

1 MINUTES OF THE TELECONFERENCE
2 OF THE PQRI PSD MASS BALANCE WORKING GROUP ON
3 3 April 2003

4 **I. PARTICIPANTS**

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| Terry Tougas (Boehringer Ingelheim), Chair | Maggie He (Schering-Plough) |
| Dave Christopher (Schering-Plough) | Lana Lyapustina (IPAC-RS) |
| Paul Curry (USP Aerosols Expert Committee) | Jolyon Mitchell (Trudell Medical) |
| Bill Doub (FDA) | Helen Strickland (GlaxoSmithKline) |
| Ken Furnkranz (FDA) | Bruce Wyka (Schering-Plough) |

5 **II. OPENING**

6 Dr. Tougas opened the teleconference and welcomed the participants. Mr. Christopher
7 introduced Dr. He who had been helping him with the bulk of statistical calculations.

8 The objectives for the teleconference were: (i) to update on the MB / APSD failure
9 survey; (ii) to review and discuss the CI variability study design; (iii) to update on other
10 activities; and (iii) to agree on next steps.

11 The Working Group approved the draft minutes of the teleconference on 3 March 2003.

12 **III. DISCUSSION**

13 *MB / APSD Failure Cause Survey*

14 Dr. Lyapustina reported that to date, eight responses to the survey of mass balance /
15 particle size distribution failure causes had been received. The Working Group agreed to
16 encourage submission of additional responses by the industry.

17 *GCIP Update*

18 Dr. Mitchell reported that the Journal of Aerosol Medicine is completing reviews of
19 several remaining papers for the special issue on cascade impactors. That issue is expected to
20 be published later this summer or early fall.

21 *Data-Mining*

22 The Working Group reviewed the status of preparations for the retrospective data-
23 mining that would help evaluate the specification of 85-115% label claim for mass balance
24 during particle size distribution testing. Participants agreed that Drs. Rogers, Strickland,
25 Tougas and Wyka will review and if necessary revise the draft data reporting template and
26 draft solicitation letter for the data mining. The Working Group will discuss the drafts at the
27 next teleconference. Dr. Furnkranz agreed to inquire about submission of the Agency's particle
28 size data to this effort.

29 *Experimental Design for CI Variability Study*

30 Ms. Strickland reminded the Working Group that the main objective of the CI variability
31 study is to identify and quantify major sources of variability in a cascade impaction
32 measurement. She reviewed the paper circulated prior to the teleconference, in which the effect
33 of various sources of variability is examined via simulations. Ms. Strickland presented two
34 potential experimental designs and explained how well each design would be able to discern
35 major variability factors depending on the nature of the experimental uncertainty.

36 An *Incomplete Block Design with Latin Square* was first discussed by the Working Group in
37 September 2002. It is logistically simple, but inadequate if some impactor-by-analyst interaction
38 exists, because such interaction would be confounded in the Incomplete Block Design.

39 A *Split Plot Design with Graeco Latin Square*, on the other hand, would allow the Working
40 Group to isolate the impactor-by-analyst interaction if indeed such interaction can be
41 reasonably expected to exist.

42 Mr. Christopher further explained that it is not necessary to limit the experimental
43 design to one type or the other. It may be beneficial to start out with the simpler design,
44 analyze the results at a certain point, and then make a decision about further experimentation
45 based on the results. For example, if the preliminary analysis shows that half of the variation is
46 due to day / time effects, the other half due to product variation, and there is no discernable
47 analyst effect and no impactor effect, then the experiment could be completed within the
48 Incomplete Block Design. If, on the other hand, analyst or impactor are shown to have an effect,
49 it might be necessary to switch to the Split Plot Design in order to investigate the impactor-by-
50 analyst interaction more deeply.

51 Ms. Strickland presented simulation results that compared the capability of each of the
52 designs to arrive at a correct conclusion given a set of different scenarios for sources of
53 variability. The two designs differ in their power to detect analyst effects and impactor-by-
54 analyst interaction. Mr. Christopher explained that in order to develop the statistical design
55 further, the Working Group should discuss whether it is reasonable to expect an impactor-by-
56 analyst effect or not. The Working Group agreed that impactor-by-analyst interaction should be
57 taken into account.

58 The participants also discussed how the within-can and between-can variability would
59 be manifested. The statisticians indicated they would explore the design capabilities further.

60 Some participants asked whether the number of actuations would have an effect. The
61 Working Group re-iterated that the number of actuation would have to conform to the
62 approved method for the tested product, and would not be varied in this experiment.

63 The Working Group discussed the suggestion to test more than one product / method in
64 more than one laboratory. It was agreed that to make it practical, the experiment should start
65 with a single product tested in a single laboratory. Three impactors and three analysts would
66 be involved. The experiment would aim to factor out day-to-day, analyst-to-analyst and
67 impactor-to-impactor variabilities under best circumstances, *i.e.*, by minimizing differences such

68 as differences between impactors, to the extent possible. If the number of variables is increased
69 through the introduction of additional laboratories in the same experiment, the power and
70 practicality of the experiment will be reduced. The Working Group therefore agreed to proceed
71 in steps. The Working Group will review the results of the first experiment with one product in
72 one laboratory before undertaking the testing of more products or in more laboratories. The
73 design developed for one product / laboratory may be repeated for other products /
74 laboratories.

75 **IV. AGREED ACTIONS**

- 76 • The survey of mass balance / particle size distribution failure causes should
77 continue. The industry should be encouraged to participate in the survey.
- 78 • Ms. Strickland, Dr. Rogers, Dr. Tougas and Mr. Wyka will review draft templates for
79 the data mining. The Working Group will discuss the drafts at the next
80 teleconference.
- 81 • Dr. Furnkranz will inquire about the Agency's submission of particle size data to the
82 survey.
- 83 • Ms. Strickland and Mr. Christopher will continue development of the experimental
84 design, assuming that it is reasonable to expect some impactor-by-analyst
85 interaction, and that the experiment will start with a single product in a single
86 laboratory. Once developed, the same design may be applied to other products and
87 other laboratories. The statisticians will present further results and considerations at
88 the next teleconference.

89 **V. NEXT TELECONFERENCE / MEETING**

90 The next teleconference of the PQRI PSD Mass Balance Working Group was scheduled
91 via email for Wednesday, 14 May at 2:00 PM Eastern Time / 1:00 PM Central / 19:00 UK.
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Finalized on 4 June 2003