

1 **MINUTES OF THE MEETING**  
2 **OF THE PQRI PSD MASS BALANCE WORKING GROUP ON**  
3 **24-25 September 2002**

4 **I. PARTICIPANTS**

Terry Tougas (Boehringer Ingelheim), Chair	Karl Lin (FDA)
Jeff Blumenstein (Pfizer), <i>2<sup>nd</sup> day only</i>	Lana Lyapustina (IPAC-RS)
Dave Christopher (Schering-Plough)	Jolyon Mitchell (Trudell Medical)
Paul Curry (USP Aerosols Expert Committee)	Guirag Poochikian (FDA)
Bill Doub (FDA)	Brian Rogers (FDA)
Ken Furnkranz (FDA)	Helen Strickland (GlaxoSmithKline)
Lisa Kammerman (FDA), <i>1<sup>st</sup> day only</i>	Yi Tsong (FDA), <i>2<sup>nd</sup> day only</i>
Martin Lavery (Aventis)	Bruce Wyka (Schering-Plough)

5 **II. OPENING**

6 Dr. Tougas opened the teleconference and welcomed the participants. The participants  
7 introduced themselves and explained their interest in the work of the Group. Several  
8 participants commented that the work under way is important, pioneering, and an excellent  
9 example of the government and industry collaborative effort to apply good science. Dr. Tougas  
10 applauded the active participation of all involved.

11 The Working Group adopted the following objectives for the meeting: (i) to review  
12 overall goals; (ii) to discuss current status of activities; (iii) to discuss and comment on the  
13 technical documents prepared by the Working Group; and (iv) to agree on next steps.

14 **III. DISCUSSION**

15 **Genesis of the Project**

16 Dr. Tougas reviewed the genesis of the project, which is based on the 1998-1999 Draft  
17 CMC Guidances for metered dose inhalers, dry powder inhalers, and nasal drug products. He  
18 recapped the research hypotheses and the Work Plan developed by the Working Group. In  
19 summary, the Working Group intends to understand: What is the mass balance really  
20 measuring? What is it useful for? And (coupled with the answers to the first two questions),  
21 what should the limits be? To answer these questions, the Work Plan includes several different  
22 activities, which will culminate in a submission of the PQRI recommendation to the FDA.

23 **Cascade Impactor (CI) Variability Experiment - Statistical Considerations**

24 Prior to the meeting, the Working Group reviewed the draft paper on statistical design  
25 of a CI experiment (draft prepared by Ms. Strickland, version dated 12 September 2002) and  
26 shared comments on the draft (blinded compilation dated 23 September 2002).

27 At the meeting, Ms. Strickland presented slides reviewing the objectives of the  
28 experiment and a particular design that would meet these objectives. She in particular  
29 explained that

30  $\text{Total Variation} = \text{Measurement Variation} + \text{Product Variation}$

31  $\text{Measurement Variation} = \text{Impactor} + \text{Analyst} + \text{Day}$

32  $\text{Product Variation} = \text{Between Unit Variation} + \text{Within Unit Variation}$

33 These various components of the CI variability could be separated out in a specially-  
34 designed experiment. Ms. Strickland reviewed diagrams summarizing how specific  
35 combinations of impactors, analysts and days could accomplish this goal while providing  
36 sufficient power to answer the experiment's questions. She noted that she and Mr. Christopher  
37 needed input from the Working Group for the further development of the scheme (such as  
38 determination of the number and assignments of tested product units).

39 Ms. Strickland presented theoretical results comparing the expected ranges of variability  
40 of a dose content uniformity (DCU) measurement versus the CI Mass Balance measurement. In  
41 her simulations, the true product variability was selected at 4% for between-unit variability and  
42 4% for within-unit variability. The measurement error selected for these calculations was 0%,  
43 2% and 4%. Using these starting conditions, the theoretical spread of results varied from less  
44 than  $\pm 5\%$  around the target (100 % label claim) to more than  $\pm 10\%$  around the target,  
45 depending on the number of units tested and the number of actuations per unit. Even with the  
46 same measurement error, the ranges of theoretically expected results were different due to  
47 sampling differences.

48 Ms. Strickland explained that because the DCU and MB tests use different sampling  
49 plans (e.g., DCU - 10 units with 1 or 2 actuations per unit; MB - 1 unit with multiple actuations  
50 per unit), the variability of MB results is higher than of DCU results even if true variabilities of  
51 the product and of the method are exactly the same for both tests.

52 Dr. Lin confirmed that this should be expected. For example, the range of a hundred  
53 results will be different depending on whether they were measured as 100 units x 1 actuation,  
54 or 10 units x 10 actuations, or 1 unit x 100 actuations. For this reason, Dr. Lin stated, DCU data  
55 cannot be used to set criteria for Mass Balance. Several Working Group members agreed, and  
56 noted that this has been one of the concerns with the Draft CMC Guidances, in which the limits  
57 for Mass Balance are the same as the limits for mean DCU (both are recommended to be within  
58 85-115% label claim). Drs. Rogers and Poochikian replied that the MB limits were not derived  
59 from DCU and that the equality of the limits was coincidental.

60 Other participants commented on the specific numbers used in Ms. Strickland's  
61 simulations (0%, 2%, 4% for different components of variability), and noted that in practice,  
62 between-actuation variability is usually less than between-unit variability. They also stressed  
63 that the CI measurement error is usually higher than DCU measurement error because CI stages  
64 are often near the limit of quantitation and because as an instrument, cascade impactor was not  
65 designed to measure total dose, so its efficiency and reproducibility in measuring the dose is

66 poor. Ms. Strickland explained that her simulations did not intend to compare the sizes of  
67 different variability factors, but rather to show that even if all factors have the same variability,  
68 the final results will be different because of different sampling strategies.

69 Dr. Rogers maintained that Mass Balance is accurate enough to judge the dose from the  
70 canister, and can be used for additional verification of DCU. Dr. Poochikian stated that mass  
71 balance is not a surrogate measure for DCU, that the role of mass balance is to assist in the  
72 interpretation of the PSD results. Dr. Tougas agreed with the view that MB should be used as a  
73 run qualification, but he pointed out that the Draft Guidances suggest that MB is a product  
74 specification. He further explained why calling MB a product specification or a run  
75 qualification makes a big difference in practice. When MB falls outside the allowed limits, an  
76 investigation is conducted to find the cause. If no assignable cause can be found and MB is a  
77 product specification, the presumption is that the product is at fault, which leads to sever  
78 regulatory repercussions. By contrast, if no assignable cause is found and MB is a run  
79 qualification, then the presumption is that the problem is with the methodology, and retesting  
80 is allowed. In the "MB is a specification" scenario, retesting is not allowed unless an assignable  
81 cause is found. Industry participants explained that the nature of CI testing is such that many  
82 non-product factors can lead to a MB failure that is difficult to prove or assign.

83 Dr. Poochikian suggested that if flexibility for retesting is the issue, perhaps the MB test  
84 should explicitly incorporate a provision for retesting. Other participants agreed and suggested  
85 that a 2-tier test may resolve the issue, so that an unassigned MB failure in the 1<sup>st</sup> tier would not  
86 automatically lead to a regulatory OOS situation. Participants explained that according to  
87 internal SOPs, laboratories would investigate all MB failures regardless of whether it's a  
88 product specification or a run qualification, but in case of a specification, a "regulatory OOS" is  
89 triggered, which has more severe implications and less flexibility for investigating and  
90 correcting the true problem, because the assumption is always on the product being at fault.

91 Returning to the planned CI experiment, Dr. Poochikian reiterated that DCU and MB are  
92 not supposed to be interchangeable, and recommended that their respective variabilities should  
93 not be compared.

94 Mr. Christopher requested that this point be elaborated, as the statistical design of the  
95 experiment crucially depends on the specific question asked, and until today the comparison of  
96 DCU to MB was among the goals, so the design presented by Ms. Strickland reflected that.  
97 However, if there is no need to demonstrate experimentally that MB and DCU variabilities are  
98 not the same, then a different statistical design would be more appropriate.

99 The Working Group discussed these issues, and agreed that comparing DCU to MB is  
100 not necessary because MB is not a surrogate measure for DCU; however, there is an interest in  
101 quantifying the various components of the CI method itself. Mr. Christopher and Ms.  
102 Strickland agreed to revise the experimental statistical design accordingly, and to present it for  
103 discussion to the Working Group at a next teleconference.

104 Mr. Christopher and Ms. Strickland requested that the Working Group confirm the main  
105 goals of the experiment, so the design would be developed to meet the goals. For example, if  
106 measuring batch-to-batch variability is not among the goals, then all tested units for a given

107 product should come from a single batch. Similarly, if determining lab-to-lab variability is not  
108 among the goals, then each product should be tested in a single lab. The statisticians cautioned  
109 that the more goals the experiment is trying to achieve, the larger and more complex the  
110 experiment will have to be.

111 The Working Group discussed and agreed that the goals of the experiment are: to isolate  
112 (i) "impactor" variability, (ii) "day" variability, and (iii) "analyst" variability. The participants  
113 clarified that the term "impactor" here is used in a general sense, and includes auxiliary and  
114 other experimental equipment used. Similarly, the term "day variability" includes variability  
115 due to day/time conditions, including temperature and humidity. The term "analyst" includes  
116 all human factors. The Working Group also clarified that the analysts participating in the  
117 experiment should be trained in the method, and that recommendations contained in the GCIP  
118 paper should be followed.

119 Dr. Lin suggested that within-unit and between-unit variabilities are also important. Dr.  
120 Rogers concurred that product variability should be a factor of interest. Mr. Wyka added that  
121 through-container-life effects may need to be considered, because an MDI tested on the first day  
122 would be at the beginning, but on the last day at the end of container life, depending on how  
123 many actuations are needed for each test, how many tests are required and how many  
124 actuations the product has per unit. Because these considerations are product-specific, the  
125 participants started to discuss what products should be studied. Some suggested Albuterol  
126 MDI as a potential candidate, because it is relatively well understood and contains sufficiently  
127 many doses per unit. Dr. Rogers suggested that at least two products, which are farthest apart  
128 in chemical properties, be studied, and the low dose - high dose comparison be looked at. Dr.  
129 Doub suggested that potency be considered, because "ng/mL" drugs may behave differently  
130 than "mg/mL" ones. Dr. Rogers emphasized that selecting a range of products is important if  
131 the Working Group would like the conclusions to be generalizable. At the same time, all  
132 participants agreed that an attempt to cover the entire space of different variability factors in  
133 one experiment may introduce so many variables that the experiment would become  
134 impossible practically.

135 Dr. Mitchell noted that the experiment may also be able to show whether a failed MB is  
136 related to a failed/abnormal PSD or not. Such information would be helpful in determining  
137 whether MB has value as an indicator of run qualification.

138 Dr. Tougas concluded this discussion by saying that both industry and Agency would  
139 benefit if the method capability is measured and understood.

140 On the second day of the meeting, the Working Group confirmed that study of the  
141 following sources of variability within the CI MB measurement are of interest: variability  
142 attributable to impactor, day, and analyst. A range of products (four products) should be  
143 studied. The experiment will not intend to separate out the following variabilities: batch-to-  
144 batch, lab-to-lab, or HPLC-to-HPLC; and therefore a single batch, a single lab and a single  
145 HPLC system will be used for each tested product.

146 Cascade Impactor (CI) Variability Experiment - Practical Considerations

147 The participants reviewed the document prepared by Dr. Doub and Mr. Wyka, entitled  
148 "Thoughts on Steps for CI Runs" (dated 20 September 2002). The paper describes practical  
149 questions that should be considered for the CI experiment. Mr. Wyka and Dr. Doub noted that  
150 many specific steps in the operation of a cascade impactor are drug product- and method-  
151 dependent, and as such can only be answered when a specific product for the study is selected.

152 The participants discussed that the experiment may be conducted at an FDA laboratory  
153 (e.g., Dr. Doub's), but in this case the analysts would have to be trained in the particular method  
154 for the tested product(s). A possibility that pharmaceutical companies would perform the  
155 testing was reviewed. The Working Group agreed that a detailed statistical design, and the  
156 requirements on the number of products, impactors and days, need to be developed before a  
157 decision can be made about specific products and laboratory resources.

158 Draft Good Cascade Impactor Practices (GCIP) Paper

159 On the second day of the meeting, the participants carefully reviewed all comments on  
160 the draft GCIP paper (version 12.0, dated 28 August 2002). For each received comment, the  
161 Working Group determined whether it should be accepted or not, and whether it could be  
162 addressed through word-smithing by the drafting group after the meeting, or whether it  
163 required a substantive discussion by the full Working Group. In many instances, the changes  
164 were made in real time directly to the electronic draft of the paper, with all participants viewing  
165 on the screen the changes being made. For minor editorial changes, it was agreed that Dr.  
166 Mitchell and the drafting group would attend to those after the meeting and circulate to the rest  
167 of the Working Group for comment.

168 The following points related to the GCIP draft were discussed at the meeting in detail:

169 *Product vs. Method Variability – Importance of Sampling Plan*

170 Based on the discussion on the 1<sup>st</sup> day about different sources of variability, some  
171 Working Group members proposed inserting language about relative size of  
172 product variability compared to method variability. However, Ms. Strickland  
173 cautioned that the total variability of the measurement depends not only on the  
174 relative amounts from the different sources (e.g., from product and from  
175 method), but also on the sampling plan employed. She conducted simulations to  
176 illustrate her point. For example, with 2% between-unit, 2% within-unit, 2%  
177 measurement variability and 10 actuations per result, the anticipated range of  
178 MB results is well within the 85-115% limits, while for the 2% between-unit, 4%  
179 within-unit, 4% measurement variability and 2 actuations per result, the  
180 anticipated range of MB results is outside the 85-115% limits, even though the  
181 product variability in both cases accounts for about half of the overall variability.

182 Other simulations showed that, conversely, the range of MB results does not  
183 change regardless of whether the variability is split 50-50 between the product  
184 and method, or is 100% due to the product.

185 The sampling plan determines how the different variabilities are combined and  
186 therefore determines the resulting spread of results no less than the underlying  
187 true variabilities of individual factors.

188 The Working Group agreed not to include language about the product error  
189 being smaller or larger than the method error.

190 *Failure Analysis*

191 During the discussion of the recommended course of action in case of MB/APSD  
192 failure, Drs. Rogers and Poochikian questioned whether analyst error should be  
193 given much prominence. They felt that if the analysts are properly trained and  
194 use a check list to ensure that they follow the method correctly, the analyst error  
195 should not be a factor. Other participants noted that even with best training, and  
196 with checking off a check list, human errors are unavoidable, and unfortunately  
197 the CI method, which involves much manual manipulation, is susceptible to  
198 human errors.

199 The Working Group agreed to include language recommending use of check  
200 lists.

201 Draft Survey for Investigation Tree

202 The draft GCIP paper includes a draft *Investigation Tree*, which was developed based on  
203 experience of the Working Group members. In order to include the broader industry's  
204 perspective, the Work Plan proposed conducting an industry survey. The draft questionnaire  
205 for the survey was prepared by Dr. Mitchell and circulated to the Working Group for comments  
206 on 12 September 2002. Dr. Mitchell provided an overview of the draft at the meeting. The  
207 survey consists of 2 parts, one focusing on general description of the operation, and the other on  
208 the number and specific causes of mass balance and/or particles size distribution failures. The  
209 meeting participants suggested certain revisions to the draft and agreed to provide further  
210 detailed comments by email.

211 Drafts For Data Mining

212 The Working Group reiterated a strong interest in data mining in order to provide basis  
213 for recommendation on the MB limits. The participants discussed the draft letter requesting  
214 such data and outlining what types of data are eligible. The Working Group reviewed and  
215 discussed the comments on the draft letter, which were shared prior to the meeting.

216 Participants asked whether FDA would be able to submit blinded data in this data  
217 mining. Dr. Poochikian replied that this is a resource issue.

218 FDA participants reiterated that the data submitted in this survey should be collected  
219 using validated methods. The Working Group agreed that this point should be made clear in  
220 the request for data.

221 The Working Group confirmed that both release and stability data are acceptable.

222 The participants reviewed and commented on the template for data reporting, which in  
223 particular includes fields for description of the used method and storage conditions.

224 The Working Group agreed that the finalized template and request for data should be  
225 posted on the PQRI website.

#### 226 **Conclusion**

227 The drafting subteams that had prepared the drafts of the documents discussed at the  
228 meeting were directed to revise their respective drafts based on the discussion during the  
229 meeting.

230 The Working Group agreed to review and discuss timelines for all activities at the next  
231 teleconference.

232 In conclusion, Dr. Tougas noted that the Working Group had made much progress in a  
233 short period of time and thanked all participants for productive discussions.

#### 234 **IV. AGREED ACTIONS**

- 235 • The Working Group agreed that because Mass Balance (MB) is not a surrogate for  
236 Dose Content Uniformity (DCU), the CI experiment need not compare DCU and MB.  
237 Furthermore, it was agreed a study of the following sources of variability within the  
238 CI MB measurement would be of practical interest: variability attributable to  
239 impactor, day and analyst. The experiment will not intend to separate out the  
240 variabilities of batch-to-batch, lab-to-lab, or HPLC-to-HPLC, and therefore a single  
241 batch, a single lab and a single HPLC will be used for each tested product. Four  
242 different products should be studied, each using the method approved for that  
243 product. Trained analysts should be used and GCIP recommendations should be  
244 followed. An FDA laboratory may be asked to conduct the study, but it would be  
245 preferable that pharmaceutical companies donating products would also conduct the  
246 testing. The request to the companies would be issued after specific requirements  
247 for the study are clarified. Mr. Christopher and Ms. Strickland will revise the study  
248 design to conform to the experiment's goals and will provide the revised design to  
249 the Working Group for consideration.
- 250 • The practical aspects and specific steps for the CI experiment will be finalized after  
251 specific products for the study are identified.
- 252 • The GCIP paper should be finalized within 2-3 months. Dr. Mitchell and the  
253 drafting group will make changes based on the discussion at the meeting and will re-  
254 circulate the draft to the Working Group for approval. The draft approved by the  
255 Working Group will be provided to the DPTC prior to its October meeting if  
256 possible.
- 257 • Dr. Mitchell will revise the draft questionnaire for the MB/APSD failure causes and  
258 will re-circulate it to the Working Group for comment.

- 259           • Ms. Strickland and Mr. Christopher will revise and re-circulate for comment the  
260           draft template for data-mining.
- 261           • The timelines for all activities will be discussed in more detail on the next  
262           teleconference.

263 **V.    NEXT TELECONFERENCE / MEETING**

264           The next teleconference was scheduled for Friday, 4 October 2002, at 9:00 AM Eastern  
265 Time. (After the meeting, the teleconference was rescheduled for 21 October.)  
266  
267

*Finalized on 5 August 2003*