

1 MINUTES OF THE TELECONFERENCE
2 OF THE PQRI PSD MASS BALANCE WORKING GROUP ON
3 3 JULY 2002

4 **I. PARTICIPANTS**

5 Terry Tougas (Boehringer Ingelheim), Chair
6 Jeff Blumenstein (Pfizer)
7 Mary Devlin Capizzi (IPAC-RS)
8 David Christopher (Schering-Plough)
9 Paul Curry (Boehringer Ingelheim)
10 Bill Doub (FDA)
11 Lana Lyapustina (IPAC-RS)
12 Jolyon Mitchell (Trudell Medical)
13 Brian Rogers (FDA)
14 Helen Strickland (GlaxoSmithKline)

15 **II. OPENING**

16 Dr. Tougas opened the meeting, welcomed the participants, and introduced Dr. Paul
17 Curry, member of the USP Aerosols Expert Committee (AEC). Dr. Curry is involved in AEC's
18 efforts to revise USP Chapter <601>, including the section on PSD mass balance. He will be
19 replacing Dr. Zaidi on this Working Group

20 The participants agreed to the following objectives of the teleconference: (i) to update
21 on the progress of the draft Good Cascade Impactor Practices (GCIP); and (ii) to discuss
22 potential sources for data mining.

23 **III. DISCUSSION AND AGREED ACTIONS**

24 *Approval of Draft Minutes of Previous Meeting and Teleconference*

25 During the discussion of the draft minutes of the meeting on 13 May and teleconference
26 on 30 May, the following points were clarified:

27 (a) For the Next Generation Pharmaceutical Impactor (NGI), the effect of leaks on the
28 PSD measurement has been studied but the results have not been published, in part
29 because the study was conducted on a prototype and not on a commercial
30 instrument. Companies are individually evaluating vacuum tightness of the NGI.
31 The FDA St. Louis laboratory is also evaluating its own NGI unit. The European
32 Pharmaceutical Aerosol Group (EPAG) plans to undertake a general evaluation of
33 the NGI performance.

34 (b) Some product development issues (such as sample solvent, quantification limits,
35 collection surface coating agents, recovery techniques, and others) are closely linked
36 to method development, and they will be treated under "Method Development"
37 section of GCIP.

- 38 (c) When two flow meters are used, one is positioned upstream and the other
39 downstream of the impactor.
- 40 (d) The reference to the article by S. Stein on CI results variability should be added as a
41 footnote to the 13 May minutes.
- 42 (e) The email messages related to analyst-to-analyst variability circulated following the
43 30 May teleconference should be appended to the 30 May minutes, provided the
44 authors of the messages do not object.
- 45 (f) The objectives of the mass balance experiment will include both the estimation of the
46 uncertainty of the total dose when determined by CI and DCU tests, and analysis of
47 the main contributors to the CI variability when standard conditions and best
48 practices are used. A subgroup of chemists and statisticians is holding separate
49 discussions to develop an experimental design which will address both objectives. A
50 draft proposal will be presented for the Working Group's consideration when ready.

51 The Working Group approved the draft minutes of the 13 May meeting and 30 May
52 teleconference with the additions per (d) and (e) above.

53 *GCIP Update*

- 54 • In late June, Dr. Mitchell presented to EPAG the slides, previously reviewed by this
55 Working Group, which outline methodological factors to be considered in GCIP.
56 EPAG will provide formal comments on GCIP when issued.
- 57 • The PQRI Steering Committee (SC) agreed with the three-tiered structure of
58 approvals for presentations related to PQRI work (see the minutes of the 30 May
59 teleconference of this Group). A formal policy on PQRI presentations and
60 publications will be issued by the SC to all PQRI participants when available.
- 61 • A discussion paper prepared by Dr. Curry (see Appendix A) reflects his
62 understanding of the discussions on MB held by the USP AEC but is not intended to
63 represent the official USP AEC position. Certain aspects of the paper may be used by
64 Dr. Mitchell and Mr. Wyka in the GCIP draft.
- 65 • Dr. Rogers disagreed with the phrase "Mass balance provides a means to find only
66 sampling errors" in Dr. Curry's paper. He stated that the mass balance can also be
67 useful for detecting incorrect emitted dose; and expressed concerns with an
68 intermittent dose problem. In response to a comment that the DCU test is more
69 discriminating at detecting emitted dose problems than a CI test, Dr. Rogers replied
70 that this has not been shown. The Working Group agreed that the word "only"
71 should be deleted from the sentence quoted above.
- 72 • The GCIP will aim to separate analytical problem issues from the product issues.
- 73 • Dr. Mitchell, Mr. Wyka and Dr. Curry will plan to complete a draft GCIP by mid-
74 August. It was suggested that a formal review of the draft by the full Working
75 Group be scheduled for mid-September, perhaps via a one-day face-to-face meeting.

76 *Potential Sources for Data-Mining*

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- 78 • The purpose of the data-mining will be to assess products' compliance with the 85-115 % LC limits on the CI mass balance.
 - 79 • The correlation between PSD and DCU results will not be part of this data-mining (a
80 separate, prospectively designed experiment will assess the PSD/DCU correlation
81 and variance).
 - 82 • Dr. Tougas will review the ITFG/IPAC-RS PSD database, which served as a basis for
83 the 2000 Initial Assessment Report,¹ and will evaluate the amount of data that could
84 potentially be used by the Working Group.
 - 85 • Dr. Rogers will consult with Dr. Poochikian regarding the possibility of using FDA
86 personnel for retrieving, sorting, and blinding the data in FDA files.
 - 87 • If a new industry survey is initiated, deposition data on individual stages (as % LC)
88 will be sought. Collecting such data will not increase the survey time compared to
89 collecting only the mass balance figures, yet it will allow insights into possible
90 reasons for MB failure. For subsequent analysis, the MB data can be easily separated
91 from the stage deposition data. Dr. Tougas, Dr. Rogers and Ms. Strickland will draft
92 a survey template for the Working Group's consideration.

93 **IV. NEXT TELECONFERENCE/MEETINGS**

94 The next teleconference of the PQRI PSD Mass Balance Working Group is scheduled for
95 **Monday, 29 July at 10:00 AM (US EDT)/15:00 UK time.**

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Finalized on 29 July 2002

¹ Available at http://ipacrs.com/PDFs/Initial_Assess_of_Particle.PDF.

98 *The following document contains only the opinions of the author and should not be construed to represent the*
99 *findings, conclusions, or opinions of the PQRI Mass Balance Working Group in any manner.*

100 Mass Balance as a Suitability Test?

101 The Purpose of a Suitability Test

102 The purpose of a suitability test is to ensure apparatus/instrument used to obtain the
103 sample and/or determine the result is functioning properly at the time the sample was
104 generated and or analyzed.

105 What Can Mass Balance Control

106 Of interest is what kind of errors can mass balance control for. The list (though not complete)
107 provided below outlines several of the testing errors that can be detected by shifts in mass
108 balance.

109 Improper impactor set-up
110 Missing after filter
111 Leakage between stages
112 Incorrect solenoid timing for DPI testing
113 Excessive accumulation of deposits in stage nozzles
114 Wrong number of inhaler actuations
115 Inadequate sample recovery
116 Incorrect dilutions
117

118 Also of interest are errors that mass balance can not detect. Again, a list (though not complete) is
119 provided below that outlines several of the testing errors that can not be detected by shifts in
120 mass balance.

121 Missing collection surfaces
122 Incorrect stage order
123 Poor seal between the induction port and the CI
124 Improper alignment of the inhaler mouthpiece in the induction port
125 Inadequate coating of the collection surfaces
126 Incorrect flow rate through the impactor

127 **Points to Consider**

- 128 • Mass balance can meet an acceptance criteria and not ensure that the sample was properly
129 collected.
- 130 • Due to the fact that once the impactor is disassembled it no longer reflects the same impactor
131 used for samples, it is recommended that a criteria based on the data for the sample being
132 tested be used as an indicator of whether or not the impactor was functioning properly at the
133 time the sample was collected.
- 134 • Wall losses of less than 5% are acceptable.
- 135 • There is variability inherent in each of the stage measurements.
- 136 • PQRI is currently discussing limits on mass balance.

137 **Ideas**

- 138 • Mass balance provides a means to find only sampling errors. It does not ensure that the
139 sample was collected properly. As such, rather than consider mass balance a suitability test,
140 consider mass balance as a good analytical practice.
- 141 • Since products behave differently and are tested differently, the acceptance criteria should be
142 product and method specific. The fewer number of actuations used to determine particle size
143 the more variable mass balance will be.

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