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Guidance for Industry

Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products

Chemistry, Manufacturing, and Controls Documentation

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
October 1998
CMC

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**Chemistry, Manufacturing, and Controls
Documentation**

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GUIDANCE FOR INDUSTRY¹

MDI and DPI Drug Products Chemistry, Manufacturing, and Controls Documentation

*(Due to the length and complexity of this draft guidance,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

1 **I. INTRODUCTION**

2 This document provides guidance for industry on the chemistry, manufacturing, and controls
3 (CMC) documentation to be submitted in new drug applications (NDAs) and abbreviated new
4 drug applications (ANDAs) for metered dose inhalation aerosols and metered dose nasal aerosols
5 (also known as oral and nasal metered dose inhalers respectively or MDIs) and inhalation powders
6 (also known as dry powder inhalers or DPIs). This guidance also covers CMC information
7 recommended for inclusion in the application regarding the components, manufacturing process,
8 and controls associated with each of these areas. The recommendations in this guidance should
9 also be considered for investigational drug applications (INDs). The guidance does not address
10 inhalation solutions and aqueous nasal sprays.

11 The guidance sets forth information that should be provided to ensure continuing drug product
12 quality and performance characteristics for MDIs and DPIs. The guidance does not impose
13 mandatory requirements but does put forth acceptable approaches for submitting CMC-related
14 regulatory information. Alternative approaches may be used. Applicants are encouraged to
15 discuss significant departures from the approaches outlined in this guidance with the appropriate
16 Agency division before implementation to avoid expending resources on development avenues
17 that may later be deemed unacceptable.

18 Reference to information in Drug Master Files (DMFs) for the CMC section of the application is
19 acceptable if the DMF holder provides written authorization that includes specific reference (e.g.,
20 submission date, page number, item name and number) to the pertinent and up-to-date
21 information (21 CFR 314.420(d)). Refer to FDA's *Guideline for Drug Master Files* (September
22 1989) for more information about DMFs.

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

23 **II. BACKGROUND**

24 **A. Metered-Dose Inhalers (MDIs)**

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

29 Metered-dose inhaler products contain therapeutically active ingredients dissolved or
30 suspended in a propellant, a mixture of propellants, or a mixture of solvents, propellants,
31 and/or other excipients in compact pressurized aerosol dispensers. An MDI product may
32 discharge up to several hundred metered doses of one or more drug substances.
33 Depending on the product, each actuation may contain from a few micrograms (mcg) up
34 to milligrams (mg) of the active ingredients delivered in a volume typically between 25 and
35 100 microliters.

36 Although similar in many features to other drug products, MDIs have unique differences
37 with respect to formulation, container, closure, manufacturing, in-process and final
38 controls, and stability. These differences need to be considered during the development
39 program because they can affect the ability of the product to deliver reproducible doses to
40 patients over the life of the product as well as the product's efficacy. Some of the unique
41 features of MDIs are listed below:

- 42 1. The container, the valve, the actuator, the formulation, any associated accessories
43 (e.g., spacers), and protective packaging collectively constitute the drug product.
44 Unlike most other drug products, the dosing and performance and, therefore, the
45 clinical efficacy of a MDI may be directly dependent on the design of the container
46 and closure system (CCS).
- 47 2. The fraction of the formulation delivered to the patient consists of a mixture of
48 micronized (or solubilized) drug substance in the desired physical form, which may
49 be within a residual matrix of oily excipient material, propellant, and/or solvent.
- 50 3. Fixed portions of medication from a multidose container can be directly
51 administered to the patient without contamination or exposure of the remaining
52 material under normal use conditions. Conversely, portions of the immediate
53 container's content cannot be removed from a pressurized container for further
54 modification or manipulation.

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- 55 4. The aerosolization of materials from a pressurized container is a complex and rapid
56 sequence of events. When the content of the metering chamber is released, it
57 undergoes volume expansion and forms a mixture of gas and liquid before being
58 discharged as a jet through the orifice of the actuator. Within the expanding jet,
59 the droplets undergo a series of processes. Subsequent to the aerosolization and
60 dispersion of the drug product into a multitude of droplets, and during the
61 propulsion of these droplets from the actuator to the biological target, the drug
62 substance particles in the droplets become progressively more concentrated due to
63 rapid evaporation of the volatile propellant components.
- 64 5. The concept of classical bioequivalence and bioavailability is usually not applicable
65 for oral inhalation aerosols. The dose administered is typically so small that blood
66 or serum concentrations are generally undetectable by routine analytical methods.
67 Moreover, bioequivalency studies are complicated by the fact that only
68 approximately 10–15 percent of the dose reaches the biological target. The
69 remainder of the dose, trapped in the mouth and pharynx, is swallowed and
70 absorbed through the gastrointestinal (GI) tract. Thus, even if determination of
71 blood or serum concentrations were possible, additional and more extensive
72 studies would be necessary to distinguish the contributions of the drug absorbed
73 from the pulmonary, buccal, and GI routes.
- 74 6. Clinical efficacy assessment of inhalation aerosols requires consideration of several
75 parameters, such as:
- 76 ● Variability in the disease itself (ventilatory and anatomic or pathologic
77 factors);
 - 78 ● Administration skills and practices, for example, breath holding and its
79 duration, patient inspiratory flow rate, discharging either via closed lips
80 around the mouthpiece or into the open mouth, coordination of aerosol
81 discharge (actuate and breathe) and inhalation by the patient, add-on
82 devices (e.g., spacers, chambers), proper priming of the valve and cleaning
83 practices for the actuator, proper handling and fitting of the actuator to the
84 valve stem;
 - 85 ● Presence of other drugs (i.e., when disease states require a multidrug
86 treatment) which may exacerbate differences between products;
 - 87 ● Drug product variability due to physical characteristics and controls of the
88 drug substance, optimized formulation, valve and actuator design,
89 manufacturing process and in-process controls, and so on.

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

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

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

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

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

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

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

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

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

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

153 The remaining portion of this guidance will focus on specific chemistry, manufacturing,
154 and controls information recommended for inclusion in the drug product section of
155 applications for MDI and DPI drug products.

156 **III. DRUG PRODUCT**

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

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

162 **A. Components**

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

171 **B. Composition**

172 1. MDIs

173 The composition of an MDI formulation is crucial, particularly in defining the
174 physical stability and the performance characteristics of a suspension MDI. In
175 suspension inhalation aerosols, the drug substance can float or settle depending on
176 the relative densities of the drug substance and the liquid phase of the formulation.
177 Moreover, the formulation composition will have a direct effect on the degree or
178 extent of agglomeration or suspendibility of the drug substance particles.
179 Preferential interaction of the suspended drug substance with the various internal
180 container and closure system components (e.g., adherence of the drug substance to
181 the walls of the container or valve components) may also contribute to a
182 nonhomogeneous distribution of drug substance. The above mentioned
183 phenomena, which may be exacerbated with time, can contribute to inconsistent
184 medication dose delivery and particle size distribution. Additionally, in a typical
185 MDI, the propellant(s) and cosolvent(s) constitute the majority of the formulation
186 composition, and the type and amount of these components determine the internal
187 pressure of an inhalation aerosol, a critical parameter related to the MDI
188 performance.

189
190 The application should include a statement of the quantitative composition of the
191 unit formula of the drug product, specifying the name and amount of each active
192 ingredient and excipient contained in a stated quantity of the drug product. These
193 amounts should be expressed in concentration (i.e., amount per unit volume or
194 weight), as well as amount per container and per actuation delivered at the valve.
195 The amount of active ingredient delivered per actuation from the mouthpiece

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196 should be provided. The target container fill weight should also be indicated.
197 Similarly, a production batch formula representative of the one to be employed in
198 the manufacture of the drug product should be included. Any calculated excess for
199 an ingredient should be designated as such, the percent excess shown, scientifically
200 justified, and documented. Information on the density of the formulation should be
201 included. Any intended change in the formulation from that used in the submitted
202 batches (e.g., clinical, biobatch, primary stability, production) should be clearly
203 indicated.

204 2. DPIs

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

216 The application should include a statement of the quantitative composition of the
217 drug product, specifying the name and amount of each active and excipient
218 contained in a stated quantity of the formulation. These amounts should be
219 expressed in concentration (i.e., amount per unit weight), as well as amount per
220 metered dose and emitted dose at the mouthpiece under defined test conditions
221 (e.g., flow rate, duration). For device-metered DPIs, the target formulation fill
222 weight should also be indicated. A production batch formula representative of the
223 one to be employed in the manufacture of the drug product should be included.
224 Any calculated excess for an ingredient should be designated as such, the percent
225 excess shown, scientifically justified, and documented in the submission.

226 **C. Specifications for the Formulation Components**

227 1. Active Ingredient(s)

228 Information regarding the comprehensive characterization of the physical and
229 chemical properties of the drug substance to be used in inhalation drug products
230 should be included in the application. Important properties of the drug substance

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231 may include, but are not necessarily limited to, density, particle size distribution,
232 particle morphology, solvates and hydrates, clathrates, morphic forms, amorphous
233 forms, solubility profile, moisture and/or residual solvent content, microbial
234 quality, pH profile and pKa(s), and specific rotation.

235 Appropriate acceptance criteria and tests should be instituted to control those drug
236 substance parameters considered key to ensuring reproducibility of the
237 physicochemical properties of the drug substance. Key specification parameters
238 may include color, appearance (visual and microscopic), specific identification,
239 moisture, residue on ignition, specific rotation, assay, microbial limits (10 g sample
240 size, USP <61>), melting range, particle size distribution, surface area, crystalline
241 form(s), residual solvents, and heavy metals. Micronized drug substance is
242 typically used in DPIs or MDIs containing a suspension of drug substance.
243 Specifications for control of particle size distribution and crystalline forms (e.g.,
244 shape, texture, surface) of the drug substance, parameters often critical for
245 reproducible drug product performance, should be included in the application.

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

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

261 2. Excipients

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

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

268 The source of each excipient should be identified in the application. Each source
269 should be assessed, and the material supplied should meet appropriate acceptance
270 criteria based on test results for several batches of excipients that were used in
271 preparing the submitted batches of drug product (e.g., clinical, biobatch, primary
272 stability, production). Likewise, when the supplier of an excipient is changed, the
273 new supplier's ability to provide material that meets the same acceptance criteria
274 should be assessed.

275 Adequate DMFs with appropriate authorization should be submitted to the agency
276 for major (e.g., propellant, carriers) and noncompendial excipients. A full
277 description of the acceptance criteria and the test methods used to ensure the
278 identity, assay, functionality, quality, and purity of each excipient should be
279 submitted. If these materials are accepted based upon certificates of analysis from
280 the manufacturers with a specific identification test, the applicant should also
281 develop validated methods or have access to all of the manufacturer's analytical
282 and other test methods to allow the applicant to verify the reliability of the test
283 results at appropriate intervals (21 CFR 211.84).

284 The suitability of excipients to be administered by the inhalation route should be
285 thoroughly investigated and documented in terms of the physicochemical
286 properties. Toxicological qualification of these excipients may be appropriate
287 under various circumstances including (1) increased concentration of an excipient
288 above that previously used in inhalation drug products, (2) excipients used
289 previously in humans but not by the inhalation route, and (3) novel excipients not
290 previously used in humans. The extent of toxicological investigation needed to
291 qualify the use of an excipient under such circumstances will vary, and the
292 applicant is encouraged to contact the responsible review division to discuss an
293 appropriate strategy for toxicological qualification.

294 When *United States Pharmacopeia* (USP) or *National Formulary* (NF)
295 monograph materials are used and the associated specifications do not provide
296 adequate assurance for inhalation use with regard to the assay, quality,
297 performance, and purity, the monograph specifications should be supplemented
298 with additional appropriate acceptance criteria and tests to ensure lot-to-lot
299 reproducibility of the components. For example,

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

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

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

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

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

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337 For noncompendial excipients (e.g., HFA-134a, HFA-227 propellants),
338 comprehensive acceptance criteria reflecting the data for the excipient batches used
339 in the submitted drug product batches (e.g., clinical, biobatch, primary stability,
340 production) should be included to ensure consistent quality of future incoming
341 material. For additional guidance on pharmacological and toxicological
342 considerations, the applicant should consult available CDER guidances or contact
343 the responsible review division. For example, for noncompendial propellants, such
344 as HFA-134a, acceptance criteria and tests should be included for the following
345 parameters: identity, appearance, assay (e.g., not less than 99.9%), acidity, total
346 residue, moisture content, related impurities, and unrelated impurities (e.g., CO,
347 N₂, O₂ gases). The related impurities acceptance criteria limits shown in Table II
348 may be adopted for HFA-134a.

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349 **Table I. Recommended Assay and Impurities Acceptance Criteria for Various**
 350 **Compendial Propellants**

351	Impurity¹	CFC-11 Acceptance Criteria (ppm)	CFC-12 Acceptance Criteria (ppm)	CFC-114 Acceptance Criteria (ppm)
352	HFC-152a		10	
353	HCFC-21	75	50	
354	HCFC-22	10	250	50
355	HCFC-123	10		200
356	HCFC-124			50
357	HCFC-124a			50
358	HCFC-133a	10	10	20
359	CFC-11	99.8% purity	2000	500
360	CFC-12	2000	99.8% purity	1000
361	CFC-13	10	300	
362	CFC-113	75	10	50
363	CFC-113a	15		50
364	CFC-114	40	150	99.8% purity
365	CFC-115		15	300
366	CFC-217			200
367	CFC-319			10
368	BCFC-12B1	15	15	
369	CFC-1112a	10	10	10 ²
370	Methyl Chloride	10	40	
371	Dichloromethane	50	10	
372	Chloroform	20	10	
373	Carbon Tetrachloride	20	10	
374	Total Chloromethanes	50	50	
375	Total Unspecified	20	20	20
376	Total Impurities	2000	2000	2000

377 ¹No number for an impurity indicates its absence (below detection limit of method).

378 ²Acceptance criteria under evaluation.

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

381	Impurity	HFA-134a Acceptance Criteria (ppm)	Impurity	HFA-134a Acceptance Criteria (ppm)
382	HCC-40	5	HCFC-133a	5
383	HFC-23	5	HCFC-161	30
384	HFC-32	5	HCFC-1121	5
385	HFC-125	5	HCFC-1122	5
386	HFC-134	1000	HCFC-1122a	5
387	HFC-143a	10	CFC-11	5
388	HFC-152	5	CFC-12	100
389	HFC-152a	300	CFC-12B1	5
390	HFC-245cb	5	CFC-13	5
391	HFC-1123	5	CFC-113	5
392	HFC-1132	5	CFC-114	5
393	HFC-1225ye	5	CFC-114a	25
394	HFC-1234yf	5	CFC-115	5
395	HFC-1243zf	5	CFC-1112a	5
396	HFC-1336mzz	5	FC-1318my-T	5
397	HCFC-22	50	FC-1318my-C	5
398	HCFC-31	5	Total unsaturates (including HCFC-1122)	5
399	HCFC-123	5	Individual unidentified impurities	5
400	HCFC-123a	5	Total unidentified impurities	10
401	HCFC-124	100	Other organic impurities	50
402	HCFC-124a	5	Any other identified saturated impurity	5
403	HCFC-132b	5	Total impurities	1000
			Assay	99.9%

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404 **D. Manufacturers**

405 The name, street address, building number, and Central File Number (CFN), if available,
406 of each facility involved in the manufacturing of the drug substance and excipients should
407 be listed along with a statement of each manufacturer's specific operations and
408 responsibilities. The same information should be provided for each facility involved in the
409 manufacturing, processing, packaging, controls, stability testing, or labeling operations of
410 the drug product, including all contractors (e.g., test laboratories, packagers, labelers).

411 **E. Method(s) of Manufacture and Packaging**

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

414 If micronization is used for the drug substance or excipient(s), the procedure (e.g., the rate
415 of feed, air pressure, air flow rate, particle size being fed, number of times a lot is
416 micronized, re-use of carry-overs from previous micronized lots), equipment, and in-
417 process controls should be described in detail. Attention should be paid to potential
418 contamination of the micronized material during the process from the grinding parts,
419 compressed gas, and collecting filter (e.g., oil, moisture, other contaminants). The
420 moisture content in the micronized material should be tightly controlled for drug
421 substances or formulations that are chemically or physically sensitive to moisture. The
422 moisture content, particle size distribution, particle morphology (shape and texture), bulk
423 density, as well as impurities, degradants, and contaminants in the drug substance and
424 drug products should be controlled with appropriate acceptance criteria and test methods
425 to ensure lot-to-lot reproducibility.

426 A copy of the actual (executed) batch record and in-process controls should be filed, as
427 appropriate, for representative submitted batches (e.g., clinical, biobatch, primary stability,
428 production). A schematic diagram of the proposed production process, a list of in-process
429 controls, and a master batch production and controls record should be submitted.
430 Information on the lag or equilibration time instituted before the release of MDIs, as well
431 as a description of the packaging operation for MDIs and DPIs and associated in-process
432 controls for these operations, should also be included. The manufacturing directions
433 should include control procedures and specific information on processing variables (such
434 as time, temperature, and moisture) to decrease controllable process variability and
435 increase consistency in the quality of the drug product.

436 A description of in-process controls, analytical tests, and appropriate data to support the
437 acceptance criteria should be provided. In-process controls should be performed at
438 specified production steps under actual operating conditions. For MDIs, in-process

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

445 Additionally, a description of the primary and protective packaging operation and relevant
446 in-process controls for this operation should also be included. For example, when blister
447 units, foil-foil, or protective packaging are used, it should be ensured that the seal area
448 functions properly in terms of adhesion (e.g., heat seal, adhesive) or mechanical seal.
449 Appropriate integrity testing and acceptance criteria for seal completeness and for seal
450 strength should be established to ensure acceptable sealing properties within a batch and
451 among batches.

452 **F. Specifications for the Drug Product**

453 A complete description of release acceptance criteria, analytical methods, and sampling
454 plans should be provided to ensure the identity, strength, quality, purity, and performance
455 of the drug product throughout its shelf life and during the period of patient use. The
456 accuracy, sensitivity, specificity, reproducibility, and ruggedness of the proposed validated
457 test methods should be documented in sufficient detail to permit duplication and
458 verification by Agency laboratories. Comprehensive and well-defined in vitro performance
459 characteristics of inhalation drug products should be established before initiating critical
460 clinical studies. Appropriate, validated test methods and corresponding acceptance
461 criteria that are reflective of the test results for submitted batches (e.g., clinical, biobatch,
462 primary stability, production) are crucial to defining and controlling these characteristics.

463 1. MDIs

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

467 a. Appearance and Color

468 The appearance of the content of the container and the appearance of the container
469 and closure system (i.e., the valve and its components and the inside of the
470 container) should conform to their respective descriptions as an indication of the
471 drug product integrity. If any color is associated with the formulation (either
472 present initially or from degradative processes occurring during shelf life), then a

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473 quantitative test with appropriate acceptance criteria should be established for the
474 drug product.

475 b. Identification

476 Specific identification tests are recommended to verify the identity of the drug
477 substance in the drug product. Chromatographic retention time alone is not an
478 adequate method to ensure the identity of the drug substance in the drug product.
479 If the drug substance is chiral, then at least one of the methods used for
480 identification should be specific for this property.

481 c. Microbial Limits

482 The microbial quality should be controlled by appropriate tests and acceptance
483 criteria for total aerobic count, total yeast and mold count, and freedom from
484 designated indicator pathogens. Acceptance criteria should be reflective of the
485 data for the submitted batches (e.g., clinical, preclinical, biobatch, primary stability,
486 production) but at a minimum should meet the acceptance criteria proposed in the
487 *Pharmacopeial Forum* (1996, Vol. 22, p. 3098). Furthermore, appropriate testing
488 should be done to show that the drug product does not support the growth of
489 microorganisms and that microbial quality is maintained throughout the expiration
490 period. The minimum sample size should be 10 grams or the full content of ten
491 containers (USP <61>).

492 d. Water or Moisture Content

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

497 e. Dehydrated Alcohol Content

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

500 f. Net Content (Fill) Weight

501 The total net weight of all formulation components in the container should be
502 determined. The net content weight of each of ten test containers should be in

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503 accordance with the release specification. For a description of this test, refer to
504 the procedure for aerosols given in USP Chapter <755> Minimum Fill.

505 g. Drug Content (Assay)

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

513 h. Impurities and Degradation Products

514 The levels of degradation products and impurities should be determined by means
515 of stability indicating methods. Acceptance criteria should be set for individual and
516 total degradation products and impurities. For identification and qualification
517 thresholds, refer to the appropriate guidance. Individual impurities or degradation
518 products appearing at levels 0.10 percent or greater should be specified. Specified
519 impurities and degradation products are those, either identified or unidentified, that
520 are individually listed and limited in the drug product specification.

521 i. Dose Content Uniformity

522 Because of the complexity of the discharged dose, the medication available at the
523 mouthpiece of the actuator should be thoroughly analyzed for an individual
524 container, among containers, and among batches. This test may be regarded as
525 providing an overall performance evaluation of a batch, assessing the formulation,
526 the manufacturing process, the valve, and the actuator. The number of actuations
527 per determination should not exceed the number of actuations in the minimum
528 dose approved in the labeling. A stability indicating method should be used. The
529 amount of drug substance discharged should be expressed both as the actual
530 amount and as a percent of label claim from the actuator. The USP Unit Spray
531 <601> sampling apparatus may be used. This test is designed to demonstrate the
532 uniformity of medication per actuation or dose, consistent with the label claim,
533 discharged from the mouthpiece of a sample of an appropriate number of
534 containers from a batch (n = 10 is recommended) . The primary purpose is to
535 ensure dose uniformity within discharges from multiple containers of a batch. The
536 following acceptance criteria are recommended:

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537 ● The amount of active ingredient per determination is not outside of
538 80–120 percent of label claim for more than one of ten containers,
539 none of the determinations is outside of 75–125 percent of the label
540 claim, and the mean is not outside of 85–115 percent of label claim.
541 If two or three of the ten determinations are outside of 80–120
542 percent of the label claim, none is outside of 75–125 percent of
543 label claim, and the mean is not outside of 85–115 percent of label
544 claim, an additional 20 containers should be sampled (second tier).
545 For the second tier of testing of a batch, the amount of active
546 ingredient per determination is not outside of 80–120 percent of the
547 label claim for more than 3 of all 30 determinations, none of the 30
548 determinations is outside of 75–125 percent of label claim, and the
549 mean is within 85–115 percent of label claim.

550 j. Dose Content Uniformity Through Container Life

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

563 ● The amount of active ingredient per determination is not outside of 80–120
564 percent of label claim for more than one of nine determinations from three
565 containers, none of the determinations is outside of 75–125 percent of the
566 label claim, and means for each of the beginning, middle, and end
567 determinations are not outside of 85–115 percent of label claim. If two or
568 three of the nine determinations are outside of 80–120 percent of the label
569 claim, none is outside of 75–125 percent of label claim, and the means for
570 each of the beginning, middle, and end determinations are not outside of
571 85–115 percent of label claim, an additional six containers should be
572 sampled at the beginning, middle and end of the canister (second tier). For
573 the second tier of testing of a batch, the amount of active ingredient per
574 determination is not outside of 80–120 percent of the label claim for more

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575 than 3 of all 27 determinations, none of the 27 determinations is outside of
576 75–125 percent of label claim, and the means for each of the beginning,
577 middle, and end determinations are not outside of 85–115 percent of label
578 claim.

579
580 k. Particle Size Distribution

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

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

592 A multistage cascade impactor fractionates and collects particles of one or more
593 drug components by aerodynamic diameter through serial multistage impactions.
594 Such a device with all associated accessories should allow determination of a size
595 distribution throughout the whole dose including, in particular, the small particle
596 size fraction of the dose. It also provides information that allows for the complete
597 mass balance of the total labeled dose to be determined. However, to minimize
598 distortions and to ensure reproducibility, it is important to specify certain
599 conditions such as information on the calibration of the equipment, flow rate,
600 duration, the size and shape of the expansion chamber, or inlet stem, the selection
601 of impaction surfaces, and the method, accessories, and adapters by which the
602 inhalation aerosol is introduced into a specified impactor. These important
603 parameters should be selected to obtain a complete profile of the dose. The
604 rationale and documentation for selection of the above parameters should be
605 presented. Additionally, criteria should be provided in the application for the
606 qualification of each cascade impactor. It is recommended that all cascade
607 impactors used in support of the drug product in the application be of the same
608 design.

609 Other critical variables that should be specified and controlled in such a test
610 procedure are relative humidity and temperature. Particles may undergo changes
611 during their passage into or through the cascade impactor depending on humidity

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612 and temperature conditions. The most common problems associated with humidity
613 are hygroscopic growth and aggregation of particles. Creating atmospheres of
614 controlled temperature and relative humidity by introducing equilibrated air into
615 the system can minimize variability from these sources.

616 The number of actuations needed to determine particle size distribution by
617 multistage cascade impactor should be kept to the minimum justified by the
618 sensitivity of the analytical method used to quantitate the deposited drug
619 substance. The amount of drug substance deposited on the critical stages of the
620 cascade impactor should be sufficient for reliable assay, but not so excessive as to
621 bias the results by masking individual actuation variation.

622 The aerodynamic particle size distribution analysis and the mass balance obtained
623 (drug substance deposited on surfaces from the valve to the cascade impactor
624 filter) should be reported. The total mass of drug collected on all stages and
625 accessories is recommended to be between 85 and 115 percent of label claim on a
626 per actuation basis. At the time of application submission, data for the mass
627 amount of drug substance found on each accessory and each of the various stages
628 of the cascade impactor should be reported. In addition, data may also be
629 presented in terms of the percentage of the mass found on the various stages and
630 accessories relative to the label claim. Acceptance criteria may be proposed in
631 terms of appropriate groupings of stages and/or accessories. However, if this
632 approach is used, at a minimum there should be three to four groupings to ensure
633 future batch-to-batch consistency of the particle size distribution. Furthermore,
634 acceptance criteria expressed in terms of mass median aerodynamic diameter
635 (MMAD) and geometric standard deviation (GSD) alone, as well as in terms of
636 *respirable fraction, respirable dose, or fine particle mass* are not considered
637 adequate to characterize the particle size distribution of the whole dose.

638 1. Microscopic Evaluation

639 Before the advent of the impactor particle sizing methods, microscopic
640 examination of the formulation was used to determine drug substance particle size.
641 This method is relatively crude in measurement capability, is subjective, and does
642 not provide a profile of the aerodynamic size of the delivered particles of drug
643 substance. Furthermore, microscopy does not usually account for density of the
644 particles and may not easily distinguish between, for example, two drug substances
645 in a formulation. However, microscopic examination of the formulation has
646 certain merits and, therefore, should be retained for release and stability purposes.
647 For example, the examination provides information on the presence of large
648 particles, changes in morphology of the drug substance particles, extent of

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649 agglomerates, crystal growth, and foreign particulate matter. Additionally, where
650 the crystalline form of the drug substance can affect the bioavailability,
651 performance, stability, or other properties of the drug product, microscopic
652 evaluation or other appropriate methods are recommended to control and monitor
653 the morphic form if changes are observed on stability.

654 m. Spray Pattern and Plume Geometry

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

665 The proposed test method for spray pattern, including sampling plans, should be
666 provided in detail to allow their duplication by Agency laboratories. For example,
667 in the evaluation of the spray pattern, the actuation distance between the
668 mouthpiece and the plate, number of actuations per spray pattern, position and
669 orientation of the plate relative to the mouthpiece, and visualization method should
670 be specified. The acceptance criteria for spray pattern should include the **shape**
671 (e.g., ellipsoid of uniform density) as well as the **size** of the pattern (e.g., no axis is
672 greater than x millimeters (mm) and the ratio of the longest to the shortest axes
673 should lie in a specified range, for example, 1.00–1.20). The spray pattern should
674 be determined, preferably by a method specific for the drug substance, at different
675 distances (e.g., two) from the mouthpiece to provide greater discriminatory
676 capability to the test. Variability in the test can be reduced by developing a
677 sensitive detection method and by providing method-specific training to the
678 analyst.

679 n. Leak Rate

680 To maintain optimal performance characteristics for the drug product, acceptance
681 criteria for the leak rate should be based on historical data including primary
682 stability data using the test and sampling plan described in the USP <601>. Leak
683 rate testing should be performed in addition to both the on-line leak test which
684 culls out the occasional gross leakers and the testing that follows the lag or

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685 equilibration time instituted before the release of MDIs. The leak rate test is
686 important in stability studies because it may provide information on pressure loss
687 and may predict, at subsequent test stations, failures in testing for dose content
688 uniformity through container life (see section III.F.1.j). It should be noted,
689 however, that leak rates are not necessarily constant over time.

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

698 o. Pressure Testing

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

706 p. Valve Delivery (Shot Weight)

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

715 q. Leachables

716 The drug product should be evaluated for compounds that leach from elastomeric,
717 plastic components or coatings of the container and closure system, such as
718 polynuclear aromatics (PNAs), nitrosamines, monomers, plasticizers, accelerators,

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719 antioxidants, and vulcanizing agents. The development of appropriate analytical
720 methods to identify, monitor, and quantify the leached compounds in the drug
721 product should be done during investigational studies. These validated methods
722 can, in turn, be used for testing of the drug product throughout the expiration
723 dating period. Appropriate acceptance criteria for the levels of leached
724 compounds in the formulation should be established. For additional discussion,
725 refer to the container and closure section of this guidance (section III.G).

726 2. DPIs

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

730 a. Appearance and Color

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

738 b. Identification

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

740 c. Microbial Limits

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

742 d. Water or Moisture Content

743 Water in the drug product should be strictly limited since it may have a significant
744 effect on characteristics such as aerosolization of the particles, particle size
745 distribution, crystallinity, dose content uniformity, microbial content, and stability.

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

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

750 f. Drug Content (Assay)

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

756 g. Impurities and Degradation Products

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

758 h. Dose Content Uniformity

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

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

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

774 j. Particle Size Distribution of Emitted Dose

775 Refer to MDIs (section III.F.1.k). The emitted particle size distribution under
776 defined test conditions should be determined by multistage cascade impaction to
777 profile the aerodynamic diameters of the drug substance particles. The equipment

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778 and accessories should be selected so that the majority of the dose is introduced
779 into the cascade impactor for fractionation. A complete profile of the dose
780 including the finer particles (e.g., less than or equal to 2 µm) should be determined.

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

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

795 k. Microscopic Evaluation

796 Appropriate acceptance criteria should be instituted for the appearance of the drug
797 product formulation using a microscopic test approach. This test is useful for
798 detection of large particles and agglomerates of the drug substance, can define
799 morphology of drug substance and carrier particles, and can detect foreign
800 particulate matter. The type, origin, and profile of foreign particulates, including
801 fine particulates, should be controlled. Refer to the section on microscopic
802 evaluation of MDIs (section III.F.1.I).

803 **G. Container and Closure Systems**

804 1. MDIs

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

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

821 Identity and concentration profiles of the leachables in the drug product or placebo
822 formulation (i.e., drug product formulation without drug substance) should be
823 determined through the end of the drug product's shelf life and correlated, if
824 possible, with the extractables profile(s) of the container and closure components
825 determined under the various control extraction study conditions. Such a
826 correlation may obviate the need to evaluate leachables in the drug product
827 formulation in future routine stability studies. Note that for ANDAs, the applicant
828 may compare the extraction profiles of the container and closure components with
829 the leachables profile(s) of the drug product (or placebo) after storage under
830 accelerated stability conditions for three months, as long as a commitment is
831 provided to confirm the results for the drug product (placebo) on initial production
832 stability batches at or near expiry. If the compared results are within the
833 applicant's acceptance criteria but there are qualitative differences, the results
834 should be discussed with the responsible review division.

835 Complete information (see below) should be provided on the characteristics of,
836 and acceptance criteria, test methods, and sampling plans used for each component
837 of the container and closure system to ensure its suitability for manufacturing the
838 drug product. For additional information on container and closure systems, refer
839 to FDA's guidance *Submitting Documentation for Packaging for Human Drugs*
840 *and Biologics* (February 1987).²

841 a. Container

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

² The 1987 packaging guidance will be superseded by FDA's draft guidance for industry *Submission of Documentation in Drug Applications for Container and Closure Systems Used for the Packaging of Human Drugs and Biologics* (July 1997) once it is issued in final form.

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- 844 ● Source(s) and fabricator(s)
- 845 ● Item number
- 846 ● Composition and quality of materials (including coating, if appropriate)
- 847 ● Schematic drawing
- 848 ● Precise dimensional measurements
- 849 ● Quality of the inside surface
- 850 ● Description of the cleaning procedures
- 851 ● Control extraction studies (when coated)
- 852 ● Examination for residual contaminants and residue from canister washing
- 853 ● Toxicological evaluation, where appropriate, of the extracted materials and
- 854 residues
- 855 ● Acceptance criteria, test methods, and sampling plans including:
 - 856 ● Physicochemical parameters and dimensional measurements
 - 857 ● Quality of inside surface
 - 858 ● Qualitative and quantitative extractable profile(s)

859 Additional information on select topics is provided below.

860 i. Source, Composition, and Physical Dimensions

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

869 ii. Control Extraction Studies

870 The purpose of the control extraction study is to define an acceptable quantitative
871 extractable profile(s) under specified test conditions, and establish acceptance
872 criteria for each of the extracts from the components used for the submitted
873 batches (e.g., clinical, preclinical, biobatch, primary stability, production). The
874 extractable profile(s) of the specified container should be established and
875 documented both qualitatively and quantitatively under defined experimental
876 conditions. The documentation should include the sampling plan, component
877 tested, type and amount of solvent, temperature, duration, extraction method,
878 methods of analysis, and data. Solvents of various polarities should be used for
879 initial determination of the profiles. Use of different solvents to maximize the

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880 extraction of different extractables may be necessary. Typically, the extraction
881 solvent(s) would include the propellant(s) and formulation cosolvent(s), but a
882 more effective extraction solvent could be used instead.

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

890
891 iii. Residue Studies

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

898 iv. Routine Extraction and Residue Tests

899 Based on the analytical and toxicological evaluation of the extractables from both
900 the control extraction and residue studies, the applicant should establish
901 discriminatory test methods and set appropriate acceptance criteria for the
902 extractable profile and the residues for routine testing of incoming containers.
903 Test methods and sampling plans should be provided. The accuracy, precision,
904 specificity, sensitivity, and ruggedness of each method should be documented with
905 proper standards during validation in the control extraction studies.

906
907 v. Acceptance Criteria

908
909 Acceptance criteria should be established for dimensional measurements,
910 particularly for critical parts of the container. Acceptance criteria should also be
911 established for the quality of the inside surface, profile(s) of the extractables (when
912 coated), and residual contaminants.

913 For the extractables and residual contaminants profiles, a reduced acceptance
914 testing schedule may be considered once the applicant establishes the reliability of

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915 the supplier's test results. The applicant should confirm the results by testing
916 multiple incoming batches of containers.

917 b. Valves

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

- 929 ● Source(s) and fabricator(s) of the assembled valve
- 930 ● Source(s) and fabricator(s) for each part of the valve
- 931 ● Item numbers of different parts of the valve
- 932 ● Item number of the assembled valve
- 933 ● Schematic engineering drawings of valve components
- 934 ● Precise dimensional measurements of valve components
- 935 ● Composition and quality of materials of the valve components
- 936 ● Treatment procedures of elastomeric components (e.g., cleaning, pre-
937 extraction, washing, drying) before valve assembly
- 938 ● Control extraction studies for elastomeric and plastic components
- 939 ● Toxicological evaluation of extractables
- 940 ● Acceptance criteria, test methods, and sampling plans
 - 941 ● Physicochemical parameters and dimensional measurements
 - 942 ● Qualitative and quantitative extractable profile(s)
 - 943 ● Performance characteristics of the valve

944 Additional information on select topics is provided below.

945 i. Source, Composition, and Physical Dimensions

946 The source, composition, and physical dimensions of the components should be
947 specified. The dimensional measurements of metering valve components should be
948 held to very tight tolerances through precision measurements. The composition of
949 the valve should be provided in the application and/or an appropriately referenced

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950 DMF. Specific citations to food additive regulations for materials used in
951 fabricating the valve, where applicable, should be included. A toxicological
952 appraisal of the extractables, which may consist of supportive citations and
953 additional safety data, should also be submitted in the application. For guidance
954 on such safety data, applicants are encouraged to contact the responsible review
955 division.

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

967 ii. Pre-extraction

968
969 Since inhalation aerosol formulations include organic liquids as the propellant or
970 the vehicle (e.g., chlorofluorocarbons, hydrofluorocarbons, alcohols), potential
971 leaching of compounds from the elastomeric and plastic components of the device
972 into the formulation is a serious concern. To ensure potential leachables in the
973 drug product are minimized, each production batch of elastomeric components
974 used in the valve should be pre-extracted prior to assembly, unless data obviate
975 such an approach. The extraction procedure should be optimized to remove the
976 maximum amount of potentially toxic leachables without compromising the
977 integrity or performance of the elastomeric valve components. A detailed
978 description of the pre-extraction procedure should include information such as the
979 quantities of elastomeric valve component(s) and selected solvent(s), method and
980 duration of extraction procedure, temperature, as well as additional cleaning,
981 washing, and drying procedures. Each of the pre-extraction processing parameters
982 may have an effect on the quality and purity of valve components and, ultimately,
983 the amount of leachables that may enter into the final drug product formulation
984 upon storage.

985 iii. Control Extraction Studies

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986 See section III.G.1.a.ii for general information on control extraction studies. To
987 verify the efficiency of the pre-extraction procedure for the elastomeric
988 components and the quality and purity of other valve components, the components
989 should be subjected to control extraction studies using selected representative
990 samples and appropriate solvent(s). The profile of each extract should be
991 evaluated both analytically and toxicologically. The application should provide
992 adequate analytical information, obtained using a variety or combination of
993 methods (e.g., chromatography with mass spectroscopy), to identify and quantify
994 each extractable and establish appropriate acceptance criteria. The toxicological
995 evaluation should include appropriate in vitro and in vivo tests. The results of
996 USP Biological Reactivity Tests (USP <87> and <88>) should be submitted. A
997 rationale, based on the available toxicological information, should be provided to
998 support the limits specified for major components of the extractable profile.
999 Because some extractable components from rubber may be carcinogenic,
1000 appropriate risk assessment models may be needed to establish acceptance criteria.
1001 Applicants are encouraged to contact the responsible review division for further
1002 guidance.
1003

1004 iv. Routine Extraction Tests

1005 Based on the analytical and toxicological evaluation of the extractables from the
1006 control extraction study, the applicant should establish discriminatory test methods
1007 and set appropriate acceptance criteria for the extractable profile(s) for routine
1008 testing of the incoming individual valve components. This testing will verify the
1009 efficiency of the pre-extraction procedure for the elastomeric components and
1010 provide continued assurance of the batch-to-batch consistency of the quality and
1011 purity of the valve components. Test methods and sampling plans should be
1012 provided. The accuracy, precision, specificity, sensitivity, and ruggedness of each
1013 method should be documented with proper standards during validation in the
1014 control extraction studies.
1015

1016 v. Acceptance Criteria

1017 The application should include specifications for each component of the valve and
1018 the assembled valve itself. The specification should be comprised of dimensional
1019 measurements, physicochemical parameters, and individual and total extractables
1020 for the different valve components as outlined above under the discussion of the
1021 control extraction studies. In addition, the specifications should include
1022 performance characteristics of the assembled valve (e.g., valve function, valve
1023 delivery, valve leakage). All proposed acceptance criteria should reflect the test
1024 results of valves used in submitted drug product batches (e.g., clinical, primary

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1025 stability, biobatch, and production batches, all using identical valves). If the
1026 information outlined above is generated by the valve manufacturer through
1027 authorized DMFs, applicants should also develop or have access to the necessary
1028 analytical and other methods that will allow them to verify the reliability of the
1029 supplier's test results at appropriate intervals.

1030 For the extractables profiles, a reduced acceptance testing schedule may be
1031 considered once the applicant establishes the reliability of the supplier's test
1032 results. The applicant should confirm the results by testing individual valve
1033 components from multiple batches of incoming valves.

1034
1035 c. Actuator/Mouthpiece and Additional Accessories

1036 For inhalation aerosols, the actuator and additional accessories, if applicable, have
1037 important roles in generating aerosol particles, directing the dose, influencing the
1038 velocity of the aerosol particles, and controlling the amount of available medication
1039 to the patient. If accessories (e.g., spacer, holding chamber) are attached to the
1040 actuator, the pertinent information and controls outlined below for the actuator
1041 should also be provided for these parts.

1042 Information submitted in support of the actuator should include the following:

- 1043 ● Source(s) and fabricator(s)
- 1044 ● Item number
- 1045 ● Schematic drawings
- 1046 ● Precise critical dimensional measurements
- 1047 ● Composition and quality of materials
- 1048 ● Control extraction studies
- 1049 ● Toxicological evaluation of the extractables
- 1050 ● Acceptance criteria, test methods, and sampling plans including:
 - 1051 ● Physicochemical parameters and dimensional measurements
 - 1052 ● Qualitative and quantitative extractable profile(s)
 - 1053 ● Performance characteristics

1054
1055 Additional information on select topics is provided below.

1056 i. Source, Composition, and Physical Dimensions

1057
1058 The source, composition, and physical dimensions of the components should be
1059 specified. The composition of the materials used in the fabrication of the actuator
1060 should be provided in the application and/or in an appropriately referenced

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1061 DMF(s). Specific citations to food additive regulations for materials used in
1062 fabricating the actuator, where applicable, should be included. If the materials are
1063 not recognized as safe for food contact under appropriate regulations, additional
1064 safety data may be needed. For guidance on such safety data, applicants are
1065 encouraged to contact the responsible review division.

1066 The size, shape, tolerances, and design of the actuator, actuator orifice, and the
1067 valve stem holder are critical to the function of the actuator. Dimensional
1068 acceptance criteria for these components should be precisely defined.

1069 ii. Control Extraction Studies

1070 See section III.G.1.a.ii for general information on control extraction studies. For
1071 actuators, the profile of each specified extract should be established and
1072 documented both qualitatively and quantitatively under defined experimental
1073 conditions. Each extract should be evaluated both analytically and toxicologically.
1074 The toxicological evaluation should include appropriate in vitro and in vivo tests.
1075 A rationale, based on available toxicological information, should be provided to
1076 support acceptance criteria for components in terms of the extractable profile(s).
1077 The toxicological information should include the results of appropriate in vitro and
1078 in vivo tests. Safety concerns will usually be satisfied if the materials in the
1079 components meet food additive regulations and the actuator meets the USP
1080 Biological Reactivity Tests (USP <87> and <88>).

1081 iii. Routine Extraction Tests

1082 Based on the analytical and toxicological evaluations of the extractables from the
1083 control extraction study, the applicant should establish discriminatory test methods
1084 and set appropriate acceptance criteria for the extractable profile(s) for routine
1085 testing of incoming actuator component(s). This will ensure batch-to-batch
1086 consistency of the components using appropriate, validated analytical methods.
1087 Test methods and sampling plans should be provided. The accuracy, precision,
1088 specificity, sensitivity, and ruggedness of each method should be documented with
1089 proper standards during validation in the control extraction studies.

1091 iv. Acceptance Criteria

1092 Appropriate acceptance criteria, test methods, and sampling plans should be
1093 provided for the dimensional measurements, physicochemical parameters,
1094 qualitative and quantitative profiles for extractables, and performance
1095 characteristics (e.g., plume geometry, spray pattern, velocity).

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1096 In terms of the extractables profiles, a reduced acceptance testing schedule may be
1097 considered once the applicant establishes the reliability of the supplier's test
1098 results. The applicant should confirm the results by testing multiple batches of
1099 incoming actuator component(s) and, if applicable, accessories.

1100 2. DPIs

1101 As with MDIs, the clinical efficacy of a DPI drug product may be directly
1102 dependent on the design, reproducibility, and performance of the container and
1103 closure system. The container and closure system consists of the overall device
1104 with all primary and protective packaging (e.g., overwrap). The design,
1105 composition, and quality control of the individual components of the container and
1106 the closure are key to maintaining the chemical and physical stability of the
1107 formulation and ensuring that the performance characteristics of the drug product
1108 (e.g., dosing and particle size distribution) are reproducible and in accord with
1109 label claim. During development and before initiating critical clinical studies, the
1110 performance characteristics of the device and its compatibility with the formulation
1111 should be thoroughly investigated. A properly performing DPI should deliver
1112 accurate, small doses of the drug substance in the desired physical form through
1113 the life of the device. Additionally, for device-metered DPIs, some type of dose
1114 counting mechanism is recommended. From a clinical perspective, it is also
1115 recommended that a mechanism that would prevent unintentional multiple dosing
1116 be included. If used, these mechanisms should be described in the application. For
1117 additional information on container and closure systems, refer to FDA's *Guideline*
1118 *for Submitting Documentation for Packaging for Human Drugs and Biologics*
1119 (February 1987).³

1120 Whereas MDIs usually consist of three basic components, i.e., the container, the
1121 valve and the actuator/mouthpiece, there is wide diversity of DPI designs with
1122 differing characteristics. Nevertheless, the drug application should include the
1123 following specific information for device components:

- 1124 ● Source(s) and fabricator(s) of the overall device
- 1125 ● Source(s) and fabricator(s) for each part of the container and closure
1126 system
- 1127 ● Item number(s) for each component
- 1128 ● Schematic engineering drawings
- 1129 ● Dimensional measurements
- 1130 ● Composition and quality of materials

³ Ibid.

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- 1131 ● Control extraction studies
- 1132 ● Toxicological evaluation of the extractables
- 1133 ● Device flow resistance
- 1134 ● Acceptance criteria, test methods and sampling plans including:
 - 1135 ● Physicochemical parameters and dimensional measurements
 - 1136 ● Extractable profile(s) of the critical components
 - 1137 ● Performance characteristics

1138 Additional information on select topics is provided below.

1139 a. Source, Composition, and Physical Dimensions

1140 A complete description of the source and composition of all device components
1141 should be provided, and each should be identified by number and in schematic
1142 drawings with dimensional measurements. Reference to an authorized DMF may
1143 be made for this information.

1144 The composition (e.g., resin and additives, colorants) and the quality of materials
1145 of each individual device and packaging component for the container and closure
1146 system should be carefully selected, and the supporting information provided in the
1147 application. The components should be compatible with the formulation, and their
1148 functionality should be well established to ensure ruggedness of the assembled
1149 device or container and closure system. Specific citations to the food additive
1150 regulations for the materials used in the fabrication of critical components of the
1151 DPI, where applicable, should be included. If the materials are not recognized as
1152 safe for food contact under appropriate regulations, additional safety data may be
1153 needed. For guidance on such safety data, applicants are encouraged to contact
1154 the responsible review division. The information to support a component's
1155 compatibility with the formulation should be provided in the application or by
1156 reference to authorized DMFs.

1157 Additionally, dimensional measurements of the critical components of the device
1158 should be held to very tight tolerances through precision measurements. Critical
1159 components of the DPI are defined as those that contact either the patient (i.e., the
1160 mouthpiece) or the formulation, components that affect the mechanics of the
1161 overall performance of the device, or any necessary protective packaging.
1162 Submission of a sample of the assembled device as well as disassembled
1163 components of the device is recommended to facilitate the application review
1164 process.

1165 b. Control Extraction Studies

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1166 Control extraction studies should be performed on the critical components, except
1167 protective packaging, under defined experimental conditions to determine the
1168 qualitative and quantitative extractable profiles. Full documentation of these
1169 studies and the resulting profiles should be provided. See section III.G.1.a.ii for
1170 additional information on control extraction studies.

1171 The profile of each critical component extract should be evaluated both analytically
1172 and toxicologically. The toxicological evaluation should include appropriate in
1173 vitro and in vivo tests. A rationale, based on available toxicological information,
1174 should be provided to support acceptance criteria for components in terms of the
1175 extractable profile(s). Safety concerns will usually be satisfied if the components
1176 that contact either the patient or the formulation meet food additive regulations
1177 and the mouthpiece meets the USP Biological Reactivity Test criteria (USP <87>
1178 and <88>). If the components are not recognized as safe for food contact under
1179 appropriate regulations, additional safety data may be needed. For guidance on
1180 such safety data, applicants are encouraged to contact the responsible review
1181 division.

1182 c. Routine Extraction Tests

1183
1184 Based on the analytical and toxicological evaluation of the extractables from the
1185 control extraction study, the applicant should establish discriminatory test methods
1186 and set appropriate acceptance criteria for the extractable profile(s) for routine
1187 testing of incoming individual critical device components. Test methods and
1188 sampling plans should be provided. The accuracy, precision, specificity,
1189 sensitivity, and ruggedness of each method should be documented with proper
1190 standards during validation in the control extraction studies.

1191 d. Flow Resistance

1192 The total flow resistance of the device and, preferably, the flow resistance of each
1193 of the individual components involved in the flow paths within the inhaler should
1194 be characterized and established. Supportive information should be included in the
1195 application.

1196 e. Acceptance Criteria

1197 To ensure batch-to-batch reproducibility of the drug product, appropriate
1198 acceptance criteria and validated test methods with adequate sampling should be
1199 established for incoming critical components of the DPI container and closure
1200 system. Specifications should include physicochemical parameters, dimensional

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1201 measurements, qualitative and quantitative extractables profile(s) of each individual
1202 component for indirect control of composition, and performance characteristics of
1203 the assembled device (e.g., dose content uniformity, medication retention, metering
1204 accuracy where appropriate, device flow resistance).

1205 For the extractables profiles for the critical device components, a reduced
1206 acceptance testing schedule may be considered once the applicant establishes the
1207 reliability of the supplier's test results. The applicant should confirm the results by
1208 testing multiple batches of incoming individual critical device components.

1209 **H. Drug Product Stability**

1210 Stability studies provide a means for checking acceptable performance of the inhalation
1211 unit, as well as the physical and chemical stability of the drug product, including the
1212 compatibility of the formulation with the components of the device. The application
1213 should contain (1) a complete, detailed stability protocol, (2) stability data, and (3)
1214 information regarding the suitability of the test methods employed.

1215 1. Content of Stability Protocol

1216 The stability protocol should be comprehensive and should include information on
1217 the following aspects:

- 1218 ● Test parameters and acceptance criteria
- 1219 ● Test methods
- 1220 ● Test intervals
- 1221 ● Container storage orientations
- 1222 ● Test storage conditions
- 1223 ● Type, size, and source of container and closure components
- 1224 ● Quality, purity, and source of drug substance and excipients
- 1225 ● Type, size, and number of batches
- 1226 ● Identification of manufacturing facilities for each stability batch (e.g., IND,
1227 NDA, ANDA, postapproval batches)
- 1228 ● Sampling plans
- 1229 ● Statistical analysis approaches and evaluation for NDAs
- 1230 ● Content and format of stability data
- 1231 ● Commitments
- 1232 ● Expiration Dating Period

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1233 For general guidance on information to support drug product stability and content
1234 and format of stability reports, refer to FDA's *Submitting Documentation for the*
1235 *Stability of Human Drugs and Biologics* (February 1987).⁴ The following
1236 additional discussion elaborates on specific aspects of information for MDIs and
1237 DPIs that should be included in the application.

1238 a. Test Parameters, Acceptance Criteria, and Methods

1239 The stability test parameters, with appropriate acceptance criteria, should include
1240 those tests identified in the release specification of the drug product (refer to
1241 section III.F) with the following exceptions: for MDIs, identity of the drug
1242 substance, spray pattern, container pressure, and net content weight; for DPIs,
1243 identity, fill weight (pre-metered and device-metered), and net content (device-
1244 metered). Test methods should be stability indicating where applicable.

1245 b. Test Intervals

1246 The stability test intervals should be indicated in the application. Long-term test
1247 intervals of 0, 3, 6, 9, 12, 18, 24 months, accelerated test intervals of a minimum
1248 of four test time-points for 6 months (e.g., 0, 1, 3, 6 months), and intermediate test
1249 intervals (e.g., 0, 3, 6, 9, 12 months) should be included. For ANDAs, the same
1250 long-term and intermediate test intervals should be used, but intervals of 0, 1, 2,
1251 and 3 months can be used for accelerated testing. However, confirmation by the
1252 Office of Generic Drugs of the acceptability of the proposed study duration is
1253 recommended. Tabular presentations of the test intervals may be used for added
1254 clarity.

1255 c. Container Storage Orientations

1256 The stability of MDIs and, potentially, of some DPIs (depending on design) can be
1257 affected by storage under differing orientations. For example, leachable levels,
1258 valve appearance, leak rate, and dose content uniformity may be affected by
1259 orientation. Stability studies should include storage under different orientations
1260 (e.g., upright and inverted or upright and horizontal) to characterize any
1261 differences in the DPI's behavior under storage and to define optimum storage
1262 orientation, if any.

1263 d. Test Storage Conditions

⁴ The 1987 stability guidance will be superseded by FDA's draft guidance for industry *Stability Testing of Drug Substances and Drug Products* (June 1998) once it is issued in final form.

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1264 Stability studies should be performed on the drug product with the packaging
1265 configuration (i.e., primary, secondary or additional protective) intended for
1266 marketing using the appropriate test storage conditions. The test storage
1267 conditions in the stability protocol for a drug product intended for storage under
1268 controlled room temperature conditions should include (1) accelerated
1269 ($40\pm 2^{\circ}\text{C}/75\pm 5\%\text{RH}$), (2) intermediate ($30\pm 2^{\circ}\text{C}/60\pm 5\%\text{RH}$), if applicable, and (3)
1270 long-term ($25\pm 2^{\circ}\text{C}/60\pm 5\%\text{RH}$) conditions. If moisture-protective packaging was
1271 deemed necessary, additional storage under conditions of $25\pm 2^{\circ}\text{C}/75\pm 5\%\text{RH}$ for
1272 one-third of the proposed expiration dating period (or to the scheduled test-
1273 interval closest to one-third of the proposed expiration dating period) should be
1274 incorporated in the stability protocol for routine testing (refer to Drug Product
1275 Characterization Studies, sections IV.A.1 and IV.B.1). Stability studies under the
1276 various storage conditions may be initiated concurrently. Due to the complexity of
1277 these types of drug products, accelerated stability studies (i.e., $40\pm 2^{\circ}\text{C}/75\pm 5\%\text{RH}$)
1278 alone may not be predictive of the product performance throughout the
1279 extrapolated expiration dating period.

1280 For NDAs, the first three production batches manufactured post-approval should
1281 be placed in the accelerated, intermediate (if applicable), and long-term stability
1282 testing program. In addition, these three batches should be placed in the stability
1283 testing program under conditions of $25\pm 2^{\circ}\text{C}/75\pm 5\%\text{RH}$, if applicable, for one-third
1284 of the proposed expiration dating period. The approved stability protocol should
1285 be used for the above studies. If stability data for the first three production
1286 batches were submitted with the original application using the approved protocol
1287 and the above cited storage conditions, then it may not be necessary for the first
1288 three production batches manufactured post-approval to be placed on stability.

1289 For ANDAs, refer to *Submitting Documentation for the Stability of Human Drugs*
1290 *and Biologics* (February 1987).⁵

1291 e. Batches, Manufacturing Process, Facilities, Components, and
1292 Container and Closure System Considerations

1293 To determine drug product stability, three batches provide a minimally acceptable
1294 evaluation of batch-to-batch variability and represent a compromise between
1295 statistics and economics. The three batches should be prepared from the
1296 formulation and container and closure system or device intended for marketing,
1297 which should be the same as those used in submitted batches (e.g., clinical,
1298 biobatch, primary stability, production). Stability batches identified in the

⁵ Ibid.

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1299 application should be described in terms of the size, manufacturing method,
1300 manufacturing site, testing methods and acceptance criteria, and packaging.
1301 Applications both for MDIs and DPIs should indicate the type, size, and source of
1302 various container and closure components that were used in generating stability
1303 data on the identified stability batches (e.g., IND, NDA, ANDA).

1304 f. Quality, Purity, and Source of Drug Substance and Excipients

1305 Data should be provided to demonstrate the quality and purity of drug substance
1306 batches and excipient batches used in the drug product stability batches. The
1307 source(s) of the drug substance and excipients used in these drug product batches
1308 should be specified. The information on these drug substance batches should
1309 include but may not be limited to the synthetic method, synthesis site,
1310 micronization site, micronization procedure, and testing. This information should
1311 also be provided for most excipients, in particular, major excipients (e.g.,
1312 propellants, carriers) and noncompendial excipients (see section III.C.2).

1313 g. Sampling Plans

1314 The design of a stability study for complex dosage forms such as MDIs and DPIs
1315 should include any special sampling plans. A special sampling plan (e.g., a
1316 predetermined number of MDI or DPI units may be randomly or otherwise
1317 sampled) may increase assurance that the resulting data for each batch are truly
1318 representative of the batch as a whole. In addition, the number of samples to be
1319 tested should be increased, if possible, near the end of the study, to better establish
1320 the various parameters and confidence levels at either side of the curve for
1321 determining the expiration dating period.

1322 h. Statistical Analysis Approaches and Evaluation

1323 Refer to *Submitting Documentation for the Stability of Human Drugs and*
1324 *Biologics* (February 1987).⁶

1325 i. Stability Commitment

1326 The applicant should verify and ensure continued stability of the drug product by
1327 placing production batches into the applicant's routine stability testing program.
1328 The applicant should provide a statement in the stability protocol committing to

⁶ Ibid.

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1329 conduct and/or complete prescribed studies on production batches of a drug after approval.

1330 j. Expiration Dating Period

1331 The expiration dating period should be based upon full shelf-life stability studies of
1332 at least three batches of drug product, preferably manufactured from three
1333 different batches of the drug substance and using different batches of container and
1334 closure components, to ensure a statistically acceptable level of confidence for the
1335 proposed expiration dating period.

1336 2. Other Stability Considerations

1337 Any change in the manufacturing facility; manufacturing procedure; source,
1338 synthesis, or micronization of the drug substance; source or type (design or
1339 composition) of device and device components; or source or grade of excipient
1340 may affect the stability of the drug product. Under such scenarios, additional
1341 stability data should be generated for the drug product prepared under the various
1342 conditions (as discussed above) so that comparability can be assessed and
1343 necessary linkages established between the various batches.

1344 If multiple manufacturing facilities, manufacturing processes, or sources for the
1345 components (device or formulation) are intended to be used in the manufacturing
1346 of an MDI or DPI, adequate stability data should be generated from each different
1347 facility, process, or source. Stability studies should be performed on all sizes of
1348 the inhalation drug products (e.g., trade and sample sizes).

1349 In general, the use of bracketing and matrixing protocols may not be appropriate
1350 for MDIs and DPIs. If applicants believe that a bracketing or matrixing protocol
1351 is justified, then they are encouraged to contact the responsible review team for
1352 further guidance.

1353 For additional stability considerations, refer to section IV below on drug product
1354 characterization studies and *Submitting Documentation for the Stability of Human*
1355 *Drugs and Biologics*.⁷

1356 **IV. DRUG PRODUCT CHARACTERIZATION STUDIES**

⁷ Ibid.

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1357 For MDI and DPI drug products, certain studies should be performed to determine appropriate
1358 stability test storage conditions. Additional studies should be performed to characterize the
1359 optimum performance properties of the drug product and to support appropriate labeling
1360 statements. Devices may vary in both design and mode of operation, and these characteristics
1361 may be unique to a particular drug product. Drug product-specific information will help define
1362 the appropriate storage conditions, facilitate correct use and maintenance of the inhaler, and
1363 contribute to patient compliance. For the most part, these are one-time studies, usually performed
1364 on a minimum of three batches of drug product intended for marketing. Additionally, this
1365 information will provide a baseline for comparison if, at a later time, the performance
1366 characteristics of a drug product are in question.

1367 **A. MDIs**

1368 The following additional types of drug product characterization studies should be
1369 performed for MDI products. Data should be collected on the product that uses the
1370 formulation, container, valve, actuator, and protective packaging (unless otherwise
1371 specified below) intended for marketing. The studies should be documented and the
1372 results submitted in the application.

1373
1374 1. Determination of Appropriate Storage Conditions

1375 Studies described below and displayed in figure 1 are recommended to determine
1376 the appropriate stability test storage conditions (refer to test storage conditions in
1377 section III.H.1.d) for the drug product intended for marketing. Moreover, in
1378 terms of stability, these studies assess formulation and container and closure
1379 system, and the necessity for secondary or additional protective packaging. The
1380 testing scheme in figure 1 is based on assessing whether a significant change
1381 occurs. The studies in figure 1 apply equally for DPIs. The following changes
1382 would generally be considered significant:

- 1383 ● A 5 percent change from the initial drug content assay value of a batch;
- 1384
- 1385 ● A failure to meet established stability acceptance criteria except for dose
1386 content uniformity and particle size distribution criteria;
- 1387
- 1388 ● For dose content uniformity, a 10 percent change in the mass of the mean
1389 dose (beginning, middle, and end means determined separately) at any test
1390 interval relative to the initial time-point value or failure to meet the
1391 established acceptance criteria for the first tier of testing (refer to sections
III.F.1.i and III.F.2.h);

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

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

- a. No significant change for all parameters after storage at $40^{\circ}\text{C}/75\%\text{RH}$

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

- b. Significant change for any parameter, except particle size distribution and dose content uniformity, after storage at $40^{\circ}\text{C}/75\%\text{RH}$

If there is any observed significant change (except for particle size distribution or dose content uniformity) after storage under conditions of $40^{\circ}\text{C}/75\%\text{RH}$ for six months, stability studies should be completed for all parameters for the product stored for one year at the intermediate conditions of $30\pm 2^{\circ}\text{C}/60\pm 5\%\text{RH}$, hereafter referred to as $30^{\circ}\text{C}/60\%\text{RH}$ (path **B**, figure 1). If no significant change is observed after storage for one year under intermediate conditions, then routine testing should proceed for stability samples stored under long-term conditions of $25^{\circ}\text{C}/60\%\text{RH}$ (path **C**, figure 1).

If a significant change occurs under intermediate storage test conditions of $30^{\circ}\text{C}/60\%\text{RH}$, there may be several options, for example, reformulation of the drug product, modification of the manufacturing procedure, use of a modified or more protective container and closure system, and/or shortening of the proposed expiration dating period (path **D**, figure 1). If the product is reformulated, the manufacturing procedure is changed, or the container and closure system is changed or modified, the assessment in figure 1 should be repeated to obtain the necessary stability data (accelerated, intermediate, and long-term) to establish the appropriate expiration dating period, test storage conditions, and stability

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1428 characteristics of the product (path **E**, figure 1). If such changes are introduced
1429 after preparation of the submitted batches (e.g., clinical, biobatch, primary stability,
1430 production), contact the responsible review division for guidance.

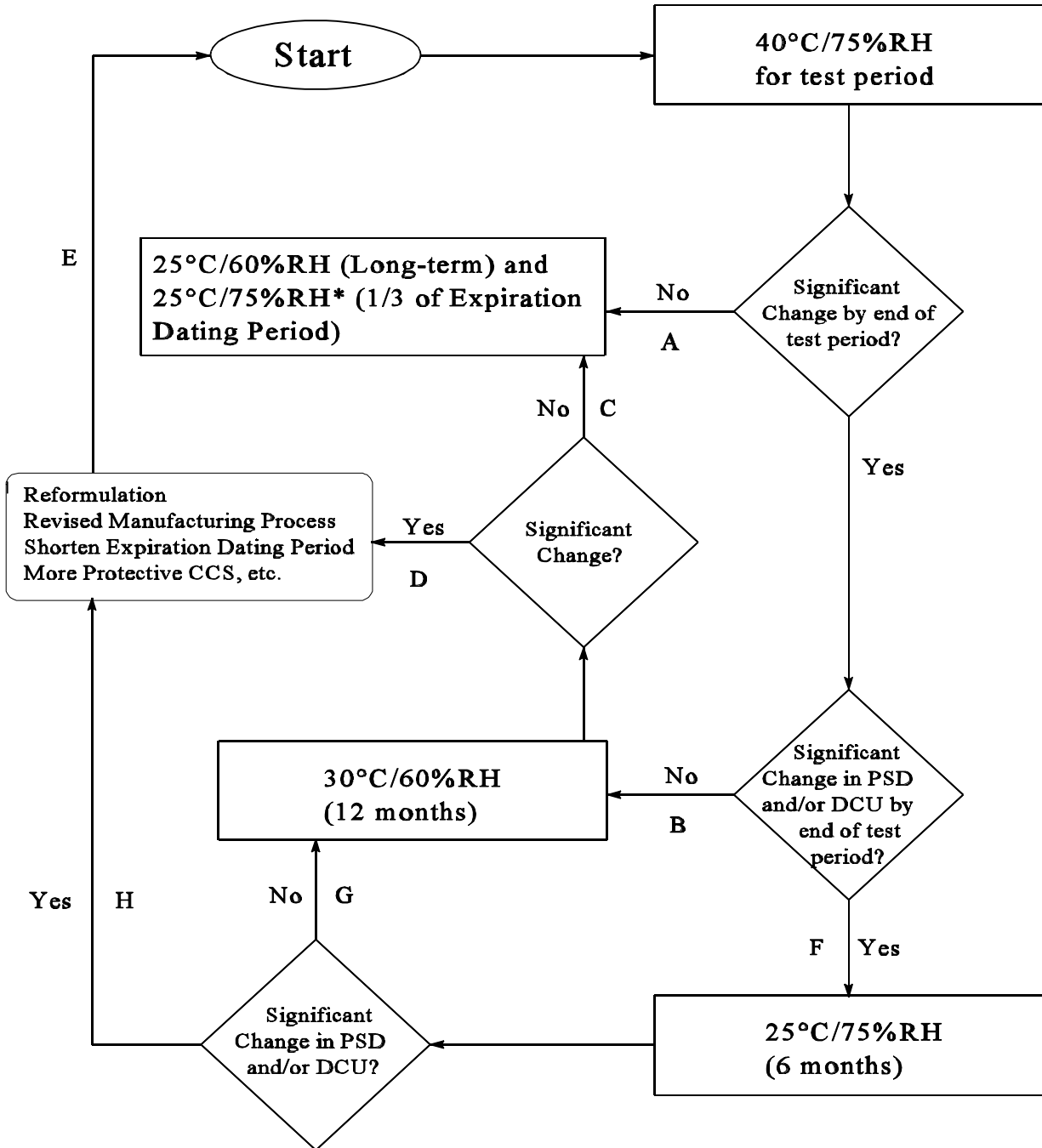
1431 c. Significant change in the particle size distribution or dose content
1432 uniformity after storage at 40°C/75%RH

1433 If a significant change was noted in the particle size distribution or in dose content
1434 uniformity for product stored at 40°C/75%RH, additional testing for the affected
1435 parameter should be performed for the drug product stored for 6 months at
1436 25°C/75%RH (path **F**, figure 1).

1437 If a significant change was noted in the particle size distribution or in dose content
1438 uniformity for product stored at 40°C/75%RH but not after storage for six months
1439 storage at 25°C/75%RH, testing for all stability parameters should proceed under
1440 intermediate conditions of 30°C/60%RH (path **G**, figure 1). The results obtained
1441 under the intermediate conditions should determine, as described above, the
1442 path(s) (**C** or **D** and **E**) that should be followed.

1443 On the other hand, if a significant change is observed in the particle size
1444 distribution or dose content uniformity for product stored under 40°C/75%RH
1445 **and** 25°C/75%RH conditions for a minimum of six months, this would indicate
1446 that protective packaging or other modification is needed (path **H**, figure 1). After
1447 modifications, the assessment outlined in figure 1 should be repeated (path **E**) to
1448 determine the appropriateness of the protective packaging or other modifications
1449 under the various stability storage conditions.

Figure 1: Stability Test Storage Conditions



*If protective/secondary packaging is used.

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1450 Moreover, if moisture-protective packaging is needed, the routine stability test
1451 storage conditions for the product in the presentation intended for marketing
1452 should include both long-term storage at 25°C/60%RH **and** testing through to
1453 one-third of the proposed expiration dating period for product stored at
1454 25°C/75%RH (or to the scheduled test-interval closest to one-third of the
1455 proposed expiration dating period).

1456 2. Stability of Primary (Unprotected) Package

1457 If secondary or additional protective packaging (e.g., foil overwrap) was deemed
1458 necessary for the drug product, adequate stability data from a study conducted at a
1459 minimum of 25°C and 75%RH should be generated on these units without the
1460 protective package to establish the maximum length of time for patient use after
1461 the protective packaging is removed. Drug products both newly manufactured and
1462 near the end of the proposed expiration dating period should be evaluated if
1463 possible. Periodic reassessment of this time period should be performed post-
1464 approval to ensure continued integrity of the primary packaging.

1465 3. Temperature Cycling

1466 For MDI inhalation aerosols, a stress temperature cyclic study should evaluate the
1467 effects of temperature and associated humidity changes on the quality and
1468 performance of the drug product, under extremes of high and low temperatures,
1469 that may be encountered during shipping and handling. Such a study may consist
1470 of three or four six-hour cycles per day, between subfreezing temperature and
1471 40°C for a period of up to six weeks. At the end of predetermined cycles, the
1472 samples should be analyzed for appropriate parameters and compared with the
1473 control drug product. At a minimum, test parameters for MDIs after cycling
1474 studies should include particle size distribution, microscopic evaluation, physical
1475 appearance of the content, valve component integrity, dose content uniformity,
1476 water content, and leak rate. With regard to the appearance of the MDI drug
1477 product, one should consider the discoloration of the contents, microscopic
1478 evaluation, distortion or elongation of valve components, valve clogging, canister
1479 corrosion, and adherence of the drug to the walls of the container or valve
1480 components.

1481 4. Effect of Resting Time

1482 A study is recommended to determine the effect of increasing resting time on the
1483 first actuation of unprimed MDI units followed immediately by the second and the
1484 third actuations. MDI units are only primed prior to initiation of the study. After

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

5. Priming/Repriming

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

6. Effect of Storage on the Particle Size Distribution

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

7. Drug Deposition on Mouthpiece and/or Accessories

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

8. Cleaning Instructions

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

9. Profiling of Actuations Near Canister Exhaustion

A study should be conducted to determine the profiles of the delivered amount and the aerodynamic particle size distribution of the drug substance of each individual actuation after the point at which the labeled number of actuations have been

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1516 dispensed until no more actuations are available (i.e., the canister is empty). These
1517 studies help to determine if a proposed overfill of the containers is justified and
1518 give a profile of the dose delivery after the labeled number of actuations. A
1519 graphical representation of the findings is also recommended.

1520 10. Plume Geometry

1521 A study should be performed to characterize the plume geometry to help evaluate
1522 the performances of the valve and the actuator. As with the spray pattern
1523 (discussed above in section III.F.1.m), various factors can affect the plume
1524 geometry, such as the size and shape of the actuator orifice, design of the actuator,
1525 size of the metering chamber, size of the stem orifice of the valve, vapor pressure
1526 in the container, and nature of the formulation.

1527 Plume geometry may be evaluated by a variety of methods, (e.g., the time
1528 sequence sound-triggered flash photography method, video tape recording and
1529 taking pictures of different frames). The approaches used should allow for a
1530 detailed study of the aerosol and droplet development. The plume geometry does
1531 not distinguish between drug substance particles and propellant droplets in the
1532 plume nor indicate the drug substance density gradient in the aerosol plume, but
1533 determines the shape of the complete aerosol mist. For assessing the performance
1534 of the valve and actuator, the study of plume geometry is complementary to the
1535 spray pattern test, which may directly examine the drug substance particles from
1536 the plume. The resulting baseline may be used to compare similar drug products
1537 by different manufacturers or when introducing certain changes to an already
1538 approved drug product.

1539 11. Microbial Challenge

1540 A study should be performed to determine the viability of microorganisms in drug
1541 product formulation that has been inoculated intentionally .

1542 12. In Vitro Dose Proportionality

1543 For MDIs with multiple-strength doses, studies should include characterization of
1544 the in vitro dose proportionality in terms of the emitted dose content uniformity
1545 and the particle size distribution.

1546 13. Effect of Varying Flow Rates

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1547 If the MDI is intended to be marketed with a spacer or similar accessory, a study
1548 should be performed to characterize the emitted dose and the particle size
1549 distribution as a function of different flow rates at constant volume (e.g., two
1550 liters). This important study assesses the sensitivity of the drug product to widely
1551 varying flow rates that will be generated by patients of different age and gender
1552 and with different severity of disease. A study to assess the effect of increasing
1553 waiting periods (e.g., 0, 5, 10 seconds) between actuation and initiation of in-flow
1554 on the emitted dose and the particle size distribution is encouraged.

1555 **B. DPIs**

1556 The following additional types of drug product characterization studies should be
1557 performed for DPI products. Data should be collected on the product that uses the
1558 formulation and the device intended for marketing (protective packaging should be
1559 included unless otherwise specified below). The studies should be well documented and
1560 the results submitted in the application.

1561 1. Determination of Appropriate Storage Conditions

1562 Studies similar to those for MDIs should be undertaken to determine the
1563 appropriate stability test storage conditions (i.e., temperature, humidity) and the
1564 necessity for any moisture-protective packaging. For details on these studies, refer
1565 to section IV.A.1 for MDIs.

1566 2. Stability of Primary (Unprotected) Package

1567 If protective packaging (e.g., foil overwrap) was deemed necessary for the drug
1568 product device or unit-dose container, adequate stability data conducted at a
1569 minimum of 25°C and 75%RH need to be generated for these units, without the
1570 protective packaging, to establish or confirm the maximum length of time for use
1571 after the protective packaging is compromised. As discussed for MDIs in section
1572 IV.A.2., these studies should consider both new and aged drug product.
1573 Additionally, a periodic reassessment of the determined period should be
1574 performed postapproval to ensure continued integrity of the primary packaging.

1575 3. Effect of Varying Flow Rates

1576 A study should be undertaken to determine the emitted dose and the particle size
1577 distribution as a function of different flow rates at constant volume. The total
1578 volume should be limited to two liters. This important study assesses the
1579 sensitivity of the device to widely varying flow rates that will be generated by

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1580 patients of different age and gender and with different severity of disease. For
1581 NDAs, to relate these in vitro tests to in vivo performance for DPIs (which are
1582 dependent on patient effort for deaggregation and dose delivery), studies should
1583 also be conducted to determine what flow characteristics are obtained through the
1584 device by adult and pediatric subjects with normal lung function and by adult and
1585 pediatric patients with varying degrees of obstructed lung function. To examine
1586 the effects of severe limitations of a patient's forced expiratory volume in one
1587 second (FEV₁) on inspiratory flow rates that can be generated through the device,
1588 the use of stable, severe COPD subjects is acceptable.

1589 4. Effect of Storage on the Particle Size Distribution

1590 During primary stability studies for device-metered DPIs, the effect of storage on
1591 the particle size distribution from the initial dose to the labeled number of doses
1592 should be evaluated to determine any trends (refer to section IV.B.1).

1593 5. Dose Buildup and Flow Resistance

1594 Studies should be conducted to determine the characteristics of the DPI in terms of
1595 dose build-up issues and flow resistance. For further discussion on device flow
1596 resistance, refer to section III.G.2.

1597 6. Effect of Orientation

1598 Studies should be undertaken to determine the performance of the device in terms
1599 of metered and emitted dose content uniformity, and the particle size distribution
1600 at various dosing orientations to demonstrate the ruggedness of the DPI. This
1601 study should also include testing the device under different handling situations
1602 (e.g., dropping, shaking).

1603 7. In Vitro Dose Proportionality

1604
1605 For DPIs with multiple strength doses, studies should be included for
1606 characterization of the in vitro dose proportionality in terms of the emitted dose
1607 content uniformity and the particle size distribution.

1608 8. Effect of Patient Use

1609 Studies should be carried out for all types of DPIs to identify the effects of patient
1610 use on the characteristics of the drug product. For NDAs, it is recommended that
1611 devices used in clinical studies be sent for testing of pertinent performance

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1612 parameters and physical attributes after use (e.g., emitted dose, particle size
1613 distribution, moisture content, microbial limits) and, if feasible, the same device be
1614 returned for continued patient use.

1615 9. Effect of Moisture

1616 A study should be conducted to determine the effect of moisture equilibration of
1617 the DPI at various high and low humidity conditions on pertinent parameters (e.g.,
1618 emitted dose content uniformity, particle size distribution, microscopic evaluation,
1619 water content). The purpose of such a study is to assess the effect of different
1620 environmental conditions on various interactive forces within the device, which
1621 together are responsible for the fluidization and aerosolization behavior of the
1622 formulation and, hence, performance.

1623 10. Photostability

1624 Photostability studies for DPIs should be performed using appropriate test
1625 conditions, if warranted by the immediate container. For example, if capsules or
1626 clear blisters are used for pre-metered DPIs or if the reservoir containing the
1627 formulation in a device-metered DPI can receive light exposure, photostability
1628 studies should be conducted. These studies should be conducted in the absence of
1629 any additional packaging (e.g., foil overwrap). For additional guidance, applicants
1630 may refer to the ICH guidance *Q1B Photostability Testing of New Drug*
1631 *Substances and Products* (November 1996).⁸

1632 11. Profiling of Doses Near Device Exhaustion

1633 For device-metered DPIs that do not incorporate any type of locking mechanism
1634 to prevent use after the labeled number of actuations, a study should be conducted
1635 to determine the metered dose and emitted dose and particle size distribution
1636 profiles from the labeled number of doses until no more formulation can be
1637 obtained. For ease of review, the resulting profile data should also be presented in
1638 a graphical format.

1639 12. Priming

1640 For device-metered DPIs, consideration should be given to priming the device, in
1641 terms of the effect of various orientations or particular handling (e.g., tapping) that

⁸ Additional information on photostability testing will be available in FDA's forthcoming guidance for industry *Stability Testing of Drug Substances and Drug Products* (draft published June 1998) when it is finalized.

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1642 is necessary to ensure reproducible dose content uniformity and particle size
1643 distribution.

1644 13. Fill Weight

1645 For device-metered DPIs, the optimum and minimum fill weight for a given
1646 reservoir size and geometry should be investigated and documented to justify the
1647 proposed overfill and to ensure consistent dose content uniformity and particle size
1648 distribution through the labeled number of doses from the device under use
1649 conditions.

1650 14. Device Ruggedness

1651 For pre-metered DPIs that may be reused repeatedly, a study should be conducted
1652 to establish the DPI's performance characteristics (emitted dose and particle size
1653 distribution) throughout the life of the device. This study may also address, where
1654 applicable, limits of use related to failure of critical device mechanisms
1655 (ruggedness). The results of this study would be useful for determining necessary
1656 replacement intervals for the pre-metered DPI device.

1657 15. Cleaning Instructions

1658 In-use studies should be performed, if necessary, to determine the frequency of
1659 cleaning and related instructions to be included in the labeling.

1660 **V. LABELING CONSIDERATIONS**

1661 **A. MDIs**

1662 To achieve consistency and uniformity in the content, product title, and format of MDI
1663 labeling, the following information pertinent to MDIs is recommended in the labeling.
1664 These comments are not all inclusive, and they are directed mainly at labeling issues
1665 unique to NDAs for prescription MDI drug products. See 21 CFR part 201 for additional
1666 information regarding the labeling of drug products. In general, labeling for ANDAs
1667 should be the same as the reference listed drug.

1668 1. Product Title

1669 To standardize the nomenclature for oral MDIs, the established name of all such
1670 drug products should include the designation (*Drug Substance*) *Inhalation*

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1671 *Aerosol*. For nasal MDIs, the drug product would include the name (*Drug*
1672 *Substance*) *Nasal Aerosol*. The established name should be followed by a phrase
1673 such as *For oral inhalation only* or *For nasal use only* as appropriate.

1674 2. Labels

1675 The label(s) should bear the following information:

- 1676 ● Established name of the drug product
- 1677 ● Amounts of the drug substance delivered from the mouthpiece and the
1678 valve
- 1679 ● Number of medication actuations per container
- 1680 ● Net content (fill) weight
- 1681 ● Usual dosage
- 1682 ● Excipients (established names)
- 1683 ● Route of administration
- 1684 ● Recommended storage conditions including any warning statements
1685 regarding temperature and humidity
- 1686 ● Manufacturer's and/or distributor's name and address
- 1687 ● "Rx Only" or "R~~x~~ Only" statement
- 1688 ● Lot number
- 1689 ● Expiration date
- 1690 ● Use period once drug product is removed from protective packaging (if
1691 applicable)
- 1692 ● NDC number(s)
- 1693 ● The instruction *Shake well before using* for suspension formulations
- 1694 ● A statement that the drug product canister should only be used with the
1695 mouthpiece provided (e.g., *For oral inhalation with (Drug Product Name)*
1696 *actuator only*).
- 1697 ● Warning statements required under 21 CFR 369.21 (e.g., *storage above*
1698 *120°F may cause bursting, keep out of reach of children, do not puncture,*
1699 *do not use or store near heat or open flame, never throw container into*
1700 *fire or incinerator, do not spray into eyes*)
- 1701 ● Warning statements required under 21 CFR 201.320(b), if applicable

1702 In the case of small labels, only some of the information listed above must be
1703 included in the label (21 CFR 201.10(i)). However, all labeling information
1704 required by the Federal Food, Drug, and Cosmetic Act (the Act) and the
1705 regulations in Title 21 of the Code of Federal Regulations must be included on the
1706 carton, outer container, wrapper, and leaflet as appropriate.

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1707 3. DESCRIPTION Section of the Package Insert

1708 In addition to the information typically required under FDA regulations for the
1709 description of the drug substance and formulation, the package insert should
1710 include the following information that is specific for MDI drug products:

- 1711 ● The medication dose delivered to the patient should be expressed by a
1712 statement in this section, such as: *Each actuation meters 'x' mcg of drug*
1713 *substance in 'w' mg of suspension (solution) from the valve and delivers*
1714 *'y' mcg of drug substance, equivalent to 'z' mcg of drug substance base (if*
1715 *applicable) from the actuator (i.e., mouthpiece or nasal adapter). The*
1716 *term approximately should not be used to modify the medication dose*
1717 *delivered.*
- 1718 ● If the drug substance forms solvates or clathrates with the propellants, this
1719 formation should be clearly specified with proper conversion for the active
1720 drug shown.
- 1721 ● A list of all excipients should be included. Substances should be identified
1722 by their established names.
- 1723 ● The number of actuations per container should be included.
- 1724 ● The number of priming actuations needed before using the MDI for the
1725 first time and in cases where the aerosol has not been used for more than a
1726 specified period of time (e.g., 24 hours, 48 hours) should be included.

1727 4. HOW SUPPLIED Section of the Package Insert

1728 The following should be included in MDI drug product labeling:

- 1729 ● The net content (fill) weight of the container should be stated.
- 1730 ● The number of medication doses expected throughout the shelf life of the
1731 drug product should be indicated for each canister fill weight. Qualifying
1732 terms such as *at least* and *approximately* should not be used.
- 1733 ● Identification of the actuator and protective cap to be used with the
1734 container and valve, including the color and appearance, should be
1735 included.
- 1736 ● A statement should be included that the drug inhalation canister should
1737 only be used with the drug inhalation aerosol mouthpiece and that the
1738 mouthpiece should not be used with any other inhalation drug product.
- 1739 ● A statement should be provided that the correct amount of medication in
1740 each inhalation cannot be ensured after the labeled number of actuations
1741 from the canister even though the canister may not be completely empty.

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- 1742 Additionally, a statement should be included that the canister should be
1743 discarded when the labeled number of actuations has been dispensed.
1744 ● Storage conditions should be clearly stated including any warning
1745 statements regarding temperature and humidity.
1746 ● Any preferred storage orientation should be indicated.
1747 ● If protective packaging (e.g., foil overwrap) was deemed necessary and is
1748 used for the MDI drug product, this should be clearly stated. In addition,
1749 appropriate statements should be included that the content of the protective
1750 packaging should not be used after a specified number of days (e.g., 2
1751 weeks, 30 days) from the date upon which the package was compromised.
1752 The length of time specified should be supported by data in the application
1753 (refer to section IV.A.2).
1754 ● A statement should be included regarding the appropriate temperature of
1755 the MDI before use as well as any requirements for shaking, if necessary
1756 (i.e., for suspension products).
1757 ● For products that contain chlorofluorocarbons or use chlorofluorocarbons
1758 during manufacturing, this section should include the warning statement
1759 required under the Clean Air Act (42 U.S.C. 7671j) and Environmental
1760 Protection Agency regulations (40 CFR part 82). **Note:** The patient
1761 instructions should include a similar warning and a statement that the
1762 patient should consult his or her physician if there are questions about
1763 alternative drug products. Refer to 21 CFR 201.320.
1764 ● NDC number(s).

1765 5. Patient Package Insert

1766 The instructions to the patient should include the following if applicable:

- 1767 ● Detailed, step-by-step, appropriately illustrated instructions for patient use
1768 should be included. The following information is also recommended:
1769
1770 ● A statement instructing the patient to confirm that the canister is
1771 fully seated in the actuator (i.e., mouthpiece or nasal adapter).
1772 ● A statement instructing the patient to confirm the absence of
1773 foreign objects in the mouthpiece before using the MDI and after
1774 removing the protective mouthpiece cap.
1775 ● A figure that displays the various elements of the MDI (e.g.,
1776 mouthpiece, cap, canister, sleeve).
1777 ● Instructions for initial priming and repriming of the MDI unit.
1778 ● A statement cautioning against spraying the eyes with the
1779 formulation.

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- 1780
- 1781 ● Storage conditions should be clearly stated, including any warning
- 1782 statements regarding temperature and humidity. A statement should be
- 1783 included regarding the appropriate temperature of the MDI at the time of
- 1784 use as well as any requirements for shaking, if necessary (i.e., for
- 1785 suspension products). Any preferred storage orientation should be noted.
- 1786 ● If protective packaging was used for the MDI drug product device,
- 1787 appropriate statements should be included that the contents of the
- 1788 protective packaging should not be used after a specified number of days
- 1789 (e.g., 2 weeks, 30 days) from the date the protective package was
- 1790 removed.
- 1791 ● A statement should be included that the drug inhalation canister should
- 1792 only be used with the drug inhalation aerosol mouthpiece and that the
- 1793 mouthpiece should not be used with any other inhalation drug product.
- 1794 ● Appropriate cleaning instructions should be included (refer to section
- 1795 IV.A.8).
- 1796 ● A statement should be included that the correct amount of medication in
- 1797 each inhalation cannot be ensured after the labeled number of actuations
- 1798 even though the canister may not be completely empty. A statement
- 1799 instructing the patient to keep track of the number of actuations used from
- 1800 the canister should also be included.
- 1801 ● Warning statements required under 21 CFR 369.21 (e.g., *storage above*
- 1802 *120°F may cause bursting, keep out of reach of children, do not puncture,*
- 1803 *do not use or store near heat or open flame, never throw container into*
- 1804 *fire or incinerator, do not spray into eyes).*
- 1805 ● The warning statement required under 21 CFR 201.320 should be included.

1806 **B. DPIs**

1807 To achieve consistency and uniformity in the content, product title, and format of DPI
1808 labeling, the following information pertinent to DPIs is recommended in the labeling.
1809 These comments are not all inclusive, and they are directed mainly at labeling specific for
1810 DPI inhalation drug products. See 21 CFR part 201 for additional information regarding
1811 the labeling of drug products.

1812 1. Product Title

1813 To standardize the nomenclature for oral DPIs, the established name of all such
1814 drug products should include the designation (*Drug Substance*) *Inhalation*
1815 *Powder*, and the metered dose. The name and strength should be followed by a
1816 phrase such as *For oral inhalation only*.

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1817 2. Labels

1818 The label(s) should bear the following information:

- 1819 ● Established name of the drug product
- 1820 ● Metered-dose
- 1821 ● Number of medication actuations per container or device
- 1822 ● Net content (fill) weight (device-metered)
- 1823 ● Usual dosage
- 1824 ● Excipients (established names)
- 1825 ● Route of administration
- 1826 ● Recommended storage conditions including any warning statements
- 1827 regarding temperature, humidity, and light
- 1828 ● Manufacturer's and/or distributor's name and address
- 1829 ● "Rx Only" or "℞ Only" statement
- 1830 ● Lot number
- 1831 ● Expiration date
- 1832 ● Use period once the unit is removed from protective packaging (if
- 1833 applicable)
- 1834 ● NDC number(s)
- 1835 ● Dispensing instructions for pharmacist and additional statements for
- 1836 physician, if applicable.
- 1837 ● Reference to the Patient's Instructions for Use and additional instructional
- 1838 statements (e.g., loading instructions for pre-metered DPIs, inhalation
- 1839 instructions, instructions pertaining to protective caps, etc.)

1840 In the case of small labels, only some of the information listed above must be
1841 included in the label (21 CFR 201.10(i)). However, all labeling information
1842 required by the Act and the regulations in Title 21 must be included on the carton,
1843 outer container, wrapper and leaflet as appropriate.

1844 3. DESCRIPTION Section of the Package Insert

1845

1846 In addition to the information typically required under Title 21 for the description
1847 of the drug substance and formulation, the package insert should include the
1848 following information that is specific for DPI drug products:

- 1849 ● Metered-dose
- 1850 ● Emitted dose delivered from the mouthpiece under specified in vitro
- 1851 conditions should be stated.

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- 1852 ● All excipients used in the formulation should be identified by their
1853 established names.
- 1854 ● A statement should be included that the amount of drug delivered to the
1855 lung will depend on patient factors such as inspiratory flow and peak
1856 inspiratory flow (PIF) through the device, which may vary for different
1857 asthma and COPD patient populations. The labeling should include typical
1858 PIF values for patients within a range of pulmonary function. The details
1859 provided on these values should relate the findings of in vivo flow rate
1860 studies and describe the relationship of these flow rates to demographics
1861 (i.e., adult vs. pediatric and any gender effect) and to the degree of airflow
1862 obstruction (i.e., the PIF obtained in subjects with a particular level of
1863 FEV₁ decrement). The flow rates given should include the mean rate for
1864 any given group and, in parentheses following the mean, the range found in
1865 that group.
- 1866 4. HOW SUPPLIED Section of the Package Insert
- 1867 ● The net content weight of the container should be stated for device-
1868 metered DPIs.
- 1869 ● The number of medication doses expected throughout the shelf life of the
1870 drug product should be indicated. Qualifying terms such as *at least* and
1871 *approximately* should not be used.
- 1872 ● If protective packaging (e.g., foil overwrap) was deemed necessary and is
1873 used for the drug product device or unit dose container, this should be
1874 clearly stated. In addition, appropriate statements should be included that
1875 the content of the protective packaging (e.g., device-metered DPIs, pre-
1876 metered multi-dose DPIs, or pre-metered single dose units) should not be
1877 used after a specified number of days (e.g., 2 weeks, 30 days) from the date
1878 the protective package was removed. The length of time specified should
1879 be supported by data presented in the application (refer to section IV.B.2).
- 1880 ● For device-metered DPIs without a locking mechanism, a statement should
1881 be provided that the correct amount of medication in each inhalation
1882 cannot be ensured after the labeled number of actuations from the unit even
1883 though the unit may not be completely empty. Additionally, a statement
1884 should be included that the DPI unit should be discarded when the labeled
1885 number of actuations has been used.
- 1886 ● Storage conditions should be clearly stated including any warning
1887 statements regarding temperature, humidity, and light.
- 1888 ● A brief description of the appearance and color of the body, cap, and other
1889 markers of the device should be provided, particularly for ease of
1890 identification of different strengths of drugs delivered by the same device.

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1891 ● Different strengths and special identification markings should be stated.

1892 5. Patient Package Insert

1893 The instructions to the patient should include the following if applicable:

- 1894 ● Detailed, step-by-step, appropriately illustrated instructions for patient use
1895 should be included.
- 1896 ● Storage conditions should be clearly stated, including any warning
1897 statements regarding temperature, humidity, and light.
- 1898 ● If protective packaging (e.g., foil overwrap) was deemed necessary and is
1899 used for the drug product device or unit dose container, this should be
1900 clearly stated. Appropriate statements should be included that the content
1901 of the protective packaging (e.g., device-metered DPIs, pre-metered multi-
1902 dose DPIs, or pre-metered single dose units) should not be used after a
1903 specified number of days (e.g., 2 weeks, 30 days) from the date the
1904 protective packaging was removed.
- 1905 ● For device-metered DPIs, a warning should be included stating that the
1906 correct amount of medication in each inhalation cannot be ensured after the
1907 labeled number of doses even though the device may not be completely
1908 empty. A statement recommending that the device-metered DPI be
1909 discarded after the labeled number of doses has been delivered can be
1910 included as well.
- 1911 ● Cleaning instructions should be included if appropriate (refer to section
1912 IV.B.15).

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GLOSSARY OF TERMS

1914 **Batch:** A specific quantity of a drug or other material that is intended to have uniform character
1915 and quality, within specified limits, and is produced according to a single manufacturing order
1916 during the same cycle of manufacture (21 CFR 210.3(b)(2)).

1917 **Container and Closure System:** For MDIs, the container, the valve, the actuator, and any
1918 associated accessories (e.g., spacers) or protective packaging collectively constitute the container
1919 and closure system. For DPIs, the device and all its parts including any protective packaging
1920 (e.g., overwrap) constitute the container and closure system.

1921 **Drug Product:** For MDIs, the formulation, container, the valve, the actuator, and any associated
1922 accessories (e.g., spacers) or protective packaging collectively constitute the drug product. For
1923 DPIs, the formulation, and the device with all of its parts including any protective packaging (e.g.,
1924 overwrap) constitute the drug product.

1925 **Drug Substance:** An active ingredient that is intended to furnish pharmacological activity or
1926 other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to
1927 affect the structure or any function of the human body (21 CFR 314.3(b)).

1928 **Dry Powder Inhalers/DPIs/Inhalation Powders:** Drug products designed to dispense powders
1929 for inhalation. DPIs contain active ingredient(s) alone or with a suitable excipient(s). A DPI
1930 product may discharge up to several hundred metered doses of drug substance(s). Current
1931 designs include **pre-metered** and **device-metered DPIs**, both of which can be driven by patient
1932 inspiration alone or with power-assistance of some type. Pre-metered DPIs contain previously
1933 measured doses or dose fractions in some type of units (e.g., single or multiple presentations in
1934 blisters, capsules, or other cavities) that are subsequently inserted into the device during
1935 manufacture or by the patient before use. Device-metered DPIs typically have an internal
1936 reservoir containing sufficient formulation for multiple doses which are metered by the device
1937 itself during actuation by the patient.

1938 **Excipient:** Formulation component(s) other than the drug substance.

1939 **Extractables:** For both MDI and DPI drug products, compounds that can be extracted from
1940 elastomeric, plastic components or coatings of the container and closure system when in the
1941 presence of an appropriate solvent(s).

1942 **Expiration Dating Period:** The time interval during which all batches of a drug product are
1943 expected to remain within approved specifications after manufacture. Expiration dating period
1944 will be used to determine the expiration date of the drug product.

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1945 **Leachables:** Compounds that leach from elastomeric, plastic components or coatings of the
1946 container and closure system as a result of direct contact with the formulation of the MDI.

1947 **Metered-Dose Inhalers/MDIs/Inhalation Aerosols:** Drug products that contain active
1948 ingredient(s) dissolved or suspended in a propellant, a mixture of propellants, or a mixture of
1949 solvent(s), propellant(s), and/or other excipients in compact pressurized aerosol dispensers. An
1950 MDI product may discharge up to several hundred metered doses of drug substance(s).

1951 **Primary Stability Data:** Data on the drug product stored in the proposed container closure
1952 system for marketing under storage conditions that support the proposed shelf life.

1953 **Random Sample:** A selection of units chosen from a larger population of such units so that the
1954 probability of inclusion of any given unit in the sample is defined. In a simple random sample,
1955 each unit has equal chance of being included. Random samples are usually chosen with the aid of
1956 tables of random numbers found in many statistical texts.

1957 **Specification:** A list of tests, references to analytical methods, and appropriate acceptance
1958 criteria that are numerical limits, ranges or other criteria for the tests described. Specifications
1959 establish a set of criteria to which a drug substance or drug product should conform using the
1960 approved analytical procedure to be considered acceptable for its intended use. Acceptance
1961 criteria are numerical limits, ranges, or other criteria for the tests described.

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ABBREVIATIONS

1963	CCS: container and closure system
1964	CFN: central file number
1965	CFR: Code of Federal Regulations
1966	COPD: chronic obstructive pulmonary disease
1967	DCU: dose content uniformity
1968	DPI: dry powder inhaler
1969	FEV ₁ : forced expiratory volume in one second
1970	GSD: geometric standard deviation
1971	mcg: microgram(s)
1972	MDI: metered dose inhalation aerosol also known as metered dose inhaler
1973	mg: milligram(s)
1974	MMAD: mass median aerodynamic diameter
1975	NF: National Formulary
1976	NMT: not more than
1977	PIF: peak inspiratory flow
1978	PNA: polynuclear aromatic
1979	PSD: Particle Size Distribution
1980	USP: United States Pharmacopeia