

1 MINUTES OF THE TELECONFERENCE
2 OF THE PQRI PSD PROFILE COMPARISONS WORKING GROUP ON
3 19 December 2003

4 **I. PARTICIPANTS**

Dave Christopher (Schering-Plough), Chair	Douglas Lee (Pfizer)
Wally Adams (FDA)	Lana Lyapustina (IPAC-RS)
Craig Dunbar (Alkermes)	Bruce Wyka (Schering-Plough)
Walter Hauck (Thomas Jefferson Univ.)	Gur Singh (FDA)
	Yi Tsong (FDA)

5 **II. OPENING**

6 Mr. Christopher welcomed the participants. The Working Group welcomed its new
7 member, Dr. Dunbar. The following objectives were adopted for the teleconference: (i) to
8 discuss status and plans of the Working Group; (ii) to comment on the draft RDD paper; and
9 (iii) to agree on next steps. The participants approved the revised draft minutes of the 5 August
10 meeting.

11 **III. DISCUSSION**

12 Mr. Christopher reminded the participants that through the previous systematic
13 investigation of the chi-square method, it was found that the test decisions are mainly
14 determined by stages with largest deposition; and the Working Group started to discuss
15 conceptually the potential ways to alleviate this drawback and ensure equal discriminating
16 ability across stages. One of the ideas proposed at the last meeting involved separating the
17 entire profile into two categories, "inside" and "outside" the impactor. This division was
18 contemplated for several reasons, the main being: (i) deposited amounts are generally much
19 larger outside the impactor (*e.g.*, stem valve, actuator, pre-separator, throat or induction port)
20 than on the inside stages; (ii) particle sizes are relatively well determined inside the impactor
21 but not outside; and (iii) drug deposited outside and inside the impactor would approximately
22 correlate with oropharyngeal and lung deposition, thus representing different clinical aspects,
23 *i.e.*, safety and efficacy, respectively.

24 Dr. Hauck was invited to elaborate on his comments regarding the 2-part approach
25 emailed on 17 September. Dr. Hauck replied that according to some industry feedback he
26 received recently, the authors of the 2003 draft Guidance should be congratulated as this
27 version (<http://www.fda.gov/cder/guidance/5383DFT.pdf>) is an improvement over the 1999
28 draft; in particular because the number of required tests is reduced from around 30 to around
29 10. In light of that, Dr. Hauck had no objection to the 2-part approach because (i) the difference
30 between 10 and 11 tests is insignificant; (ii) the "additional" test would not require additional
31 experimental work but only separate treatment of the numbers measured as part of the
32 impactor testing anyway; and (iii) the separation of the profile into the proposed two categories
33 seems to be reasonable from both the statistical and biological perspectives.

34 Dr. Lee concurred with Dr. Hauck that the 2-part approach would not add burden from
35 the operational standpoint. He added that the main benefit of separating the profile in these
36 two parts is the ability to apply different statistical procedures to each. This way, the procedure
37 could be optimized with regard to the goals of comparison and the properties of deposition in
38 each region. When the two regions are combined and treated together, statistical stability is
39 difficult to achieve with a single test.

40 A participant questioned the purpose of comparing depositions outside the impactor at
41 all and suggested that perhaps the Agency should revisit that issue, because earlier, for MDIs,
42 the MMAD and respirable fractions were used, and set based on the inside, not outside
43 impactor deposition. Another participant asked what information would be obtained from
44 comparing the "outside" impactor deposition that is not already obtained from a dose content
45 uniformity test. Dr. Adams explained that the ex-valve and ex-actuator amounts need to be
46 compared for equivalence purposes because they are stated on the label.

47 The Working Group discussed that statistically, the comparison of depositions "outside"
48 the impactor could be accomplished via a simple test, such as confidence intervals around
49 means. On the other hand, the depositions on stages inside the impactor would be analyzed by
50 a more complex, chi-square type test. Considerations for setting alpha levels for "inside" and
51 "outside" the impactor will be discussed in more detail at a later teleconference.

52 Dr. Tsong noted that the chi-square procedure referenced in the Cheng-Shao paper (see
53 the minutes of the 5 August meeting) is based on the 1999 draft Guidance, which was not
54 entirely correct. The more correct description of the procedure is contained in the slides
55 presented to the Advisory Subcommittee on Orally Inhaled and Nasal Drug Products in 2000
56 (<http://www.fda.gov/ohrms/dockets/ac/00/slides/3609s1e/index.htm>).

57 Dr. Dunbar proposed that the stages within the impactor be weighted based on the
58 width of the size interval. Several participants commented that it would be difficult to get
59 consensus on any weighting scheme. Dr. Tsong noted that cascade impactor design addresses
60 equalized weighting of the stages from an aerodynamic perspective, and therefore additional
61 weighting in the statistical test is not necessary. Dr. Adams replied that Dr. Dunbar's approach
62 is different from weighting based on clinical relevance, and may have merit. Dr. Dunbar agreed
63 to prepare a written description of the weighting scheme based on interval widths and a
64 rationale for using it in this context. Mr. Christopher proposed that the discussion of this and
65 other possible approaches continue in more detail at the next teleconference.

66 The Working Group discussed the draft of the paper by Dr. Lee, which summarizes the
67 algorithm and properties of the test proposed in the 1999 draft Guidance. The paper
68 demonstrates how due to insufficient stability of its response, the statistic proposed in that
69 Guidance is not amenable to setting a general equivalence value, *i.e.*, such that could be applied
70 without resorting to product-by-product estimation of the degree of PSD skewness and
71 variance-covariance matrix. Dr. Lee's paper does not make any statements or recommendations
72 on behalf of PQRI; nevertheless, comments from the Working Group will be welcomed and
73 considered if emailed before 10 January. Several Working Group members commented that the
74 paper is helpful in summarizing the technical issues and explaining the crux of the problem
75 with chi-square testing.

