System (P7)**

972  
973 As described in ICH M4Q, section 3.2.P.7 of the application should contain the information for  
974 the container closure system (which includes the device constituent part and the primary and  
975 secondary packaging). The application for MDIs and DPIs should also include the following  
976 information, as provided in Table 7, below.

977

---

<sup>29</sup> See [http://pqri.org/wp-content/uploads/2015/08/pdf/LE\\_Recommendations\\_to\\_FDA\\_09-29-06.pdf](http://pqri.org/wp-content/uploads/2015/08/pdf/LE_Recommendations_to_FDA_09-29-06.pdf).

**Contains Nonbinding Recommendations**

*Draft — Not for Implementation*

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

978  
979  
980

	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 <sup>1</sup>	•				
Qualitative and Quantitative Extractable Profile(s)	•	•			
Toxicological Evaluation of Extracted Materials (and Residues <sup>1</sup> )	•	•			
Specification and Analytical Sampling Plans <sup>2</sup>	•	•	•	•	•
CoA or Representative Test Data	•	•	•	•	•
Functional and Performance Characteristics <sup>3</sup>		•			
Identity, Composition, and Treatment Procedures of Elastomeric Components		•			
Flow Resistance <sup>4</sup>					•
USP Biological Reactivity Testing <87> and <88> and Food Additive Regulation <sup>5</sup>			•		•

981  
982  
983  
984  
985  
986  
987  
988  
989  
990

<sup>1</sup> Process contaminants (where appropriate)

<sup>2</sup> Can include for example, dimensions, qualitative and quantitative extractables and residues, physicochemical parameters, compositional controls, and/or performance characteristics

<sup>3</sup> For example: valve actuation force, stroke length, valve delivery, and valve leakage of the assembled valve/canister combination containing placebo formulation

<sup>4</sup> Supportive information and data should be provided to characterize any dependence of the drug delivery and formulation deagglomeration on the flow resistance of the device constituent part

<sup>5</sup> If the components are not recognized as safe for food contact under appropriate regulations, extractables (e.g., organic solvent(s), water), obtained under defined experimental conditions, should be established analytically both qualitatively and quantitatively. In addition to in vitro and in vivo tests and other safety data for these components

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

991 not recognized as safe for food contact, extractables profiles with multiple solvents should be assessed  
992 toxicologically and a rationale provided to support limits for extractables that can be applied on a routine basis.  
993

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

1000

1001 For ANDAs, the applicant can compare the extraction profiles of the container closure system  
1002 with the leachables profile(s) of the MDI or DPI product (or placebo) after storage under  
1003 accelerated stability conditions as long as the applicant confirms that post-approval verification  
1004 activities will include an assessment of initial production stability batches to confirm the results  
1005 for the MDI or DPI product (or placebo) through the expiration dating period. If equilibrium is  
1006 not reached by six months, real-time long-term data should be used to establish an appropriate  
1007 expiration dating period. If the compared results are within the applicant's acceptance criteria  
1008 but there are qualitative differences, the results should be discussed with the responsible review  
1009 division.

1010

1011 For additional information on container closure systems, refer to appropriate Agency guidance  
1012 and available standards.

1013

### **I. Stability (P8)**

1014

1015  
1016 Stability studies should be conducted as recommended in ICH Q1A(R2), Q1C, Q1D, and  
1017 Q1E.<sup>30,31</sup> The MDI or DPI product should be packaged as intended for commercialization,  
1018 including secondary packaging. Stability data collected during the clinical investigations phase  
1019 on the MDI or DPI product packaged in a different container closure system configuration can be  
1020 provided as supporting data, with appropriate justification.

1021

1022 If protective secondary packaging is used, the routine stability test storage conditions for the  
1023 product in the presentation intended for distribution should include both long-term storage at  
1024 25°C/60 percent relative humidity (RH) and at 30°C/65 percent RH for one-half of the proposed  
1025 expiration dating period.

1026

1027 Table 8 below describes the attributes that should be tested during stability studies. During the  
1028 conduct of stability studies, the MDI or DPI product should be stored in upright, horizontal, and  
1029 inverted orientations. If sufficient data demonstrate that orientation does not affect the product  
1030 quality, routine stability studies can be conducted on product stored in only one orientation.

1031

Alternatively, if data demonstrate a certain orientation is detrimental to product stability, that

---

<sup>30</sup> 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.

<sup>31</sup> 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*.



## Contains Nonbinding Recommendations

Draft — Not for Implementation

1032 orientation should be used in routine stability studies. However, shipping and storage of the  
1033 marketed product should utilize the most favorable orientation.

1034

1035

1036

**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	

1037

1038

1039

1040

1041

1042

1043

1044

1045

1046

1047

### J. Labeling

1048

1049

1050

1051

1052

1053

1054

1055

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.<sup>32</sup> 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*.<sup>33</sup>

<sup>32</sup> 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.

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

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

1056  
1057  
1058  
1059  
1060  
1061  
1062  
1063  
1064  
1065  
1066  
1067  
1068  
1069  
1070  
1071  
1072  
1073  
1074  
1075  
1076  
1077  
1078  
1079  
1080  
1081  
1082  
1083  
1084  
1085  
1086  
1087  
1088  
1089  
1090  
1091  
1092  
1093  
1094  
1095  
1096  
1097  
1098  
1099  
1100

### 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.

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

- 1101 • A statement should be included that the canister should be discarded when the  
1102 labeled number of actuations has been used.  
1103
- 1104 b. HOW SUPPLIED/STORAGE AND HANDLING Section of the  
1105 Prescribing Information  
1106
- 1107 • The net content (fill) weight of the container should be stated.  
1108
- 1109 • The medication amount delivered (TDD) from the actuator.  
1110
- 1111 • The number of actuations for each canister fill weight should be included.  
1112 Qualifying terms such as “at least” and “approximately” should not be used.  
1113
- 1114 • A description of the actuator and protective cap to be used with the container  
1115 and valve, including the color and appearance, should be included.  
1116
- 1117 • A statement should be provided that the canister should only be used with the  
1118 accompanying actuator and that the actuator should not be used with any other  
1119 inhalation drug product.  
1120
- 1121 • A statement should be provided that the correct amount of medication in each  
1122 inhalation cannot be ensured after the labeled number of actuations from the  
1123 canister has been used, even though the canister may not be completely  
1124 empty. Additionally, a statement should be included that the canister should  
1125 be discarded when the labeled number of actuations has been used.  
1126
- 1127 • Storage conditions should be clearly stated, including any warning statements  
1128 regarding temperature and humidity.  
1129
- 1130 • Any preferred storage orientation should be indicated.  
1131
- 1132 • A statement should be included regarding the appropriate temperature of the  
1133 MDI before use, as well as any requirements for shaking, if necessary. In  
1134 addition, the impact of the cooling effect from multiple successive actuations  
1135 on product performance should be described, if applicable.  
1136
- 1137 • If protective secondary packaging (e.g., foil overwrap) is used, this should be  
1138 clearly stated. In addition, appropriate statements should be included that the  
1139 contents enclosed in the protective secondary packaging should not be used  
1140 after a specified number of days (e.g., 2 weeks, 30 days) from the date the  
1141 protective package was compromised (in-use period).  
1142
- 1143 • Any warning statements required under 21 CFR 369.21 (e.g., storage above  
1144 120°F may cause bursting, keep out of reach of children, do not puncture, do  
1145 not use or store near heat or open flame, never throw container into fire or  
1146 incinerator, do not spray into eyes).

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

- 1147
- 1148
- 1149
- 1150
- 1151
- 1152
- 1153
- 1154
- 1155
- 1156
- 1157
- 1158
- 1159
- 1160
- 1161
- 1162
- 1163
- 1164
- 1165
- 1166
- 1167
- 1168
- 1169
- 1170
- 1171
- 1172
- 1173
- 1174
- 1175
- 1176
- 1177
- 1178
- 1179
- 1180
- 1181
- 1182
- 1183
- 1184
- 1185
- 1186
- 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<sup>34</sup>.
    - 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

---

<sup>34</sup> 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.

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

1187 packaging should not be used after a specified number of days (e.g., 2 weeks,  
1188 30 days) from the date the protective package was opened (in-use period).

- 1189
- 1190 • Cleaning instructions should be included, if appropriate.
  - 1191
  - 1192 • A statement should be included that the canister should be discarded when the  
1193 labeled number of actuations has been used.<sup>35</sup> Also, a statement should be  
1194 included that the correct amount of medication in each inhalation cannot be  
1195 ensured after the labeled number of actuations even though the canister may  
1196 not be completely empty.
  - 1197
  - 1198 • Warning statements required under 21 CFR 369.21 (e.g., storage above 120°F  
1199 may cause bursting, keep out of reach of children, do not puncture, do not use  
1200 or store near heat or open flame, never throw container into fire or incinerator,  
1201 do not spray into eyes).
  - 1202

### d. Container Labels and Carton Labeling

1203 In addition to the information typically required to be included on the container label and/or  
1204 carton labeling under Title 21, the container label should include the following information  
1205 specific to MDI products:  
1206  
1207

- 1208
- 1209 • Amount of the drug delivered per actuation from the mouthpiece/nosepiece  
1210 and the valve.
  - 1211
  - 1212 • Number of usable actuations per container.
  - 1213
  - 1214 • Recommended storage conditions including any warning statements regarding  
1215 temperature and humidity.
  - 1216
  - 1217 • Use period once the MDI product is removed from protective packaging (if  
1218 applicable).
  - 1219
  - 1220 • The instruction “Shake well before using” for suspension formulations.
  - 1221
  - 1222 • A statement that the MDI product should only be used with the mouthpiece  
1223 provided (e.g., “For oral inhalation with (*Drug Product Name*) actuator  
1224 only”).
  - 1225
  - 1226 • Reference to the patient’s Instructions for Use and additional instructional  
1227 statements (e.g., instructions for initial priming and repriming the MDI unit,  
1228 inhalation instructions, instructions pertaining to protective caps, etc.).
  - 1229

---

<sup>35</sup> See FDA guidance for industry *Integration of Dose-Counting Mechanisms into MDI Drug Products*.

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

- 1230
- 1231
- 1232
- 1233
- 1234
- 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).

1235 In the case of small labels, only some of the information listed above must be included on the  
1236 label (21 CFR 201.10(i)). However, all labeling information required by the FD&C Act and the  
1237 regulations in Title 21 of the Code of Federal Regulations must be included on the carton, outer  
1238 container, wrapper, and leaflet as appropriate.

1239

1240 2. *DPIs*

1241

1242 The labeling of oral DPIs should state the established name of the product as *(Drug) Inhalation*  
1243 *Powder* and provide the strength as the amount per metered dose unit. For nasal DPIs, the  
1244 product labeling should state the established name of the product as *(Drug) Nasal Powder* and  
1245 provide the strength as the metered dose. The established name and strength should be followed  
1246 by a phrase such as “For oral inhalation only” or “For nasal inhalation only,” as appropriate.

1247

1248 In addition to the information typically required under Title 21 for the description of the drug  
1249 substance and formulation (21 CFR part 201), the product labeling should include the following  
1250 information specific to DPI products:

1251

1252 a. DESCRIPTION Section of the Prescribing Information

1253

- 1254
- 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
- 1275

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

- 1276 delivery system, which may vary for asthma, COPD, and other patient  
1277 populations.  
1278
- 1279 • A list of all excipients should be included. Substances should be identified by  
1280 their established names.  
1281
  - 1282 • If the drug substance that exits the mouthpiece is a hydrate, solvate, or  
1283 complex, this information should be clearly specified with proper strength  
1284 conversion for the active moiety.  
1285
  - 1286 • For DPIs that contain lactose, a statement should be included that the  
1287 formulation may contain residual amounts of milk-related proteins.  
1288
  - 1289 • The number of usable actuations per container if appropriate.  
1290
- 1291 b. HOW SUPPLIED Section of the Prescribing Information  
1292
- 1293 • The net weight of the container contents should be stated for device-metered  
1294 DPIs.  
1295
  - 1296 • The number of medication actuations expected throughout the shelf life of the  
1297 drug product should be indicated. Qualifying terms such as “at least” and  
1298 “approximately” should not be used.  
1299
  - 1300 • Protective secondary packaging (e.g., foil overwrap) should be described. In  
1301 addition, appropriate statements should be included that the content of the  
1302 secondary protective packaging should not be used after a specified number of  
1303 days (e.g., 2 weeks, 30 days) from the date the protective package was  
1304 compromised (in-use period).  
1305
  - 1306 • Storage conditions should be stated, including any warning statements  
1307 regarding temperature, humidity, and light.  
1308
  - 1309 • A brief description of the appearance and color of the body, cap, and other  
1310 markers of the device constituent part should be provided, particularly for ease  
1311 of identification of different strengths of drugs delivered by the same device  
1312 constituent part.  
1313
  - 1314 • A statement should be included that the DPI unit should be discarded when  
1315 the labeled number of actuations has been used, if appropriate.  
1316

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

- 1317 c. Instructions for Use<sup>36</sup>  
1318  
1319 • Detailed, step-by-step, appropriately illustrated instructions for patient use  
1320 should be included. Important elements of the DPI (e.g., body, cap, other  
1321 instructive markings such as arrows depicting direction or alignment, etc.)  
1322 should be clearly identified with illustrations.  
1323  
1324 • Storage conditions should be stated, including any warning statements  
1325 regarding temperature, humidity, and light.  
1326  
1327 • If secondary protective packaging (e.g., foil overwrap) is used for the DPI  
1328 product, device constituent part, or unit dose container, this should be stated.  
1329 Appropriate statements should be included that the content of the secondary  
1330 protective packaging (e.g., device-metered DPIs, pre-metered DPIs) should  
1331 not be used after a specified number of days (e.g., 2 weeks, 30 days) from the  
1332 date the secondary protective packaging was opened (in-use period).  
1333  
1334 • For device-metered DPIs without a locking mechanism, a statement should be  
1335 included stating that the correct amount of medication in each inhalation  
1336 cannot be ensured after the labeled number of doses, even though the device-  
1337 metered DPI may not be completely empty. A statement recommending that  
1338 the device-metered DPI be discarded after the labeled number of doses has  
1339 been delivered should be included as well.  
1340  
1341 • Cleaning instructions should be included, if appropriate.  
1342  
1343 d. Container Labels and Carton Labeling  
1344

1345 In addition to the information typically required to be included on the container label and/or  
1346 carton labeling under Title 21, the container label should include the following information  
1347 specific to DPI products:  
1348

- 1349 • Amount of the drug per metered unit.  
1350  
1351 • Number of usable actuations per container or device-metered DPI or for the  
1352 device constituent part (if re-used), as appropriate.  
1353  
1354 • Recommended storage conditions including any warning statements regarding  
1355 temperature, humidity, or light.  
1356  
1357 • Use period once the DPI product is removed from protective packaging, if  
1358 applicable.  
1359

---

<sup>36</sup> Ibid



## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

- 1360 • A statement that the DPI product should only be used with the device  
1361 constituent part provided, where applicable (e.g., “For oral inhalation with  
1362 *(Drug Product Name)* actuator only”).
- 1363
- 1364 • Any special dispensing instructions for the pharmacist and additional  
1365 statements for the physician, if applicable.
- 1366
- 1367 • Reference to the patient’s Instructions for Use and additional instructional  
1368 statements (e.g., loading instructions for pre-metered DPIs, inhalation  
1369 instructions, instructions pertaining to protective caps, etc.).
- 1370

1371 In the case of small labels, only some of the information listed above must be included on the  
1372 label (21 CFR 201.10(i)). However, all labeling information required by the FD&C Act and the  
1373 regulations in Title 21 of the Code of Federal Regulations must be included on the carton, outer  
1374 container, wrapper, and leaflet as appropriate.

1375

**Contains Nonbinding Recommendations**

*Draft — Not for Implementation*

1376 **V. APPENDIX**

1377

1378 **A. Tables**

1379

1380 **Table A. General Relationship Between QTPP Elements and CQAs for MDIs**

1381

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

1382

1383 **Table B. General Relationship Between QTPP Elements and CQAs for DPIs**

1384

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

**Contains Nonbinding Recommendations**

*Draft — Not for Implementation*

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

1385  
1386  
1387  
1388

**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

1389 \* When present

1390  
1391  
1392  
1393  
1394  
1395  
1396  
1397  
1398  
1399  
1400  
1401  
1402

**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.

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

### 1403 1. *General Considerations for Significant Change*

1404

1405 For any of the characterization studies described in this section that involve stability testing,  
1406 significant change should be considered:

1407

1408 • In general, failure to meet the acceptance criteria for any attribute normally tested  
1409 during stability studies.

1410

1411 • For assay, a change from the initial value of five percent or more.

1412

1413 • For DDU, a change in the mass of the mean dose of 10 percent or more (determined  
1414 separately on samples taken from the beginning and end of product life), or a failure  
1415 to meet the acceptance criteria for first tier testing.

1416

1417 • For APSD, a change in the total mass of fine particles (e.g., particles less than five  
1418 micrometers) more than 10 percent.

1419

1420 • For the description, changes such as: discoloration or other changes in the  
1421 appearance of the contents, distortion of valve components, valve clogging or  
1422 malfunction, canister corrosion, and adherence of the drug to the walls of the  
1423 container or valve components.

1424

### 1425 2. *Recommendations for Specific Characterization Studies*

1426

#### 1427 a. *In-Use Period*

1428

1429 The purpose of these studies is to demonstrate, for MDI or DPI products marketed in protective  
1430 secondary packaging, that the product will perform in accordance with its specification for the  
1431 entire length of the proposed in-use period after the protective secondary packaging is opened.

1432

1433 Study Design: Conduct stability studies under intermediate conditions (e.g., 30°C/65 percent  
1434 RH) on samples of the MDI or DPI product with the protective secondary packaging opened.  
1435 Measure appropriate parameters (e.g., DDU, APSD, water content). Include samples of product  
1436 at the beginning and near the end of its proposed shelf life. It is recommended that the study  
1437 duration period be twice the proposed in-use period.

1438

#### 1439 b. *Temperature Cycling*

1440

1441 The purpose of these studies is to demonstrate that fluctuating changes in temperature and  
1442 humidity (such as those encountered during shipping and handling) will not have an adverse  
1443 effect on the quality and performance of the MDI or DPI product. This information, in  
1444 conjunction with stability data, should support the proposed storage conditions in the product  
1445 labeling.

1446

1447 Study Design: Conduct cycling studies for 3-4 weeks using two different storage conditions, one  
1448 subzero (–10 to –20°C) and the other above room temperature (40°C). Cycle between these

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

1449 conditions every 12 hours. (Alternative conditions and durations can be used, if they can be  
1450 justified.) Compare test results to results from control samples (stored under the proposed long-  
1451 term storage conditions as opposed to the temperature cycling conditions) tested at the same  
1452 intervals.

1453

1454 c. Priming and Repriming

1455

1456 The purpose of these studies is to support the instructions in the product labeling for priming  
1457 (how many times a patient should actuate a unit before initial use) and repriming (how many  
1458 times a patient should actuate a unit before using it again after defined periods of rest).

1459

1460 Study Design: Measure the delivered amount of drug substance from consecutive actuations of  
1461 individual units after defined resting intervals (e.g., 0, 6, 12, 24, 48 hours, 3 days). After each  
1462 resting interval, repeat actuations until the delivered amount of drug substance per actuation  
1463 consistently meets the acceptance criteria for DDU. Test units at the beginning and near the end  
1464 of the proposed shelf life. If resting orientation affects the results, test units in various resting  
1465 orientations (upright and inverted, or upright and horizontal). Testing can be performed  
1466 concurrently on separate samples with progressively longer resting periods.

1467

1468 d. Effect of Patient Use

1469

1470 The purpose of these studies is to confirm that the MDI or DPI product functions properly after  
1471 repeated patient uses of the product.

1472

1473 Study Design: Collect a number (e.g., 50-100) of partially used product units (including units  
1474 near the labeled number of actuations) from clinical studies and measure appropriate parameters  
1475 (e.g., DDU and APSD) and dose counter function. Also collect and investigate any MDI or DPI  
1476 products that were reported as malfunctioning.

1477

1478 e. Effect of Storage and Shaking (suspension formulated MDIs only)

1479

1480 The purpose of these studies is to confirm that shaking instructions in the product labeling for  
1481 suspension formulated MDIs are adequate to assure satisfactory dose delivery performance.

1482

1483 Study Design: Measure appropriate parameters (e.g., DDU and APSD) on the MDI product  
1484 stored for increasing periods of time subsequent to shaking. From the results, determine the  
1485 maximum allowable use time after shaking. Include the effects of shaking duration and storage  
1486 orientation if these factors affect the results.

1487

1488 f. Effect of Orientation of the DPI Product on Delivered Dose

1489

1490 The purpose of these studies is to support any statements made in the product labeling about the  
1491 DPI product orientation during use.

1492

1493 Study Design: Measure appropriate parameters (e.g., DDU and APSD) for DPI products  
1494 actuated while oriented at various angles.

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

1495  
1496  
1497  
1498  
1499  
1500  
1501  
1502  
1503  
1504  
1505  
1506  
1507  
1508  
1509  
1510  
1511  
1512  
1513  
1514  
1515  
1516  
1517  
1518  
1519  
1520  
1521  
1522  
1523  
1524  
1525  
1526  
1527  
1528  
1529  
1530  
1531  
1532  
1533  
1534  
1535  
1536  
1537

### **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 Actuators 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.

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

1538 k. Effect of Flow Rate and Inhalation Delay on MDIs with Spacers

1539  
1540 The purpose of these studies is to characterize the sensitivity of the delivery performance to  
1541 variation in inspirational flow rates and inhalation delay on MDI products used with a spacer or  
1542 holding chamber.

1543  
1544 Study Design: Using a flow rate range and volume consistent with the intended patient  
1545 population, measure appropriate parameters (e.g., DDU and APSD) as a function of flow rate at  
1546 the recommended constant volumes. Also assess the effect of increasing waiting periods (e.g., 0,  
1547 5, 10 seconds) between actuation and initiation of in-flow. For breath-activated MDI products,  
1548 determine the ranges of flow rates that generate actuations containing the label claim amount of  
1549 delivered dose and the corresponding acceptable APSD.

1550  
1551 l. Robustness

1552  
1553 The purpose of these studies is to confirm that the MDI or DPI product is of sufficiently robust  
1554 design to withstand shipping conditions and typical patient usage.

1555  
1556 Study Design: Subject a number of units to actions (e.g., dropping, agitation, shipping) that will  
1557 simulate conditions the product could be exposed to after it is released, including during patient  
1558 use. Determine the effect of these actions on MDI or DPI product performance by measuring  
1559 DDU, APSD, and dose counter function.

1560  
1561 **C. Approaches to Evaluating Delivered Dose Uniformity (DDU)**

1562  
1563 1. *Parametric Tolerance Interval Testing (PTIT)*

1564  
1565 FDA recommends that applicants establish test parameters (e.g., sample size, tolerance interval  
1566 factor (k factor)) and acceptance criteria that will ensure, to a confidence level of 95 percent, that  
1567 at least 90 percent of the units in a batch (i.e., the coverage) will meet the established upper and  
1568 lower limits (i.e., 80-120 percent of TDD).

1569  
1570 FDA recommends the use of a two one-sided tolerance interval (TOSTI) test and a two-tiered  
1571 approach to setting acceptance criteria:

1572  
1573 First tier acceptance criteria:

1574  
1575 • For pre-metered DPIs, measure the amount of drug substance discharged from the  
1576 mouthpiece as a percentage of TDD ( $X$ ) from  $n$  units and calculate the mean ( $\bar{X}$ ) and  
1577 standard deviation(s). For MDIs and device-metered DPIs, measure the initial dose  
1578 and the last of the labeled doses for each of the  $n$  units for a total of  $2*n$   
1579 measurements. The batch passes if:

1580

## Contains Nonbinding Recommendations

Draft — Not for Implementation

$$\bar{X} + (k_1 \cdot s) \leq 120$$

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  $2 \cdot n$  for MDIs and device-metered DPIs), coverage, and confidence level.

1581 Second tier acceptance criteria:

1582

- 1583 • If the batch does not pass tier one testing, measure the amount of drug substance  
1584 discharged from the mouthpiece as a percentage of TDD ( $X$ ) from an additional  $m$   
1585 units for pre-metered DPIs (or the initial dose and the last of the labeled doses for  
1586 each of the additional  $m$  units for MDIs and device-metered DPIs), combine the  
1587 results with those from the first tier, and calculate the mean ( $\bar{X}$ ) and standard  
1588 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  $2 \cdot (n+m)$  for MDIs and device-metered DPIs), coverage, and confidence level.

1589 Table D below shows  $k_1$  factors specific to a confidence level of 95 percent and 90 percent  
1590 coverage for a range of sample sizes.

1591

1592 **Table D. One-sided Tolerance Interval Factors ( $k_1$ ) for 95**  
1593 **Percent Confidence Level and 90 Percent Coverage<sup>37</sup>**

1594

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

1595

1596 FDA recommends that applicants adopt a 1:3 ratio for the change in sample size from tier 1 to  
1597 tier 2 testing (i.e., if  $n = 10$ , then  $n+m = 30$ ). Furthermore, FDA recommends that the tier 1  
1598 sample size should not be smaller than ten units. Applicants can set sample sizes much larger  
1599 than  $n = 10$  and  $n+m = 30$ , but should consider the cost/benefit ratio before setting sample sizes

<sup>37</sup> For example, see Hahn and Meeker, *Statistical Intervals – A Guide for Practitioners*, John Wiley and Sons, Inc. 1991.



## *Contains Nonbinding Recommendations*

*Draft — Not for Implementation*

1600 that are very large. FDA believes that tier 2 sample sizes larger than about 90 (i.e.,  $n+m = 90$ )  
1601 will provide very little additional benefit.

1602

### 1603 2. *Counting Test*

1604

1605 The application of a counting test for evaluating DDU was in use before other approaches such  
1606 as PTIT were developed. If an applicant chooses to evaluate DDU using a counting test, the  
1607 Agency recommends a two-tiered approach to acceptance criteria, as described below:

1608

1609 First tier acceptance criteria:

1610

1611 • For pre-metered DPIs, the amount of drug substance measured by the test is not  
1612 outside 80-120 percent of TDD for more than 1 determination (out of 10). For MDIs  
1613 and device-metered DPIs, for each of 10 units, the initial dose and the last of the  
1614 labeled doses are measured. The amount of drug substance is not outside 80-120  
1615 percent of TDD for more than 2 determinations (out of 20).

1616

1617 • The amount of drug substance measured by the test is not outside 75-125 percent of  
1618 TDD for any determination.

1619

1620 • For pre-metered DPIs, the mean is not outside 85-115 percent of TDD.

1621

1622 • For MDIs and device-metered DPIs, the mean of separate determinations made for  
1623 the initial dose from each unit and the mean of separate determinations made for the  
1624 last of the labeled number of doses for each unit are not outside 85-115 percent of  
1625 TDD.

1626

1627 If the above acceptance criteria are met, the batch passes the test for DDU.

1628

1629 If the amount of drug substance is outside 80-120 percent of TDD in more determinations than  
1630 are permitted by the first criterion, testing can be performed on 20 additional units to determine  
1631 if the batch meets second tier acceptance criteria, provided that the other two criteria described  
1632 above are met.

1633

1634 Second tier acceptance criteria:

1635

1636 • The amount of drug substance measured by the test is not outside 80-120 percent of  
1637 TDD for more than 3 of 30 determinations for pre-metered DPIs or for more than 6 of  
1638 60 determinations for MDIs and device-metered DPIs (30 for the initial dose from  
1639 each unit and 30 for the last of the labeled number of doses for each unit).

1640

1641 • The amount of drug substance measured by the test is not outside 75-125 percent of  
1642 TDD for any determination.

1643

1644 • For pre-metered DPIs, the mean is not outside 85-115 percent of TDD.

1645

***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

1646  
1647  
1648  
1649

- 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.