

1 MINUTES OF THE TELECONFERENCE
2 OF THE PQRI PSD MASS BALANCE WORKING GROUP ON
3 23 February 2004

4 **I. PARTICIPANTS**

Terry Tougas (Boehringer Ingelheim), Chair	Ken Furnkranz (FDA)
Dave Christopher (Schering-Plough)	Michael Golden (GlaxoSmithKline)
Jon Clark (FDA)	Lana Lyapustina (IPAC-RS)
Bill Doub (FDA)	Jolyon Mitchell (Trudell Medical)

5 **II. OPENING**

6 Dr. Tougas welcomed the participants and especially Dr. Clark, member of the Steering
7 Committee and of its subgroup on data mining. The objectives of the teleconference were (i) to
8 review completed activities, (ii) to discuss the status of remaining tasks, and (iii) to agree on
9 next steps.

10 **III. DISCUSSION**

11 Dr. Tougas reminded the participants that the paper on Good Cascade Impactor
12 Practices (GCIP)¹ and a Letter to the Editor² summarizing findings of the subsequent survey
13 have been published. These are major accomplishments, representing the Working Group's
14 best thinking. The two major items that still need to be addressed are:

15 (a) data mining of existing "raw" data from Andersen Cascade Impactor (ACI)
16 measurements

17 → in order to assess whether products in general can meet the 85-115%
18 label claim limits on ACI mass balance, as proposed in the FDA
19 guidances for orally inhaled and nasal drug products; and

20 (b) a prospective experiment to measure variability of the mass balance due to
21 the ACI method itself, and compare it to the variability due to other factors
22 (e.g., product quality)

23 → in order to assess whether ACI mass balance is an appropriate metric
24 for a product specification.

25 The template for data mining and the detailed statistical design of the experiment were
26 developed by the group last year, and calls for data and volunteer labs have been issued
27 through PQRI website and at meetings. Despite these efforts, no data has been received and no

¹ D. Christopher, P. Curry, B. Doub, K. Furnkranz, M. Lavery, K. Lin, S. Lyapustina, J. Mitchell, B. Rogers, H. Strickland, T. Tougas, Y. Tsong, B. Wyka, "Considerations for the Development and Practice of Cascade Impaction Testing, Including a Mass Balance Failure Investigation Tree," *J Aerosol Med.* **16** (3), 235-247 (2003).

² J. P. Mitchell, "Regarding the Development and Practice of Cascade Impaction Testing, Including a Mass Balance Failure Investigation," *J Aerosol Med.* **16** (4), 433 (2003).

28 laboratories/products have been identified for these two tasks. Dr. Tougas explained that one
29 of the main deterrents appears to be the uncertainty of industry about potential use of its data,
30 and uncertainty of the Agency about providing information from its own files for PQRI
31 research. (Note that in either case, the data would be blinded with respect to its source).

32 The participants reviewed the discussion of these issues by the DPTC and SC, as follows:

- 33 • During the recent DPTC meeting, Dr. Uppoor stated that the Agency would not be
34 able to provide any data to PQRI. Dr. Clark during the teleconference clarified that
35 this might be possible in some circumstances, and has been done in the past, but it
36 would require additional resources from the Agency to clear all legal issues, as well
37 to mine, organize and blind the data; therefore in the short term should not be
38 considered as a likely possibility.
- 39 • The Steering Committee (SC) recognized the issue of data as very important and
40 central to all future PQRI data-based research. A subgroup has been formed,
41 comprising Dr. Clark, Dr. Blumenstein and Dr. Massa, to map out all issues and
42 identify possible solutions. The Mass Balance Working Group was selected as a test
43 case.
- 44 • The SC subgroup is addressing the three major types of implications of providing
45 data to PQRI, especially providing data on marketed products, i.e., legal, regulatory
46 and compliance implications. The solution may well take the form of case-by-case
47 memoranda of understanding between companies and the Agency.
- 48 • Existing draft guidances (e.g., stability, blend uniformity, PAT), contain paragraphs
49 that deal with the issue of data collected for research purposes, and make it clear that
50 such data shall not be the focus of typical inspections. Nevertheless, any collected
51 data is ultimately discoverable.
- 52 • The challenge is to create a mechanism for appropriate research and data sharing to
53 support or justify change in existing policy and quality requirements. Once the
54 mechanism is drafted, the subgroup will work with the Agency's legal counsel and
55 will also solicit comments from companies to assure that the conditions and
56 stipulations of the proposed mechanism meet the main needs of all parties.

57 The Working Group also brainstormed ideas for the CI experiment, which would be on
58 marketed products, as requested by FDA participants. For example, if a contract research
59 laboratory, instead of the company itself, were testing a blinded product according to the
60 approved method, the chain of evidence could be broken and the company's potential liability
61 limited. However, testing in a different lab rather than in a company lab could in itself increase
62 the variability of the mass balance results. A cascade impactor was not designed to provide an
63 accurate measurement of the emitted dose. As explained in the GCIP paper, mass balance
64 results depend on many factors, many unrelated to the product itself, and subtle, often
65 imperceptible differences in the set-up, operator technique, etc. could affect the measured mass
66 balance determination. In fact, the point of the experiment was to document this fickleness,
67 well known to the practitioners of the method, and to argue that because of this limitation, the
68 CI test should only be used for particle sizing, not mass balance (emitted dose) confirmation.
69 Dr. Clark asked whether the GCIP paper has addressed this issue sufficiently enough, and

70 perhaps the experiment is not now necessary. Mr. Furnkranz and Dr. Doub agreed to consult
71 with the FDA colleagues on the PQRI PSD Working Groups to clarify the current position of the
72 members. Certain members of the Working Group re-iterated that measuring mass balance as
73 part of the CI test is useful, but not with the limits proposed (85-115%), and not for the purpose
74 proposed (product specification).

75 Additional suggestions discussed during the brainstorming included the following: (i)
76 testing batches near expiry; (ii) conducting the CI portion of the test in the company itself, but
77 then shipping the samples to a contract lab for HPLC analysis and eventual direct transmission
78 of the data from that lab to PQRI; (iii) conducting the experiment on products in late NDA
79 stages, before approval.

80 Working Group members were encouraged to think of other ways to conduct the
81 experiment. In addition, industry representatives agreed to consult internally within their
82 organizations to assess the feasibility of a CI experiment on near-expiry batches, of shipping
83 samples to an outside lab for analysis, and of using late-NDA products. In addition, company
84 representatives were encouraged to find out and report to the Working Group at the next
85 teleconference:

- 86 – specific concerns with submitting mined data to PQRI;
- 87 – specific concerns with conducting the CI experiment on company's product; and
- 88 – potential ways to resolve such concerns, from the company perspective ("wants,"
89 "needs" and "must-haves").

90 These issues will be discussed at a future teleconference of the Working Group.
91 Sensitive issues may be communicated to Dr. Lyapustina by phone or email, who would blind,
92 compile and present the feedback to the Working Group for discussion.

93 **IV. AGREED**

- 94 • Mr. Furnkranz and Dr. Doub will consult internally to clarify whether the CI
95 experiment and data mining are still needed or whether the concerns have already
96 been addressed through the previous discussions and the GCIP paper. The
97 objectives of any additional data collection will have to be re-stated.
- 98 • Company representatives on the Working Group will clarify internally the concerns
99 with data mining and CI experiment, as well as the feasibility of potential ways to
100 resolve such concerns, for discussion on the next teleconference.
- 101 • Relevant materials about purpose and requirements of the Working Group's data
102 mining and CI experiment will be forwarded to Dr. Clark as background
103 information for the Steering Committee's subgroup on the data issue.
- 104 • The Mass Balance Working Group and the SC data subgroup will stay in active
105 communication. Joint meeting(s) and/or teleconference(s) may be beneficial.

106 **V. NEXT TELECONFERENCE / MEETING**

107 The next teleconference was scheduled by email and held on 19 March 2004.

108 *Finalized on 19 March 2004*

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