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Particle Size Distribution Mass Balance Working Group

Spring 2002

WORK PLAN

Establishment of the Appropriate Use of the Particle Size Distribution Mass Balance Determined by Cascade Impactor for Orally Inhaled and Nasal Drug Products

*Finalized by Working Group on 25 February 2002**

*Forwarded for review to DPTC on 25 February 2002
Approved by DPTC on 2 April 2002*

*Forwarded for review to SC on 23 April 2002
Approved by SC on 26 April 2002*

* This version reflects the revised timelines agreed during the 25 March 2002 Working Group teleconference.

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62 **I. BACKGROUND¹**

63 Particle size distribution (PSD) measurements of orally inhaled and nasal drug products
64 (OINDP) are performed in order to characterize the size distribution of particles emitted from
65 the device. PSD measurements are performed during drug product development. In addition,
66 some type of PSD measurement is usually required of the final product as part of a
67 comprehensive program to ensure quality of commercial batches.

68 In November 1998 and May 1999, the FDA issued two draft CMC Guidances for
69 Industry addressing OINDP: (i) *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug*
70 *Products Chemistry, Manufacturing, and Controls Documentation*² (referred to here as the
71 “MDI/DPI draft Guidance”); and (ii) *Nasal Spray and Inhalation Solution, Suspension, and Spray*
72 *Drug Products Chemistry, Manufacturing, and Controls Documentation*³ (referred to here as the
73 “nasal spray draft guidance”). These two draft Guidances contain recommended limits for the
74 mass balance obtained during particle size measurements on the final product.

75 In particular, the MDI/DPI draft Guidance, in Section III.F “Specifications for the Drug
76 Product” states that:

77 *The total mass of drug collected on all stages and accessories is recommended to be*
78 *between 85 and 115 percent of label claim on a per actuation basis.* (Lines 624-626)

79 The nasal spray draft Guidance, in Section III.F “Specifications for the Drug Product” states
80 that:

81 *The total mass of drug collected on all stages and accessories is recommended to be*
82 *between 85 and 115 percent of label claim on a per spray basis.* (Lines 759-761)

83 In industry’s view, the use of the PSD mass balance (MB) as suggested by these draft
84 Guidances deviates from the approaches recommended by the U.S. Pharmacopeia. The USP
85 recommends that the test be repeated if the material balance (mass balance) is not within 75% to
86 125% of the average minimum recommended dose determined by the test for Uniformity of
87 Dosage Units (see Appendix B, p. 19, lines 593-597). The pharmaceutical industry provided
88 comments to the draft Guidances (see FDA dockets No. 98D-0097 and No. 99D-1454) and
89 expressed their opinion of PSD mass balance in the paper entitled *Initial Assessment of the*
90 *ITFG/IPAC Aerodynamic Particle Size Distribution Database*, submitted to the FDA in August 2000.
91 In that paper, it was concluded that “orally inhaled products do not in general comply with the
92 proposed mass balance requirement in the draft CMC Guidances (85-115% LC) and that the
93 proposed requirement is not suitable as a drug product specification but could be appropriate
94 as a system suitability test defined on a case by case basis.”⁴

1 The format of this Work Plan follows the general outline suggested by the *Guidance for Working Groups/PQRI* (see Appendix A).

2 *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation*, CDER/FDA, October 1998, (Docket No. 98D-0997), available at <http://www.fda.gov/cder/guidance/2180.pdf>.

3 *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products Chemistry, Manufacturing, and Controls Documentation*, CDER/FDA, May 1999, (Docket No. 99D-1454), available at <http://www.fda.gov/cder/guidance/2836.pdf>.

4 Available at http://www.fda.gov/ohrms/dockets/ac/00/techrepro/3609_reports.htm.

95 In July 2001, the PQRI Steering Committee considered the proposal to establish
96 appropriate use of the PSD mass balance, and approved the formation of a Working Group
97 (WG) on this topic, with participation from industry, academia, FDA and USP. The present
98 document represents a Work Plan developed by this Working Group.

99 II. RESEARCH OBJECTIVES

100 A. Current Challenges

101 In developing the Work Plan, the Working Group recognized that several factors
102 complicate the issue of the PSD MB, such as:

- 103 • A PSD determination involves numerous complicated manual operations,
104 which require highly specialized analytical skills.
- 105 • Multiplicity of error sources means that it may not be easy to assign a
106 failed MB to a specific cause.
- 107 • OINDP are complex dosage forms that generate aerosols. Aerosols by
108 their nature are unstable and therefore difficult to measure accurately.⁵
- 109 • There is no “standard” MDI or DPI to verify the cascade impactor
110 performance.
- 111 • A true calibration of an impactor cannot be done routinely, but has to be
112 undertaken as a separate project in a specialized laboratory, and can take
113 many months to complete.
- 114 • A valid mass balance determination can only be made during the same
115 run as the PSD test itself.

116 These and other difficulties inherent in a cascade impactor test, have inhibited the
117 development of a consistent, across-industry approach for use of the mass balance obtained in a
118 cascade impactor test. (Although the procedure in Chapter <601> of the US Pharmacopeia is
119 often quoted as the “standard CI method,” in practice there are several variations of this
120 procedure, and <601> does not provide sufficient guidance for verifying that a “valid”
121 measurement has been made).

122 Nevertheless, the Working Group feels it would be possible, and extremely important,
123 to establish appropriate use of the PSD MB and the associated acceptance criteria. To this end,
124 the Working Group proposes to conduct literature reviews, experimentation, data mining and
125 data analyses as described below. As a result of this work, the industry and the Agency will
126 obtain a clear, consistent recommendation on the use of PSD MB, based on science and
127 supported by valid data.

⁵ See, for example: (i) Marple, V.A. and Willeke, K. 'Inertial Impactors: Theory, Design and Use', pp.411-446 in *Fine Particles*, ed. B.Y.H. Liu, Academic Press, N.Y., 1986; and (ii) Lodge, J.P. and Chan, T.C. 'Cascade Impactor: Sampling and Data Analysis', Amer. Ind. Hyg. Assoc., Akron, Ohio, 1986.

128 **B. Hypotheses**

129 The Working Group proposes to investigate the following hypotheses:

130 **Hypothesis 1a:**

131 *For OINDP, the Particle Size Distribution Mass Balance, as a measure of the*
132 *drug substance delivered per actuation, has a larger random uncertainty per*
133 *determination than the dose content uniformity (DCU) test.*

134 **Hypothesis 1b:**

135 *For OINDP, Particle Size Distribution Mass Balance deviates from the mean*
136 *mass of drug substance delivered from the valve due to systematic uncertainties from*
137 *multiple sources.*

138

139 **As a consequence of 1a and 1b:**

140 *Mass Balance is not the best test of product quality.*

141 **Despite 1a and 1b:**

142 *Mass Balance can be used to qualify the delivery/collection/analysis system for*
143 *PSD measurement via a cascade impactor.*

144

145 **Hypothesis 2:**

146 *Orally inhaled and nasal drug products do not consistently meet the mass*
147 *balance acceptance criterion of between 85 and 115 percent of label claim on a per*
148 *actuation/spray basis. Appropriate Mass Balance limits should be based on data and*
149 *method capability.*

150

151 **C. General Outline of Work Plan**

152 To investigate the above hypotheses, the following 5-step work plan is proposed. The
153 details of each of the proposed steps are outlined in the following section.

154 1. First, draft "Failure Investigation Tree" based on the WG experience,
155 then survey the industry to obtain data on all known causes and
156 frequencies of failure for the mass balance determined via cascade
157 impactors. Analyze the survey and finalize the *Investigational Tree*, based
158 on reported causes and frequencies of MB failure.

159 2. Design and conduct an experiment to compare variances of the
160 delivered dose as determined in a USP DCU apparatus as opposed to
161 those determined in a cascade impactor. Prepare a document defining
162 how PSD Mass Balance should be used for product quality control.

- 163 3. Prepare and publish a *Good Cascade Impactor Practices* paper, which
164 would include the *Investigational Tree* developed in step 1.
- 165 4. Based on PSD data gathered through data-mining, establish what
166 general procedures and limits are appropriate for MB as a PSD run
167 qualification.
- 168 5. Make recommendations for FDA's CMC Draft Guidances for OINDP.

169 **D. Specifics of Work Plan**

170 This section outlines the specifics of the Work Plan. As work in each of the areas
171 progresses, the Working Group will prepare and present to PQRI project updates and Progress
172 Reports. The currently proposed Work Plan will also be updated accordingly.

173 **STEP 1. DEVELOP INVESTIGATIONAL TREE**

174 (a) STEP 1: GOAL

175 The goal of this step is to develop an *Investigational Tree*, which would help determine
176 the cause of a failed mass balance through a consistent, logical process. The investigation of a
177 failed MB would start with the most probable (most frequent) cause of failure and then proceed
178 to less likely (less frequent) causes of failure. The *Investigational Tree* should have a description,
179 at each stage of the investigation, of the evidence necessary to draw a conclusion as to the
180 reason for the Mass Balance failure.

181 First, the list of all possible causes would have to be prepared. Broadly, the causes could
182 be categorized as those due to: (i) cascade impactor, (ii) CI operator; (iii) HPLC apparatus ; (iv)
183 HPLC operator; or (v) drug product. In each category, a listing of specific causes will have to be
184 identified. For example, for the CI, the following factors could cause a failing MB: inadequate
185 flow rate, leakages, misalignment of stages, misalignment of the actuator with the inlet port or
186 other misactuation, miscalculation, *etc.* Second, these causes will have to be ranked on a certain
187 scale, (*e.g.*, frequent/occasional/rare or from 0-10, or from 0-100).

188 (b) STEP 1: MEANS

189 In order to accomplish the goal, the Working Group plans to prepare and conduct an
190 industry-wide confidential survey, which would both help identify possible causes of MB
191 failure, and rank the frequency/probability of these causes. The Working Group will involve
192 statisticians with experience in surveys and Probabilistic Risk Assessment (PRA) to assist in
193 both the design of the survey and analysis of the data obtained from the survey. The IPAC-RS
194 Secretariat will assist in blinding the data from the submitted questionnaire forms.

- 195 (c) STEP 1: TIMELINE⁶
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- Prepare initial draft of the *Investigational Tree* **by 13 May 2002**.
 - Identify statisticians with expertise in survey analysis and probabilistic risk assessment **by the end of May 2002**.
 - With the participation of statisticians, draft the survey for investigation of causes and frequencies of MB failure **in June-July 2002**.
 - Finalize survey **in July-August 2002**.
 - Send out the survey **in September 2002**, to as many companies and testing laboratories as possible (via IPAC-RS, ITFG, PhRMA, GPhA, EPAG).
 - Collect answers by **November 2002**.
 - Clarify ambiguities in submitted questionnaires **in December 2002-February 2003**.
 - Perform statistical analysis of submitted data **in February-April 2003**.
 - Finalize the *Investigational Tree* within the WG **in May – June 2003**.
 - Prepare a written report of findings of step 1 **in July-August 2003**.
 - Present the report, with the developed *Investigational Tree* to the PQRI DPTC and SC **in September 2003**.
 - Present the report, with the developed *Investigational Tree* to the wider scientific community through a presentation at a PQRI workshop, or conference, or a publication in **Q4 2003**.

217 (d) STEP 1: OUTCOME

218 The Working Group may develop a recommendation, based on the assembled
219 information, that a failed MB be treated as follows:

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- If MB is **within inner limits**, GREEN situation – test results are valid, no additional PSD testing/investigation required.
 - If MB is **between inner and outer limits**, AMBER situation - an Out of Trend (OOT) investigation required. The operator will use the *Investigational Tree* to establish the cause of failure, if possible, and will document the undertaken steps of the investigation in the laboratory notebook. Depending on results of the OOT investigation, a conclusion will be made, if possible, whether this was a test failure or a product failure.

⁶ The timelines proposed in this work plan were agreed during the 25 March 2002 Working Group teleconference. They may be optimized by the Working Group further as needed.

- 229 • If MB is **outside of outer limits**, RED situation – an Out of
230 Specification (OOS) investigation required. The operator will use the
231 *Investigational Tree* to establish the cause of failure, if possible, and will
232 document the undertaken steps of the investigation in the laboratory
233 notebook. Depending on results of the OOS investigation, a
234 conclusion will be made, if possible, whether this was a test failure or
235 a product failure.

236 Note that data-based recommendations for the numerical values of the inner and outer
237 limits will be developed at a later stage (steps 2 and 4). These limits may be drug product
238 specific (different limits for different drugs/strengths) and dosage form specific (different limits
239 for nasal sprays or orally inhaled products, MDIs or DPIs, etc.).

240 The work carried out in step 1 will be used in the development of *Good Cascade Impactor*
241 *Practices* (see below).

242 **STEP 2. COMPARE PSD AND DCU VARIANCES**

243 (a) STEP 2: GOAL

244 The goal of step 2 is to compare the variance of the drug substance delivered per
245 actuation as determined in a USP DCU apparatus as opposed to the variance of the same
246 obtained from a cascade impactor. The outcomes of this work will be summarized in a paper
247 explaining how PSD mass balance fit in overall product quality control. This step will involve
248 generation of detailed data on PSD and DCU replicates obtained from the same canister and in
249 the same approximate range of actuations within canister. The type of products on which the
250 experiment will be performed, the exact experimental procedure, and the procedure for data
251 analysis will be determined by the Working Group (which will be expanded to include
252 statisticians, see below).

253 (b) STEP 2: MEANS

254 In order to accomplish the goal, the Working Group plans to design and oversee the
255 conduction of an experiment. The Working Group will prepare a draft protocol and will
256 request feedback and comments from the broad scientific community on the draft protocol, in
257 order to assure that the experiment is appropriately designed. The Working Group will request
258 the support of statisticians with expertise in uncertainty analysis to analyze the results of this
259 experiment.

260 (c) STEP 2: TIMELINE

- 261 • Prepare a preliminary draft protocol for comparing variances of the
262 delivered dose as determined in a USP DCU apparatus and in a
263 cascade impactor, **by 13 May 2002**.

- 264 • Identify statisticians with expertise in uncertainty analysis **by the end**
265 **of May 2002.**
- 266 • With the participation of statisticians, prepare a mature draft protocol
267 for prospective research (*e.g.*, characteristics of the products on which
268 the experiment will be performed, the exact experimental procedure,
269 and the procedure for data analysis), **by July 2002.**
- 270 • Ask for input from wider scientific community to improve the draft
271 protocol **in September–November 2002.**
- 272 • Conduct experiment **in January-March 2003** by a neutral party (FDA
273 laboratories or academic laboratories or CROs).
- 274 • Summarize results in a paper **in May-June 2003.**
- 275 • Paper will be sent to DPTC, SC for review and approval before
276 publication.

277 (d) STEP 2: OUTCOME

278 The data obtained in this step will be used to:

- 279 (i) quantify random uncertainty of a mass balance cascade impactor
280 determination;
- 281 (ii) identify sources and quantify systematic uncertainties of a mass
282 balance cascade impactor determination;
- 283 (iii) compare variability per determination of the emitted drug substance
284 as determined from a cascade impactor and a USP DCU apparatus;
- 285 (iv) develop *Good Cascade Impactor Practices*;
- 286 (v) recommend limits for PSD mass balance that are reflective of studied
287 batches of OINDP; and
- 288 (vi) help resolve the debate over using MB as a measure of product
289 quality.

290 **STEP 3. DEVELOP GOOD CASCADE IMPACTOR PRACTICES**

291 (a) STEP 3: GOAL AND MEANS

292 The goal of this step is to prepare and publish a *Good Cascade Impactor Practices* paper,
293 with finished *Investigational Tree*, based on outcomes of steps 1-2 and survey of literature.

- 294 (b) STEP 3: TIMELINE
- 295 • Start **in June 2002**.
- 296 • Finish **in June 2003**.
- 297 • Eventually publish (after review and approval by DPTC and SC of
- 298 PQRI), in DIA Journal, or Journal of Aerosol Medicine, or Journal of
- 299 Aerosol Science, or Pharmacopeial Forum, or other appropriate
- 300 publication.

301 **STEP 4. DETERMINE APPROPRIATE PSD MB LIMITS**

302 (a) STEP 4: GOAL AND MEANS

303 The goal of this step is to recommend what general procedures and limits are

304 appropriate for MB as a run qualification criterion, or as a batch release criterion. The basis for

305 this work will be PSD data for approved products, collected through an industry-wide

306 confidential survey (data-mining). The IPAC-RS Secretariat will assist in blinding the submitted

307 data files. Statistical support will be employed to finalize the data template, compile the data

308 into a Master File, and analyze the data.

309 (b) STEP 4: TIMELINE

- 310 • Draft data inclusion/exclusion criteria **by 13 May 2002**
- 311 *e.g.*,
- 312 – number of actuations per determination;
- 313 – type of impactor;
- 314 – flow rate; and
- 315 – product status (*e.g.*, approved after a certain date, in
- 316 development after a certain stage, *etc.*).
- 317 • Identify statisticians with expertise in analyzing large sets of QC data
- 318 (*i.e.*, designing a data template for an industry-wide survey,
- 319 compiling submitted data, and analyzing the database) **by the end of**
- 320 **May 2002**. Use internet sites of pqri.org, ipacrs.com, epag.co.uk, and
- 321 other contacts for soliciting interest.
- 322 • With the participation of statisticians, develop survey template –
- 323 **June-August 2002**.
- 324 • Evaluate appropriateness (qualitatively and quantitatively) of the
- 325 ITFG/IPAC-RS PSD database. Obtain approval of data sponsors to
- 326 use relevant parts of the ITFG/IPAC-RS PSD database. **September -**
- 327 **October 2002**.
- 328 • Issue solicitation for additional data, possibly through FDA FTEs
- 329 and industry (data-mining). **September - October 2002**.

- 330 • Complete data collection by **December 2002**.
- 331 • Clarify ambiguities and resolve inconsistencies in assembled data. –
- 332 **January – February 2003**.
- 333 • Analyze data and prepare a draft report. **March-April 2003**.
- 334 • Finalize the report within WG. **May - June 2003**
- 335 • Send paper to DPTC, SC for approval.
- 336 • Publish.

337 **STEP 5. MAKE RECOMMENDATIONS FOR CMC OINDP DRAFT GUIDANCES**

338 (a) STEP 5: GOAL AND MEANS

339 Based on the results of work accomplished in steps 1-4, the Working Group will prepare
340 a recommendation(s) for the FDA draft CMC Guidances for OINDP, regarding appropriate use
341 of the PSD mass balance, its role in the overall system of product quality control, and good
342 cascade impactor practices.

343 (b) STEP 5: TIMELINE

- 344 • Prepare a recommendation, finalize it within the WG, send to the
- 345 DPTC and SC for review and approval, and submit to the FDA **Q3-4**
- 346 **2003**.

347 It is anticipated that in mid-2003, the recommendation could be developed and finalized.
348 However, this timeline may be adjusted as needed, based on the progress made steps 1-4. As
349 each of the proposed steps progresses, the Working Group will prepare a report of
350 accomplished work, and an updated Work Plan.

351 **III. REQUIRED RESOURCES**

352 **A. Human Resources**

353 Current members of the Working Group are:

- 354 • Terry Tougas (Boehringer Ingelheim), Chair
- 355 • Ken Furnkranz (OGD/FDA)
- 356 • Martin Lavery (Aventis)
- 357 • Deborah Miran (GPhA)
- 358 • Jolyon Mitchell (Trudell Medical)
- 359 • Brian Rogers (ONDC/FDA)
- 360 • Bruce Wyka (Schering-Plough)
- 361 • Kahkashan Zaidi (USP)

362 In addition, Guirag Poochikian (ONDC/FDA) and Jeffrey Blumenstein (Pfizer) serve as
363 DPTC liaisons to these Working Groups, and the IPAC-RS Secretariat provides administrative
364 support.

365 The expertise of current members lies in the areas of product development, analytical
366 technologies, and regulatory guidance. In order to carry out certain steps of the proposed work
367 plan (specifically steps 1, 2, 4), additional expertise in specialized areas of statistics will be
368 required. The Working Group plans to solicit participation of qualified statisticians from the
369 member organizations of PQRI, both through direct contacts and through postings on home
370 pages of interested member organizations (e.g., www.pqri.org, www.ipacrs.com, www.usp.org,
371 www.aaps.org, etc.). It is expected that the direct employer of the statisticians involved in this
372 work will be responsible for the expenses incurred by the statistician(s).

373

374 **B. Laboratory Resources**

375 For certain parts of the Work Plan (step 2), laboratory experimentation will be required.
376 Currently, it is proposed, that the Agency's laboratory should be used for this purpose as the
377 Working Group's first choice.

378

379 **C. Financial Resources**

380 No additional financial support from PQRI is requested at this time.

381 **IV. POTENTIAL IMPACT**

382 Several important outcomes are anticipated from this work. First, both the Agency and
383 industry will obtain science-based and data-supported conclusions regarding the appropriate
384 use of the PSD mass balance and its role in the overall system of ensuring product quality. As
385 one of its work products, the Working Group will prepare the document *Good Cascade Impactor*
386 *Practices*, which will be a unique, comprehensive guide for the developers of OINDP and the
387 Agency's reviewers. Secondly, the proposed work may help harmonize the FDA's and USP
388 requirements with respect to PSD MB. Ultimately, the scientifically sound regulatory guidance
389 documents developed on the basis of this work would benefit the Agency, industry and the
390 patient. For the Agency, better guidance translates into improved, more consistent submissions
391 that are easier to review; for the industry, into testing requirements that are optimized and
392 better understood; and for the patients, into expedient availability of diverse, new, high-quality
393 pharmaceutical products.

394 **V. GLOSSARY AND ABBREVIATIONS**

395 **Fine Particle Dose:** The total mass of drug found on the stages of the apparatus and the filter in
396 the fine particle range appropriate for the particular drug being tested divided by the
397 number of actuations (designated as R/n in USP <601>).

398 **Fine Particle Fraction:** The ratio of the total mass of drug found on the stages of the apparatus
399 and the filter in the fine particle range appropriate for the particular drug being tested to
400 the total mass of drug found on all stages and accessories of the apparatus (R/Sigma A
401 in USP <601>).

402 **Mass Balance (MB)** (*in cascade impactors*): A measurement of the ability of an MDI/DPI device
403 to deliver, a/an (Cascade) Impactor to collect, and the Analytical (Chromatographic)
404 system to detect (measure) an adequate dose of drug for the purpose of Particle Size
405 Distribution determination. In the context of particle size analysis by cascade impactor
406 in accordance with <601> of the US Pharmacopeia, MB is the sum of masses contained in
407 the inhaler mouthpiece adapter, induction port, pre-separator (if used), all stages of the
408 impactor and the back-up filter. MB is defined as part of the system suitability test in
409 USP Chapter <601>, which specifically comments that the mass balance is not a test of
410 the inhaler, but serves to ensure that the test results are valid. USP <601> uses the term
411 “total mass” and designates it as Sigma A.

412 **Non-Ideal Impactor Behavior:** Deviation in the performance of the impactor from a perfect
413 size-separating device. Assuming that the cut-point size (size at which 50% of incoming
414 particles are collected by a given stage) is representative of that stage, the following
415 processes can bias this parameter:

- 416 (a) stage nozzle wear and/or corrosion;
417 (b) improper selection or absence of a suitable collection surface; or
418 (c) leakages into the impactor between stages.

419 Ways to minimize bias from these causes are described in <601> of the US
420 Pharmacopeia. In addition, impactors of a given design have internal losses, caused
421 largely by deposition of particulate on inter-stage passageways and within the nozzles.
422 These are largely unavoidable, but should be verified as being no greater than 5% for a
423 given formulation, or an alternative apparatus should be used (USP <601>).

424 **Particle Size Distribution:** The size characterization (*e.g.*, by mass), of a material (aerosol cloud,
425 liquid spray or solid).

426 **Aerodynamic Particle Size Distribution:** The separation, by size, of a material (aerosol cloud,
427 liquid spray or solid) utilizing aerodynamic particle characteristics. A quantity of
428 material entering the cascade impactor is separated by gradient airflow into a size/mass
429 distribution.

430 **Run Qualification:** An assessment of the adequacy of the operation of the
431 delivery/collection/analysis system each time a Particle Size Distribution (PSD)
432 determination is made. A “run qualification” measurement can be used as a (de-facto)
433 measurement of “system suitability” each time the system is operated.

434 ABBREVIATIONS

435

436	CI	Cascade Impactor
437	DCU	Dose Content Uniformity
438	DPTC	(PQRI's) Drug Product Technical Committee
439	EPAG	European Pharmaceutical Aerosol Group
440	FTE	Full-Time Employee
441	GCIP	Good Cascade Impactor Practices
442	ICH	International Conference on Harmonization of Technical Requirements for
443		Registration of Pharmaceuticals for Human Use
444	IPAC-RS	International Pharmaceutical Aerosols Consortium on Regulation and Science
445	ITFG	Inhalation Technology Focus Group of the American Association of Pharmaceutical
446		Scientists (AAPS)
447	MB	Mass Balance
448	OGD	(FDA's) Office of Generic Drugs
449	OINDP	Orally Inhaled and Nasal Drug Products
450	ONDC	(FDA's) Office of New Drug Chemistry
451	OOT	Out of Trend
452	OOS	Out of Specification
453	PQRI	Product Quality Research Institute
454	PSD	Particle Size Distribution
455	SC	(PQRI's) Steering Committee
456	WG	Working Group
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Guidance for Working Groups Product Quality Research Institute

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The Working Groups of the Product Quality Research Institute (PQRI) are essential to the success of the Institute. As such, each Working Group should understand what it is expected to do in carrying out its charge from the Technical Committee. The PQRI Steering Committee is therefore providing this guidance for Working Groups to help establish what the expectations are for the Working Groups. This guidance will be revised if necessary based on the on-going experience gained by each Working Group.

The Technical Committees will define the research objectives of the project as approved by the Steering Committee that the Working Group will study. The Technical Committee will nominate Working Group members from the names provided by the constituent PQRI member organizations. The Technical Committee chair may recommend additional Working Group members after assessing the expertise of member organization nominees. If a member organization nominee is not selected by the Technical Committee to be on the Working Group, the reason for that rejection will be provided. Nominations to Working Groups should be made based on the technical expertise of the candidates and their willingness to devote the time and effort necessary to successfully complete their assigned project according to the project timeline. The Technical Committee also will designate a Working Group chairperson from the members of the nominated Working Group and a Technical Committee member will be assigned to the Working Group to provide a continual link between the Working Group and the Technical Committee. The PQRI Steering Committee will approve the membership and chair of each Working Group recommended by the Technical Committees.

Once a Working Group has been established and approved the Group should meet within thirty (30) days to begin development of a work plan to address its assigned topic and establish a definitive timeline when the plan will be completed. It is the responsibility of the Steering Committee to provide each Working Group with an orientation to PQRI and an explanation of the PQRI research process.

A formal work plan should be prepared for the topic assigned to the Working Group. It is anticipated that each plan will contain at a minimum the following:

1. Background*

- What is the specific topic being addressed?
- What is the regulatory/compendium history of this topic?
- What are the scientific issues surrounding the topic and what specific questions are being addressed?

* Items 1 and 2 should be provided by the Technical Committee.

- 501 2. Why is the work being done?*
- 502 • What regulation or guidance is impacted by this research?
- 503 • What is the current guidance/regulation?
- 504
- 505 3. Research Objective**
- 506
- 507 • What is the specific research objective that this work plan would address? (Include a
- 508 statement of hypothesis.)
- 509
- 510 4. Work Plan
- 511
- 512 • What specific work will be needed to address the research question?
- 513 • Will the study utilize data mining or prospective research?
- 514 • Can the work be conducted using “sweat equity” from the Working Group membership
- 515 or does the work have to be contracted? Any decision to contract work will be made by
- 516 the Steering Committee.
- 517 • What is the plan timeline? (Should include milestones, data analysis and report
- 518 preparation)
- 519 • What are the anticipated costs of the project?
- 520
- 521 5. Potential Impact
- 522
- 523 • How will this regulation/guidance change if the research is “positive”?
- 524 • What will the impact of this change be on FDA and/or Industry? (Should try to address
- 525 safety, timing and financial considerations)
- 526

527 It should be noted that the PQRI process is intended to be a very public exercise. Study plans,

528 meeting minutes and all reports will be made public on the PQRI web site. Additionally,

529 Working Groups should consider by what mechanisms they would solicit necessary public

530 input. The Working Group must consider the impact of public solicitation for comment on

531 project timelines.

532

533 Once the Working Group completes the formal proposal, it will be reviewed and approved by

534 the Technical Committee and the Steering Committee. The Steering Committee will then

535 recommend project funding to the Board of Directors.

536

537 As the project evolves, the Working Group is to keep the Technical Committee informed on a

538 monthly basis of plan status relative to the timeline. Any issues that cannot be resolved at the

539 Working Group level should be raised to the Technical Committee and/or the Steering

540 Committee to insure timely progress and completion of the project. The Technical Committee

541 shall inform the Steering Committee of status and/or issues associated with each project at the

542 regularly scheduled Steering Committee meeting at least two (2) weeks prior to each Steering

543 Committee meeting. If necessary, a Technical Committee may request a special ad hoc meeting

** Item 3 will be provided by the Working Group and incorporated into the overall document, which will be sent to the Steering Committee for approval.

544 of the Steering Committee to address specific, urgent issues. The Steering Committee may at
545 any time recommend changes to the Working Group study plan based on study progress
546 and/or information obtained from other sources.

547
548 Once the work is completed, the Working Group will prepare a comprehensive report and
549 make a recommendation regarding potential changes to existing or draft guidance/regulation.
550 The report should be suitable for publication in a peer reviewed scientific journal. The
551 Technical Committee will review, recommend any changes if necessary, approve the report and
552 send it to the Steering Committee for review and approval. The Steering Committee is
553 responsible for sending the completed report and regulatory recommendation to FDA for
554 consideration.

555
556 Under the PQRI process, FDA has agreed to review the report and regulatory recommendation.
557 If the Agency rejects the conclusions and recommendations made by PQRI, a written
558 explanation for the rejection will be provided to the PQRI Steering Committee. These results
559 will be communicated to the Technical Committee and Working Group. If there is an
560 opportunity to revise the report and/or conduct additional work to make the initial
561 recommendation acceptable based on feedback from the Agency; the Working Group will take
562 necessary actions to successfully revise the report. The process will continue until the Working
563 Group recommendation is accepted by FDA or it is determined by the Steering Committee that
564 further work will not result in successful resolution of remaining issues. In any case, the report
565 and actions taken by FDA will be made available to the public via the PQRI web site and
566 publication in an appropriate scientific journal.

567

568 **FDA, USP AND ICH APPROACHES TO THE USE OF PSD MASS BALANCE**
569 **AND PRINCIPLES FOR ESTABLISHING APPROPRIATE SPECIFICATIONS**

570 **PARTICLE SIZE DISTRIBUTION**

571 The **particle or droplet size distribution** in the spray discharged from
572 metered-dose inhalers, and the particle size distribution in the cloud discharged from dry
573 powder inhalers, are important characteristics used in judging inhaler performance. While
574 particle size measurement by microscopy can be used to evaluate the number of large
575 particles, agglomerates, and foreign particulates in the emissions of metered-dose inhalers
576 (e.g., Epinephrine Bitartrate Inhalation Aerosol), whenever possible this test should be
577 replaced with a method to determine the aerodynamic size distribution of the drug
578 aerosol leaving the inhaler. The aerodynamic size distribution defines the manner in
579 which an aerosol deposits during inhalation. When there is a log-normal distribution, the
580 aerodynamic size distribution may be characterized by the mass median aerodynamic
581 diameter (MMAD) and geometric standard deviation (GSD). The aerodynamic size
582 distribution of the drug leaving metered-dose and dry powder inhalers is determined
583 using Apparatus 1, 2, 3, or 4, as specified in this chapter. A fine particle dose or fine
584 particle fraction can also be determined as that portion of the inhaler output having an
585 aerodynamic diameter less than the size defined in the individual monograph. This may
586 be expected to correlate with the drug dose or that fraction of the drug dose that
587 penetrates the lung during inhalation. Individual monographs may also define the
588 emitted fractions of the delivered dose in more than one aerodynamic size range.

589 *USP 25 <601>*

590 **AERODYNAMIC SIZE DISTRIBUTION.** Cascade impaction devices
591 classify aerosol particles and droplets on the basis of those particles' aerodynamic
592 diameters. The principle of their operation, whereby they separate aerosol particles and
593 droplets from a moving airstream on the basis of particle or droplet inertia, is shown in
594 Figure 3. Because the dimensions of the induction port used to connect inhalers to the
595 cascade impactors and impingers (shown in Apparatus 1, 2, 3, and 4) also define the mass
596 of drug that enters the aerodynamic sizing device, these are carefully defined and, where
597 possible, are held constant between each apparatus (see Figures 4, 6, 7, and 8). Because the
598 size distributions produced by different impactors are often a function of impactor design
599 and the airflow rate through them, there is a need to standardize the instruments that are
600 used to test inhalers (i.e., Apparatus 1 for metered-dose inhalers) or to provide guidelines
601 on system suitability where different apparatuses may be used (i.e., Apparatus 2, 3, or 4
602 for dry powder inhalers).

603 *USP 25 <601>*

604 The total mass of drug collected in all of the components (material balance)
605 divided by the total number of minimum recommended doses⁷ discharged is not less than
606 75% and not more than 125% of the average minimum recommended dose determined
607 during testing for Uniformity of Dosage Units. If the total mass is outside of this range, the
608 test must be repeated.

609 *USP 25 <601>*

610 **ROBUSTNESS**

611 The **robustness** of an analytical method is a measure of its capacity to
612 remain unaffected by small but deliberate variations in method parameters and provides
613 an indication of its reliability during normal usage.

614 *USP 25 <1225>*

615 **RUGGEDNESS**

616 The **ruggedness** of an analytical method is the degree of reproducibility of
617 test results obtained by the analysis of the same samples under a variety of conditions,
618 such as different laboratories, different analysts, different instruments, different lots of
619 reagents, different elapsed assay times, different assay temperatures, different days, etc.
620 Ruggedness is normally expressed as the lack of influence on test results of operational
621 and environmental variables of the analytical method. Ruggedness is a measure of
622 reproducibility of test results under the variation in conditions normally expected from
623 laboratory to laboratory and from analyst to analyst.

624 *USP 25 <1225>*

625 **SPECIFICATION**

626 A **specification** is defined as a list of tests, references to analytical
627 procedures, and appropriate acceptance criteria which are numerical limits, ranges, or
628 other criteria for the tests described. It establishes the set of criteria to which a new drug
629 substance or new drug product should conform to be considered acceptable for its
630 intended use. "Conformance to specifications" means that the drug substance and / or
631 drug product, when tested according to the listed analytical procedures, will meet the
632 listed acceptance criteria. Specifications are critical quality standards that are proposed
633 and justified by the manufacturer and approved by regulatory authorities as conditions of
634 approval.

635 *ICH Guideline Q6A, sections 1.2 and 3.1.1*
636 *(Available at <http://www.ifpma.org/pdfifpma/q6a.pdf>)*

637 **Specification.** A list of tests, references to analytical procedures, and
638 appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the

⁷ "A single dose is defined as the number of sprays specified in the product labeling as the minimum recommended dose." (USP 25 <601>).

639 test described. It establishes the set of criteria to which a material should conform to be
640 considered acceptable for its intended use. “Conformance to specification” means that the
641 material, when tested according to the listed analytical procedures, will meet the listed
642 acceptance criteria.

643 *ICH Guideline Q7A, section 20*
644 (Available at <http://www.ifpma.org/pdfifpma/Q7Astep4.PDF>)

645 **Specification:** The quality standards (i.e., tests, analytical procedures, and
646 acceptance criteria) provided in an approved application to confirm the quality of the
647 drug substances, drug products, intermediates, raw materials, reagents, and other
648 components including container closure systems, and in-process materials.

649 *FDA Draft Guidance for Industry*
650 *‘Analytical Procedures and Methods Validation’, Lines 1277-1280*
651 (Available at <http://www.fda.gov/cder/guidance/2396dft.pdf>)

652 **Specifications** are an important component of quality assurance, but are
653 not its only component.

654 *ICH Guideline Q6A, section 1.3*
655 (Available at <http://www.ifpma.org/pdfifpma/q6a.pdf>)

656 When a **specification** is first proposed, justification should be presented for
657 each procedure and each acceptance criterion included. The justification should refer to
658 relevant development data, pharmacopoeial standards, test data for drug substances and
659 drug products used in toxicology and clinical studies, and results from accelerated and
660 long term stability studies, as appropriate. Additionally, a reasonable range of expected
661 analytical and manufacturing variability should be considered. It is important to consider
662 all of this information.

663 *ICH Guideline Q6A, section 3.1.2*
664 (Available at <http://www.ifpma.org/pdfifpma/q6a.pdf>)

665 **SYSTEM SUITABILITY**

666 **System suitability** testing is an integral part of many analytical procedures.
667 The tests are based on the concept that the equipment, electronics, analytical operations
668 and samples to be analyzed constitute an integral system that can be evaluated as such.
669 System suitability test parameters to be established for a particular procedure depend on
670 the type of procedure being validated. See Pharmacopoeias for additional information.

671 *ICH Guideline Q2B, section 9*
672 (Available at <http://www.ifpma.org/pdfifpma/q2b.pdf>)

673 If measurements are susceptible to variations in analytical conditions, these
674 should be suitably controlled, or a precautionary statement should be included in the
675 method. One consequence of the evaluation of robustness and ruggedness should be that
676 a series of **system suitability** parameters is established to ensure that the validity of the
677 analytical method is maintained whenever used. Typical variations are the stability of

678 analytical solutions, different equipment, and different analysts. In the case of liquid
679 chromatography, typical variations are the pH of the mobile phase, the mobile phase
680 composition, different lots or suppliers of columns, the temperature, and the flow rate. In
681 the case of gas chromatography, typical variations are different lots or suppliers of
682 columns, the temperature, and the flow rate. **System suitability** tests are based on the
683 concept that the equipment, electronics, analytical operations, and samples to be analyzed
684 constitute an integral system that can be evaluated as such. System suitability test
685 parameters to be established for a particular method depend on the type of method being
686 evaluated. They are especially important in the case of chromatographic methods, and
687 submissions to the USP should make note of the requirements under the System
688 Suitability section in the general test chapter Chromatography <621>.

689 *USP 25 <1225>*

690 **System suitability** testing is recommended as a component of any
691 analytical procedure, not just those that involve chromatographic techniques. Regardless
692 of the type of analytical procedure, testing should be used to confirm that the system will
693 function correctly independent of the environmental conditions. For example, titration
694 analytical procedures should always include the evaluation of a blank (commonly referred
695 to as a blank titration).

696 *FDA Draft Guidance for Industry*
697 *'Analytical Procedures and Methods Validation', Lines 283-287*
698 *(Available at <http://www.fda.gov/cder/guidance/2396dft.pdf>)*

699 **System Suitability Testing:** Each analytical procedure submitted should
700 include an appropriate number of system suitability tests defining the critical
701 characteristics of that system. Criteria for all system suitability testing should be provided.

702 *FDA Draft Guidance for Industry*
703 *'Analytical Procedures and Methods Validation', Lines 834-838*
704 *(Available at <http://www.fda.gov/cder/guidance/2396dft.pdf>)*

705 **System Suitability**— Because of the varied nature of the formulations and
706 devices being tested, the cascade impaction system and technique selected for testing an
707 inhaler should fulfill a number of criteria.

708 **Stage Mensuration**—Manufacturers of cascade impaction devices
709 provide a definitive calibration for the separation characteristics of each impaction
710 stage in terms of the relationship between the stage collection efficiency and the
711 aerodynamic diameter of particles and droplets passing through it as an aerosol.
712 Calibration is a property of the jet dimensions, the spatial arrangement of the jet
713 and its collection surface, and the airflow rate passing through it. Because jets can
714 corrode and wear over time, the critical dimensions of each stage, which define
715 that impaction stage's calibration, must be measured on a regular basis. This
716 process, known as stage mensuration, replaces the need for repetitive calibration
717 (using standard aerosols) and ensures that only devices that conform to
718 specifications are used for testing inhaler output. The process involves the
719 measurement and adjustment of the critical dimensions of the instrument.

720 **Inter-Stage Drug Loss (wall losses)** — Where method variations
721 are possible and there is no apparatus specified in the monograph, the selected
722 technique should ensure that not more than 5% of the inhaler's total delivered
723 drug mass (into the impactor) is subject to loss between the impaction device's
724 sample collection surfaces. In the event that inter-stage drug losses are known to
725 be greater than 5%, either the procedure should be performed in such a way that
726 wall losses are included along with the associated collection plate, or an alternative
727 apparatus should be used. As an example, the following procedures described for
728 Apparatus 1 and 3 have been written to include wall losses along with the
729 associated collection plate. Provided, however, that such losses are known to be
730 less than or equal to 5% of the total delivered drug mass into the impactor and that
731 there are no instructions to the contrary in an individual monograph, the technique
732 may be simplified by only assaying drug on the collection plates.

733 **Re-Entrainment**—Where method variations are possible, the
734 selected technique should seek to minimize particle re- entrainment (from an
735 upper to a lower impaction stage) on stages that contribute to size fractions
736 defined in the individual monograph, especially where this may affect the
737 amounts of drug collected. Minimizing the number of sampled doses, the use of
738 coated particle collection surfaces, and proving that multiple-dose techniques
739 produce statistically similar results to those from smaller numbers of doses, are all
740 methods that can be used for this purpose. In the event that re-entrainment cannot
741 be avoided, the number of doses collected, the time interval between doses, and
742 the total duration of airflow through the cascade impaction device should be
743 standardized. Under these circumstances, the presentation of impaction data
744 should not presume the validity of the impactor's calibration (i.e., aerodynamic
745 diameter ranges should not be assigned to drug masses collected on specific
746 stages). By using appropriate assay methods and a suitable mensurated impaction
747 device, aerodynamic particle size distributions can be determined for drugs
748 leaving the mouthpieces of metered-dose or dry powder inhalers. If temperature
749 or humidity limits for use of the inhaler are stated on the label, it may be necessary
750 to control the temperature and humidity of the air surrounding and passing
751 through the device to conform to those limits. Ambient conditions are presumed,
752 unless otherwise specified in individual monographs. In addition to the size
753 distribution, good analytical practice dictates that a complete **mass-balance** must
754 be performed in order to confirm that all of the drug discharged from the inhaler
755 was captured and measured in the induction port-cascade impactor apparatus.
756 **This is not a test of the inhaler but serves to ensure that the test results are valid.**

757 Use one of the multistage impaction devices shown below, or an
758 equivalent, to determine aerodynamic particle size distributions of drugs leaving
759 the mouthpieces of metered-dose or dry powder inhalers. Apparatus 1 (Figure 4) is
760 intended for use with metered-dose inhalers at a single airflow rate. Apparatus 2,
761 3, and 4 (Figures 6, 7, and 8, respectively) are intended for use with dry powder
762 inhalers at the appropriate airflow rate, Q , determined earlier, provided that the
763 value of Q falls in the range 30 to 100 liters per minute. [NOTE—If Q is greater

764 than 100 liters per minute, testing should be performed at 100 liters per minute; if
765 Q < 30 liters per minute, testing is performed at 30 liters per minute.]
766 *USP 25 <601>*