

1 **MINUTES OF THE TELECONFERENCE**  
2 **OF THE PQRI PSD MASS BALANCE WORKING GROUP ON**  
3 **13 OCTOBER 2004**

4 **I. PARTICIPANTS**

Terry Tougas (Boehringer Ingelheim), Co-Chair	Ken Furnkranz (FDA)
Bruce Wyka (Schering-Plough), Co-Chair	Zoë Heaton (Aventis)
Dave Christopher (Schering-Plough)	Rick Lostritto (FDA)
Paul Curry (USP)	Lana Lyapustina (IPAC-RS)
Bill Doub (FDA)	Brian Rogers (FDA)
	Helen Strickland (GlaxoSmithKline)

5 **II. OPENING**

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

12 The objectives of the teleconference were: (i) to review OC curves requested at the previous  
13 teleconference, (ii) to discuss draft recommendations for the treatment of mass balance, and (iii)  
14 to agree on next steps.

15 **III. DISCUSSION**

16 Dr. Tougas explained the operating characteristic (OC) curves provided to the participants  
17 before the teleconference. The OC curves represent the probability of various versions of the  
18 MB specification test to accept a batch of a given mean and standard deviation (SD). Dr. Tougas  
19 had provided plots demonstrating performance of several versions of the MB test, using 2 and 3  
20 cycles of retesting and  $\pm 15\%$  and  $\pm 20\%$  limits. The curves were displayed as functions of the  
21 mean (with the standard deviation fixed at 5.0, 7.5, 10.0 and 12.5%) and as functions of the  
22 standard deviations (with the mean fixed at 0, 2 and 5% off the 100%).

23 The results showed that the performance of the test with 3 cycles and  $\pm 15\%$  limits is very similar  
24 to the performance of the test with 2 cycles and  $\pm 20\%$  limits.

25 Dr. Rogers strongly objected to the standard deviations used in these simulations, since they  
26 were derived from a dataset which has not been shown to be adequate and representative of  
27 US-approved drugs, as well as from an unacceptable data set including data from European  
28 drug products and investigational drugs, and to the use of statistical calculations using results  
29 calculated from this dataset when analyzing and choosing appropriate specifications.

30 Dr. Tougas noted that statistical analyses such as these are standard scientific practice. Several  
31 participants also commented that standard deviations used here are not unusual for CI mass

32 balances observed with OINDP. Dr. Tougas requested that the Agency review its files of data  
33 submitted by the industry, and state the typical ranges for MB standard deviations observed in  
34 OINDP. Dr. Rogers indicated that this is not possible at this time, as has been previously  
35 discussed. He stated that it must be clear that the lack of data to support proposals by this  
36 working group will not justify using a dataset that contains data unacceptable to FDA.

37 Dr. Tougas further stressed that the OC curves do not represent quality of products but rather  
38 represent the performance and capability of the test, from the statistical perspective. Dr. Rogers  
39 disagreed that the dataset used is acceptable for making assignments of typical SDs for the  
40 purpose of establishing specifications.

41 The participants discussed advantages and disadvantages of 3 cycles with  $\pm 15\%$  limits versus 2  
42 cycles with  $\pm 20\%$  limits. The probability to pass or fail a given batch is almost identical with  
43 these cases, but the former involves more retesting. Dr. Lostritto indicated that the Agency may  
44 have difficulty accepting a 2-cycle retest utilizing the  $\pm 20\%$  limit. On the other hand, he agreed  
45 that a 3-cycle retest of the MB/PSD determination with the  $\pm 15\%$  limit may appear as "testing  
46 into compliance", and the Agency probably would not be in favor of that option either. Dr.  
47 Lostritto proposed that the Agency's statisticians review the OC curves, and discuss these issues  
48 internally further.

49 Dr. Lostritto pointed out that even at 12.5% SD, the OC curves for a 100% mean appeared to  
50 show insignificant difference between the three curves. He requested that the data be submitted  
51 in tabular format so that the actual values at the SDs of interest could be evaluated. Dr. Tougas  
52 agreed that this would be done since the data were already calculated and available.

53 Dr. Doub stated that from his recollection they, in performing analyses in the St. Louis FDA  
54 laboratory, would be quite nervous if the SD for mass balance determinations were approaching  
55 8-10%, thus we could assume that these levels were uncommon.

56 Dr. Tougas requested that his calculations be first double-checked by the Working Group's  
57 statisticians.

#### 58 **IV. AGREED**

- 59 • The Working Group's statisticians will verify accuracy of the calculated OC curves,  
60 after which the curves will be discussed internally at FDA, in order to continue  
61 selection of the most appropriate MB specifications for OINDP.
- 62 • A meeting of the Working Group will be planned to coincide with the AAPS annual  
63 meeting.

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

65 The next teleconference will be scheduled by email.  
66

67 *Finalized on 9 December 2004*