

1 MINUTES OF THE TELECONFERENCE  
2 OF THE PQRI PSD MASS BALANCE WORKING GROUP ON  
3 28 JUNE 2004

4 **I. PARTICIPANTS**

Terry Tougas (Boehringer Ingelheim), Chair	Zoë Heaton (Aventis)
Dave Christopher (Schering-Plough)	Rick Lostritto (FDA)
Paul Curry (USP)	Lana Lyapustina (IPAC-RS)
Craig Dunbar (Alkermes)	Jolyon Mitchell (Trudell Medical)
Ken Furnkranz (FDA)	Brian Rogers (FDA)
	Helen Strickland (GlaxoSmithKline)

5 **II. OPENING**

6 Dr. Tougas welcomed the participants and opened the meeting. Dr. Lyapustina  
7 reminded the participants that their discussion is subject to the anti-trust guidelines applicable  
8 in the United States and European Union, and that nothing discussed at this meeting may be  
9 intended to restrict trade or individual decision-making of any company; she further instructed  
10 the participants to avoid discussion of competitively sensitive subjects, such as confidential  
11 marketing, sales, and pricing information.

12 The main objectives of the teleconference was to discuss (i) draft recommendations for  
13 mass balance, including the flowchart (draft dated 28 June 2004) and (ii) the statistical paper  
14 prepared by Ms. Strickland, which compared the impact of MB vs DCU limits for the same  
15 canister.

16 **III. DISCUSSION**

17 Dr. Tougas invited the Working Group to discuss draft interim recommendations for  
18 mass balance requirements. The FDA participants stressed that they would have to discuss  
19 internally any draft recommendations before they are finalized by PQRI, and that supporting  
20 data is critical to validating a change in guidances.

21 The participants discussed the terms “product specification” vs “run qualification” and  
22 the fact that naming MB one or the other has different consequences if MB “fails”. Industry  
23 participants explained that naming MB a product specification means that a failing MB impacts  
24 on disposition of the batch immediately, whereas naming it something else may or may not lead  
25 to decisions about the batch, depending on additional evidence. The naming is particularly  
26 important for compliance officers. The Working Group also discussed that MB is not strictly a  
27 system suitability test because the tested article itself rather than an independent standard is  
28 involved in the measurement.

29 Dr. Lostritto agreed that a failing MB should not automatically create a batch failure. If  
30 MB is not met, retesting should be allowed under certain conditions. However, after a certain  
31 number of retests, batch failure should be possible, and therefore Dr. Lostritto believed that MB  
32 may need to be part of product specifications. The Working Group agreed to revisit the  
33 question of terminology later, after the actions for the failed MB are defined.

34 Dr. Lostritto suggested that a decision tree for a failed MB be revised so that (i)  
35 consequences for failing MB by a small amount and infrequently be different than if failing  
36 significantly and frequently, and (ii) the number of allowed retests be limited to prevent testing  
37 into compliance. This scheme may require multiple-tiered testing, with different windows for  
38 MB “action limits” at different tiers. Participants added that the decision tree should also  
39 account for the possibility that no assignable cause could be found. With all these revisions to  
40 the flowchart, Dr. Lostritto preferred that the designation “specification” be kept, and that the  
41 flowchart be incorporated in the specification description.

42 The Working Group discussed how to treat situations where MB fails repeatedly but the  
43 emitted dose test passes. Some suggested that this situation could indicate that the MB limits  
44 were chosen incorrectly. Ms. Strickland noted that this scenario could be due to the limits for  
45 MB and DCU not being synchronized, and she briefly reviewed her paper illustrating this effect  
46 (draft dated 28 June 2004). Ms. Strickland’s calculations show that given the same variability,  
47 the way one samples out of population affects the distribution of results. One practical  
48 consideration is that MB limits for a single canister should be broader than emitted dose limits,  
49 since the CI method is more variable because more manual operations are involved, and errors  
50 from the more numerous steps are accumulating to a higher overall variability than that  
51 observed with emitted dose test, all other factors being equal.

52 Dr. Lostritto inquired about group’s plans to investigate different contributions to the  
53 overall variability. Dr. Curry explained that the Working Group had designed an experiment to  
54 address this, but no company volunteered to test real products, mainly because of (i)  
55 uncertainty over potential regulatory actions with respect to the observed results; (ii)  
56 intellectual property concerns; and (iii) time and resource commitment. Dr. Lostritto mentioned  
57 that FDA had not seen submissions where MB would be a problem and requested a copy of the  
58 technical report submitted by the industry to FDA earlier.<sup>1</sup> Dr. Lostritto also offered to clarify  
59 internally the progress of creating some safe harbor mechanisms to facilitate data sharing.

#### 60 **IV. AGREED**

- 61 • The terminology for mass balance will be discussed after the actions following a  
62 failed MB are defined.
- 63 • Dr. Lostritto will revise the flowchart and will provide it for comment to the  
64 Working Group prior to the next teleconference.
- 65 • The Working Group will continue to exchange ideas on the draft recommendations  
66 via email.

#### 67 **V. NEXT TELECONFERENCE / MEETING**

68 The next teleconference was provisionally scheduled for 12 July but was cancelled due  
69 to insufficient input on the draft recommendations.

70 The next meeting of the Working Group was scheduled to be held in Rockville, MD, on  
71 20 July 2004.

72 *Finalized on 23 August 2004*

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<sup>1</sup> [http://www.fda.gov/ohrms/dockets/ac/00/techrepro/3609\\_rpt2.pdf](http://www.fda.gov/ohrms/dockets/ac/00/techrepro/3609_rpt2.pdf).