

1 **Minutes of the Teleconference**
2 **of the PQRI PSD Mass Balance Working Group**
3 **on 17 August 2005**

4 **I. PARTICIPANTS**

Terry Tougas (BI) <i>Co-Chair</i>	Ken Furnkranz (FDA)
Bruce Wyka (Schering-Plough) <i>Co-Chair</i>	Lana Lyapustina (IPAC-RS)
Dave Christopher (Schering-Plough)	Jolyon Mitchell (Trudell Medical)
	Helen Strickland (GSK)

5 **II. OPENING**

6 Mr. Wyka opened the teleconference and welcomed the participants. Dr. Lyapustina read the
7 antitrust admonition. The participants reviewed and approved the proposed objective of the
8 teleconference, which was to comment on the draft slides for presentation to the DPTC.

9 **III. DISCUSSION**

10 Dr. Tougas noted that the DPTC meeting is being rescheduled from mid-September to early
11 October. He also stated that Helen Winkle has assured him that the FDA will be ready to
12 present their viewpoint at the October DPTC meeting.

13 Mr. Christopher drew the participants' attention to an upcoming AAPS/ISPE workshop in
14 early October, where among other thing, specification setting and new regulatory approaches
15 will be discussed (<http://www.aapspharmaceutica.com/meetings/files/51/CMCPrelim.pdf>).

16 Mr. Wyka confirmed his willingness and availability to present the slides at the DPTC meeting.

17 The participants discussed draft slides dated 17 August and made the following suggestions:

- 18 • Historical and background slides should be distilled to 1-2 slides while the more
19 detailed account could be provided as a separate appendix.
- 20 • The overlaid pictures should be presented on separate slides, for cleaner print-outs.
- 21 • Pictures of HPLC should be added, highlighting the broader range of concentrations for
22 CI testing compared to ED testing, and the longer overall runs (because there are many
23 more sub-samples with interspersed standards to analyze).
- 24 • Tables illustrating real products' performance should be added for reference.
- 25 • An explanation should be added to address the question of 'multiple' actuations in a CI
26 test *vs* 'single' actuation in an ED test. Discussing this topic, the Working Group noted
27 that:

28 - Recent FDA guidance and practice actually require using a minimally
29 possible number of actuations even in a CI test.

30 - The physical averaging of actuations in a CI test allows increasing the
31 deposition amount above the limit of detection but it does not remove the
32 variability associated with recovering drug from multiple stages and the
33 execution of multiple steps, and the consequent accumulation of errors. The
34 physical uncertainty from multiple measurements is compounded in the final
35 MB result even when multiple actuations are allowed for CI testing.

36 • The comparison of FDA's MB and ED specifications should be expanded to note that in
37 a DDU test, 10 actuations are taken from different inhalers, so that their mean is closer to
38 the true mean dose. In a CI test according to the FDA April 2005 proposal, if multiple
39 actuations are allowed, they will all be taken from a single inhaler, so that if that inhaler
40 happens to be slightly off-target, the probability of random failure is increased.

41 • The statistical slides should make it clear that even though the MB test may fail more
42 frequently than the DDU test, it will not fail more correctly. Information about Type II
43 error with both tests should be added, as well as plots and verbal explanations about the
44 discriminating ability of respective tests.

45 • For the purposes of this presentation, the November 2004 proposal will be used in the
46 version "3 tiers, $\pm 15\%$ LC limits" and the April 2005 proposal as "single re-test with
47 $\pm 15\%$ LC limits".

48 The participants agreed to provide further comments on the draft slides by email, to have
49 another telephone discussion of the revised slides in September, and to hold a 'run-through'
50 rehearsal before the DPTC meeting.

51 **IV. AGREEMENTS**

52 • Working Group members will provide further comments on the draft slides by email.

53 • Ms. Strickland will provide the OC curves and other information as discussed on the
54 teleconference within the next two weeks.

55 **V. NEXT TELECONFERENCE/MEETING**

56 The next teleconference was scheduled for Thursday, 22 September, at 11:00 AM ET.

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Finalized on 23 September 2005