

1 MINUTES OF THE TELECONFERENCE  
2 OF THE PQRI PSD MASS BALANCE WORKING GROUP ON  
3 19 MARCH 2004

4 **I. PARTICIPANTS**

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

5 **II. OPENING**

6 Dr. Tougas welcomed the participants. The objectives of the teleconference were (i) to  
7 review FDA position regarding the need for additional data gathering; and (ii) to agree on next  
8 steps.

9 The participants reviewed the draft minutes of the teleconference on 23 February and  
10 approved them with several editorial changes.

11 **III. DISCUSSION**

12 In continuation of the discussion on the previous teleconference, Dr. Tougas reminded  
13 the participants that the Working Group needs to review the purpose of the planned data  
14 mining and CI variability experiment. Both of these activities are being held up because of the  
15 difficulties with gathering data on commercial products. Recognizing that the issue of data  
16 gathering is central to all future PQRI research, the Steering Committee had established a  
17 Subgroup to address this issue in collaboration with the Mass Balance Working Group as a test  
18 case. On the previous teleconference, Dr. Clark of that Subgroup suggested that the motivation  
19 for data gathering be re-considered, in light of the notorious variability of the CI method and  
20 the publications on this topic prepared by the Working Group. On that teleconference, Mr.  
21 Furnkranz and Dr. Doub agreed to consult with the other FDA members of the Mass Balance  
22 Working Group to clarify the current FDA thinking.

23 Mr. Furnkranz reported that since the February teleconference, he and Dr. Doub had  
24 contacted a number of FDA staff involved in this Working Group and in the review of  
25 pulmonary products, such as Dr. Poochikian, Dr. Rogers, Dr. Adams, Dr. Singh, Dr. Bertha. No  
26 consensus opinion emerged, however. Mr. Furnkranz noted that the Working Group's Work  
27 Plan is based on the industry's objection to the use of the mass balance metric as a product  
28 specification, and as such, to the limits of 85-115% LC as too stringent. Mr. Furnkranz further  
29 noted that despite numerous discussions in the last two years, the Working Group has not  
30 come to any conclusion regarding proper use of the mass balance measurement, namely  
31 whether it should be used as a product specification or a run qualification. He suggested that if  
32 the Working Group agrees on how mass balance should be used, the resolution of the issue of

33 limits and data gathering could become more straightforward. Dr. Lostritto requested that Dr.  
34 Poochikian, as the main author of the draft CMC Guidances for OINDP, explain his current  
35 position on this issue.

36 Dr. Poochikian indicated that the Guidances were written intentionally in the way they  
37 are written, recommending that the mass balance be between certain limits. He asked the  
38 Working Group to forget about naming it “specification” or “run qualification” and comment  
39 whether the mass balance is a valid measurement by itself. Several Working Group members  
40 replied that the answer depends on the intended use, and that the genesis of this Working  
41 Group is precisely in the use of mass balance as a specification, so the question of the naming  
42 cannot be dismissed.

43 Dr. Tougas further clarified that the answer to Dr. Poochikian’s question depends on the  
44 sources and magnitude of variability of the method, and the utility of the metric cannot be  
45 separated from a specific intended use. How valid the MB metric is depends on how accurately  
46 and how precisely it can be measured, and what it is being used for. Dr. Poochikian maintained  
47 that the MB concept is useful because it sensitized the community to the issues of variability; as  
48 a result, there has been a noticeable reduction in variability of data submitted to the Agency in  
49 recent years. Dr. Poochikian said that “how to apply MB is a different issue” but the  
50 measurement itself is an important attribute.

51 Mr. Furnkranz pointed out that several other FDA participants he had contacted felt that  
52 the MB measurement is needed to validate a cascade impactor run, so that if the MB is outside  
53 certain limits, the particle size distribution data from that run would be invalid, and the  
54 product’s dose uniformity results should be checked.

55 Dr. Rogers stated that the utility of MB as a run qualification is useful, but without data,  
56 the position in the Guidances will not be changed, and mass balance will be used as a drug  
57 product specification. Several members asked how this product specification will be  
58 implemented in conjunction with the dose uniformity specification. For example, if MB fails but  
59 the dose uniformity test passes, should the batch be rejected or accepted? The following logical  
60 inconsistency was also pointed out: a mass balance outside the limits means that the CI data  
61 from that run is not valid to assess PSD, and yet it is viewed by Dr. Rogers as valid to reject the  
62 batch? During and especially after the teleconference, Dr. Rogers provided clarifications,  
63 summarized in the Addendum below.

64 The Working Group requested that Dr. Rogers explain what should be done if a failing  
65 MB result is observed. For example, if the CI test is repeated on the same unit and MB passes,  
66 could the first observation be taken as a comment on the test and not on the product? Dr.  
67 Rogers replied that this would be a review decision by the Agency’s reviewers.

68 Dr. Lostritto suggested that the issue of accuracy, precision and variability be addressed  
69 with data. Several Working Group members supported this proposal. The Working Group  
70 agreed that data gathering will be necessary. Dr. Rogers emphasized that the data has to be  
71 across the board, representing majority of the products, of different product types and  
72 strengths, in order to allow generalizations and provide sufficient support for any derived PQRI  
73 recommendations.

74 A subgroup was formed to identify specific barriers to data gathering and potential  
75 mechanisms to overcome them. A standard letter to the companies could be developed, with a  
76 request that QA, legal and other pertinent departments in companies be consulted. It was  
77 agreed that the subgroup would discuss this in detail on a separate teleconference.

78 **IV. AGREED**

- 79 • The Working Group should proceed with the data gathering as envisioned in the  
80 Work Plan.
- 81 • A subgroup comprised of Terry Tougas, David Christopher, Paul Curry, Craig  
82 Dunbar, Helen Strickland and Bruce Wyka will explore in a separate teleconference  
83 potential ways to identify and address concerns with data gathering.

84 **V. NEXT TELECONFERENCE / MEETING**

85 The next teleconference is scheduled for 1 June at 10:00 AM ET.  
86

87 **ADDENDUM**

88 According to Dr. Rogers, the following is a possible scenario that may be considered if a  
89 failing MB is observed. Either the CI test could be repeated, or an emitted-dose test could be  
90 performed on the same unit, both should be accomplished within the label claim number of  
91 actuations. If the second test (PSD MB or emitted dose) fails, then the original MB failure, in  
92 conjunction with the failure of the checking result, should be considered a product failure. If the  
93 check analysis passes, then a new PSD determination should be accomplished (if the test was  
94 emitted dose) on a new canister. If the check testing was performed as a PSD determination,  
95 then the check result (along with the CI stage data) should replace the original determination  
96 results since the original PSD determination was judged to be disqualified by the original OOS  
97 MB result and not judged as a product failure owing to the acceptable results obtained in the  
98 check test. According to Dr. Rogers, the dose uniformity results are not comparable to the MB  
99 result because the DDU test is comprised of one or two actuations from numerous units (10 - 30)  
100 and may also be assessed at various points throughout the container life, whereas the MB result  
101 is composed of one result combining multiple actuations from a single unit.

102 *Finalized on 1 June 2004*