

1 **MINUTES OF THE TELECONFERENCE**
2 **OF THE PQRI PSD MASS BALANCE WORKING GROUP ON**
3 **20 SEPTEMBER 2004**

4 **I. PARTICIPANTS**

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

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 participants agreed to the following objectives of the teleconference: (i) to review
13 voting results; (ii) to discuss the recent analysis of acceptance criteria; and (iii) to discuss draft
14 recommendations for the treatment of the mass balance measurement.

15 **III. DISCUSSION**

16 **Voting Results**

17 Dr. Tougas announced that Mr. Wyka had received the majority of votes in the election
18 of the next chair for this Working Group. Dr. Tougas thanked both Mr. Wyka and Dr. Curry for
19 their willingness to serve in the leadership position. The participants congratulated Mr. Wyka.
20 Dr. Tougas confirmed that he would continue to co-chair the Working Group through the
21 transition period.

22 **Evaluation of Acceptance Criteria**

23 Dr. Tougas reviewed the results of simulations he had conducted to study the
24 performance of the 85-115% acceptance criterion for the CI mass balance test. At the suggestion
25 of Dr. Lostritto, Dr. Tougas had also studied the 80-120% limits and a test with three cycles and
26 85-115% limits. For each of the scenarios, Dr. Tougas calculated the frequency of “false
27 negatives”, i.e., failures to meet a given criterion due to statistical chance. The mass balance
28 values were drawn randomly from normal distributions centered at 97% label claim, with
29 standard deviations of 5%, 7.6%, 10% and 15%. These parameters were selected based on
30 industry experience, the IIFG/IPAC earlier survey and in line with the USP approach to wall
31 losses. Dr. Lostritto confirmed that standard deviations up to 10% are not unusual for dose

32 content uniformity (DCU) for these product types, and that exceptional cases with DCU
33 SD>10% have been seen. The participants noted that mass balance results are likely to be more
34 variable than DCU results because of the more involved analytical method and propagation of
35 error from the multiple stages and other sources inherent in cascade impaction testing. Dr.
36 Rogers expressed reservations about the IITFG/IPAC database because it included non-US and
37 investigational (phase IIB through NDA) products. Dr. Tougas explained that the use of the
38 database is incidental and not critical to the analysis. The database was only used to suggest the
39 mean and standard deviations for the simulations.

40 The results of Dr. Tougas' simulations (see Exhibit A for details) show that for a normal
41 distribution N(97,15), the probability to get a single result outside 85-115% is 31.9%. The
42 probability of getting two consecutive results leading to an OOS investigation per the current
43 draft recommendation, is 10.2%. For the N(97,10), the probabilities to fail in the first and second
44 cycle are 13.4% and 1.8%, respectively. The participants stressed that these random failures
45 refer to a single test on a single inhaler. If n inhalers are tested for release, the random failure
46 rates will increase,¹ and if multiple stability testing stations are taken into account, the random
47 failure rates will increase even further due to the multiplicity. All these "failures" or "outside-
48 the-limits" results would be coming from the same underlying distribution, meaning that the
49 batch quality is not changing, and that no assignable cause can be identified. With the
50 broadened criteria or with an additional retesting cycle, random failures diminish. FDA
51 participants commented that they had not seen as high failure rates as suggested by the
52 calculations, but Dr. Lostritto admitted that the Agency's dataset is limited, and the Agency's
53 ability to conduct detailed analyses is hampered by the lack of resources, reorganization, and
54 the fact that some of the MB data exist only on paper, not electronically.

55 The Working Group agreed that the simulation results should be developed into a
56 technical paper and published in a scientific journal, while the recommendations to FDA would
57 only contain a brief statement referring to this work. The Working Group also suggested that
58 Ms. Strickland's earlier studies of the relationship between MB and DCU limits be included in
59 this paper, although at the end of the teleconference Dr. Rogers expressed strong reservations
60 about the validity of using statistical arguments to relate the DCU variability to the MB
61 variability. A statistical drafting group comprising Mr. Christopher, Ms. Strickland and Dr.
62 Tougas was formed.

63 Discussing the content of this upcoming article, the participants suggested to use OC
64 curves, as well as the current tables, to characterize the test. They also considered whether
65 analysis of non-normal distributions should be included. Overall, the Working Group felt that
66 this article would be a valuable addition to the Good Cascade Impactor Practices paper
67 published in the Journal of Aerosol Medicine last year. Dr. Mitchell commented that the GCIP
68 paper is providing a good service and is being used by the industry as a standard in this field.

69 Revising Draft Recommendations

70 The participants discussed options for revising the draft recommendations and agreed
71 that keeping the 85-115% limits but allowing three retesting cycles for unassignable causes
72 would be most appropriate, as it would minimize random failures of acceptable batches, and at

¹ The probability of random failure in a sample of n articles is $p(n) = 1 - (1-p)^n$ where p is probability to fail a single article.

73 the same time would emphasize the investigation of possible causes. Therefore, this scenario
74 was agreed for the recommendation rather than the others that have been considered. It was
75 also agreed that the detailed justification would be presented in the technical paper to be
76 prepared, while the actual recommendations would be kept as simple and straightforward as
77 possible. The participants also agreed to eliminate the assignable-cause retesting as a separate
78 loop, for simplicity, even though this will increase the producer risk.

79 During the discussion of the draft recommendations, the Working Group clarified the
80 following:

- 81 • An observation outside the limits would be documented in the lab records in
82 accordance with GMPs and SOPS but will not necessarily lead to contacting the
83 FDA. If three unassignable failures are observed in a row, then the company would
84 start an OOS investigation, and depending on its outcome it may contact the FDA.
- 85 • The recentering would not affect the allowed $\pm 15\%$ interval, i.e., the specification
86 centered at 95% would be 80-110%.
- 87 • The recommendation on the treatment of the mass balance should be included both
88 in the product specification and in the method description of a drug application.

89 Other Business

90 Dr. Mitchell mentioned that he would like to present a synopsis of the Working Group's
91 activities to the European Pharmaceutical Aerosols Group (EPAG) next week. Dr. Curry would
92 like to provide a similar update to the USP Aerosol Experts Committee in October. The
93 Working Group agreed.

94 **IV. AGREED**

- 95 • Dr. Tougas, Mr. Christopher and Ms. Strickland will draft a paper summarizing
96 statistical studies related to the mass balance acceptance criteria. The draft will be
97 later reviewed and commented on by the full Working Group.
- 98 • The drafting subgroup led by Drs. Dunbar and Lostritto will revise the mass balance
99 recommendations as suggested on the teleconference and will provide the next draft
100 for discussion to the full group before the next teleconference. Dr. Curry will
101 support this subgroup in light of Dr. Dunbar's limited availability in October.

102 **V. NEXT TELECONFERENCE / MEETING**

103 The next teleconference is scheduled for 13 October 2004.
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105 *Finalized on 18 October 2004*

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EXHIBIT A

AN EVALUATION OF PROPOSED MASS BALANCE CRITERIA: ESTIMATION OF 'MANUFACTURER'S RISK' BASED ON SIMULATIONS AT VARIOUS ASSUMED PRECISIONS

This evaluation examines the proposed Mass Balance (MB) criteria from the PQRI Mass Balance Working Group with respect to projected rates of failure associated with false negatives (i.e. rate of failures when a tested batch is from the parent population of 'good' batches). This is often termed the 'Producer Risk' since it represents the risk of failing a 'good' lot.

The proposed MB criteria have a decision tree that allows limited retesting of samples. While more complex, the essence of the decision tree can be reduced to the requirement that a batch must be subjected to an OOS investigation when two consecutive MB results without an assignable cause are outside the limits of $\pm 15\%$ of the target MB. Further, the target MB should be between 95 and 100%. This latter requirement recognizes the material losses that are inherent in this determination.

An evaluation of the rate of false negatives was produced by generating large numbers of random normal values with the appropriate characteristics and then examining these sets of values to determine the frequency with which the MB criteria were exceeded. A previous survey conducted by ITFG/IPAC-RS (attached) was used to select the characteristics of the specific model distributions. This survey included summary MB results from 23 products that spanned different types of OINDP and included commercial products approved in the US and Europe, as well as, products still under development. The summary tables from that report are reproduced below.

These tables organize the survey results by product status, product type and number of actuations employed. The overall characteristics of all surveyed results were a mean MB of 97.0% and an RSD of 7.6%. The range of RSDs for individual products was from 3.6 to 16.7%.

Table 3. Summary characteristics for different groups by product status.

Product status	Number of products	Total number of determinations	Mean MB* % LC	RSD %			f15*** %		
				Mean	Median	Range	Mean	Median	Range
US commercial	6	866	96.7	5.4	5.2	3.6-8.4	1.8	0.5	0.0-4.9
Non-US commercial	6	622	96.8	7.5	8.0	4.4-10.0	7.2	6.2	0.0-16.8
Phase IIB/III/NDA	10	1404	97.8	8.7	7.8	5.2-16.7	6.9	4.7	0.0-23.8
Not Disclosed	1	35	91.5	11.8	**	**	28.6	**	**
All	23	2927	97.0	7.6	7.1	3.6-16.7	6.6	4.8	0.0-28.6

Table 4. Summary characteristics for different groups by product type.

Product type	Number of products	Total number of determinations	Mean MB* % LC	RSD %			f15*** %		
				Mean	Median	Range	Mean	Median	Range
Device metered DPI	13	1706	97.4	8.7	8.1	5.2-16.7	8.1	6.7	0.0-23.8
CFC suspension pMDI	5	854	97.7	5.6	5.3	3.6-8.4	2.1	0.6	0.0-4.9
HFA suspension pMDI	4	166	93.6	7.3	6.5	4.3-11.8	8.4	2.5	0.0-28.6
HFA solution pMDI	1	201	101.4	6.2	**	**	1.5	**	**

Table 5. Summary characteristics for different groups by numbers of actuations per determination.

Number of actuations per determination	Number of products	Total number of determinations	Mean MB* % LC	RSD %			f15*** %		
				Mean	Median	Range	Mean	Median	Range
1	5	890	98.9	7.1	6.9	5.8-8.6	4.7	4.3	0.7-12.2
2	2	267	100.9	6.9	6.9	5.3-8.4	2.8	2.8	0.6-4.9
10	5	536	95.9	9.8	10.4	7.1-11.8	15.0	13.6	1.7-28.6
>10	11	1234	95.9	7.0	5.5	3.6-16.7	4.3	1.5	0.0-16.8

* mean of the product MB means
 ** not meaningful (n=1)
 *** frequency of mass balance determinations outside 85-115% LC

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 137
 138 MINITAB version 14 was used to perform this analysis. Based on the characteristics observed
 139 in the ITFG/IPAC-RS survey, simulations were performed using a mean MB of 97% and normal
 140 distributions with standard deviations of 5%, 7.6%, 10% and 15%. For each assumed standard
 141 deviation, a 100,000 pairs of random normal values were generated to represent a 100,000 pairs
 142 of MB determinations all from the same population. These pairs were examined to determine the
 143 number of instances where the first value was outside the limits of 82-112% (97±15%) and the
 144 number of instances where both members of the pair were outside these limits. The latter
 145 estimates the number of times per 100,000 that an OOS investigation would be triggered when
 146 the values in question were all from the same parent population. This is a direct estimate of the
 147 producer risk for the given distributional characteristics. The following table summarizes the
 148 results.
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Summary Results Estimating Producer Risk Associated with Proposed Mass Balance Criteria (±15%)		
Assumed Normal Distribution (mean±s.d.)	First result outside limits (# per 100,000)	Both results outside limits (# per 100,000)
97±5%	280	0
97±7.6%	4,788	220
97±10%	13,456	1,811
97±15%	31,914	10,156

151 This suggests that at the mean variability observed in the cited study (RSD=7.6%), one should
 152 expect about 0.2% false negatives, but at the upper end of the observed range (RSD=16.7%) the
 153 anticipated rate of false positives is greater than 10%.

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 155 Based on discussion with Rik Lostritto, this analysis was extended to consider some alternate
 156 scenarios. The same exercise was conducted on broadened MB criterion of $\pm 20\%$ and $\pm 25\%$.
 157 The following tables show estimates for 'Producer Risk' under these situations.
 158

Summary Results Estimating Producer Risk Associated with Mass Balance Criteria of $\pm 20\%$		
Assumed Normal Distribution (mean \pm s.d.)	First result outside limits (# per 100,000)	Both results outside limits (# per 100,000)
97 \pm 5%	10	0
97 \pm 7.6%	900	12
97 \pm 10%	4505	212
97 \pm 15%	18,311	3,350

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Summary Results Estimating Producer Risk Associated with Mass Balance Criteria of $\pm 25\%$		
Assumed Normal Distribution (mean \pm s.d.)	First result outside limits (# per 100,000)	Both results outside limits (# per 100,000)
97 \pm 5%	0	0
97 \pm 7.6%	102	0
97 \pm 10%	1215	16
97 \pm 15%	9641	906

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 161 A third scenario considered was to add a third tier to the testing while retaining the $\pm 15\%$
 162 criterion. This represents allowing three MB failures without an assignable cause before an OOS
 163 investigation is required. The results are shown in the following Table:
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Summary Results Estimating Producer Risk Associated with Three Stage Mass Balance Criterion of $\pm 15\%$			
Assumed Normal Distribution (mean \pm s.d.)	First result outside limits (# per 100,000)	First and second results outside limits (# per 100,000)	All three results outside limits (# per 100,000)
97 \pm 5%	280	0	0
97 \pm 7.6%	4,788	220	9
97 \pm 10%	13,456	1,811	243
97 \pm 15%	31,914	10,156	3207

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