

1 **MINUTES OF THE TELECONFERENCE**
2 **OF THE PQRI PSD MASS BALANCE WORKING GROUP ON**
3 **17 AUGUST 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)
Craig Dunbar (Alkermes)	Brian Rogers (FDA)
Zoë Heaton (Aventis)	Helen Strickland (GlaxoSmithKline)
	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 were reminded of the 20 August deadline for submitting comments on
13 the previously circulated draft minutes.

14 **III. DISCUSSION**

15 **Draft Recommendations**

16 Dr. Dunbar explained the draft recommendations which he and Drs. Lostritto, Rogers
17 and Mitchell prepared after the 20 July meeting of the full Working Group (see Exhibit A). The
18 Working Group confirmed the points of consensus and considered the points needing
19 discussion. The following comments were made:

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- 21 • Dr. Lostritto had examined FDA data for 16-17 products and with the exception of
22 one product did not notice problems with the mass balance requirements. In
23 response to a question he clarified that the number of actuations was small in all
24 cases, close to the minimal clinical dose. (These empirical observations form the
25 basis of the recommended 85-115% limits; the theoretical considerations of statistical
26 inconsistency with the unit dose limits are deemed to be of lesser importance). The
27 participants agreed to maintain the 85-115% limits but specify that the number of
28 actuations per mass balance determination should be selected based on analytical
sensitivity.
 - 29 • The decentering in the >100% direction should not be precluded by the
30 recommendations. The sponsor would have to justify any decentering (e.g.,
31 evaporative loss, sampling method, etc.).

- 32 • When re-testing, either the same container at a slightly different life stage (e.g., near-
33 beginning) could be used, or a new container with the same life stage (e.g.,
34 beginning). This choice will be left up to the sponsor.

35 *Chairmanship of the Working Group*

36 Dr. Tougas reminded the participants that since he had taken on the responsibilities of a
37 DPTC Chair, a new Chair of this Working Group should be identified; he further explained that
38 the DPTC reviewed the process for selecting a new Chair at its recent meeting, and agreed that
39 the Working Group should make a recommendation, which then would be considered by DPTC
40 for ratification. Dr. Tougas indicated that Dr. Curry and Mr. Wyka had expressed an interest in
41 serving in the leadership role.

42 The Working Group requested that Dr. Tougas remain in the Chairman position until
43 the PQRI Mass Balance Recommendations are submitted to FDA. Dr. Tougas agreed to co-
44 Chair the Working Group for this period. Dr. Curry and Mr. Wyka were requested to provide
45 bios and statements of interest for consideration by the Working Group and confidential
46 electronic voting.

47 **IV. AGREED**

- 48 • Drs. Lostritto, Rogers, Dunbar and Mitchell will produce the next version of the
49 draft recommendations and provide it to the full Working Group for comments.
- 50 • Because the recommendations being currently prepared are carefully thought out,
51 and will reflect the consensus position of all parties involved, and therefore should
52 be entitled "Recommendations..." rather than "Interim Recommendations." If data
53 collection and analysis proves possible at a future time, that work could be
54 conducted as a separate follow-up project.
- 55 • Dr. Curry and Mr. Wyka will provide bios and statements of interest for the position
56 of the Working Group's next Chair. The Working Group will vote confidentially by
57 email. Dr. Tougas will continue in the leadership role as a co-Chair until the
58 Recommendations are submitted to FDA.

59 **V. NEXT TELECONFERENCE / MEETING**

60 The next teleconference was scheduled for 20 September 2004.

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Finalized on 13 September 2004

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EXHIBIT A

DRAFT RECOMMENDATIONS FOR TREATMENT OF MASS BALANCE FOLLOWING MEETING OF 20 JULY 2004 (DISCUSSION DRAFT, V.3)

Points of Consensus

1. Recentering Target Mass Balance

It was acknowledged by consensus that the cascade impactor procedure (equipment, method, etc.) may lead to the unavoidable and non-recoverable loss of drug material which tends to drive the mass balance below the expected target of 100% of the emitted dose (USP26<601> Christopher, D. et al., J. Aerosol Med., 235-247, 2003; Mitchell, J.P., J. Aerosol Med., 433, 2003). These test bias losses are not related to the functional performance of the drug product and may be accounted for by recentering the target below 100% of the emitted dose. The degree of net test loss will be product specific and recentering must therefore be based on scientific evidence and supported by data. Recentering based on net test loss should not exceed 5% (not lower than 95% of emitted dose), which is consistent with USP26<601> cascade impactor system suitability requirements.

2. Target Mass Balance Range

There was general agreement that the range about the mass balance target should remain unchanged from the current standard of $\pm 15\%$.

3. Mass Balance Investigation Process

The mass balance investigation process has been modified from that described in GCIP to accommodate iterations around the probable cause assigned to the mass balance failure. A limit of two iterations for MB failures that could not be assigned to the method was selected. This follows the recommendations of GCIP that a MB failure can occur due to a method related error, even when no assignable cause was identified. A limit of three iterations for MB failures assigned to the method was selected to prevent testing to compliance. Repeatable MB failures lead to an out of specification (OOS) investigation.

Summary

1. Proposed mass balance acceptance criteria as follows:

$$|MB - T_{MB}| \leq 15\%$$

where MB is the mass balance determination and T_{MB} is the target mass balance.

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2. Target mass balance (T_{MB}) may be recentered from 100% emitted dose (ED) to account for net systematic loss of cascade impactor method.

a. Recentering criteria as follows:

$$95\% ED \leq T_{MB} \leq 100\% ED$$

b. Recentering to be justified for specific product based on scientific evidence and supported by data.

c. Recentering criteria is consistent with USP26<601> cascade impactor system suitability requirements.

3. Mass balance investigation process (Figure 1).

a. Method failure analysis should follow Good Cascade Impactor Practices (GCIP) (Christopher, D., et al., J. Aerosol Med., 16(3), 235-247, 2003; Mitchell, J.P., J. Aerosol Med., 16 (4), 433, 2003)

b. The failure mode analysis developed for the Good CI Practices (GCIP) Paper was based on a consensus within the WG. A survey of industry confirmed that failure mode investigation process as outlined in the paper are in line with expectations (Mitchell, J.P., J. Aerosol Med., 16 (4), 433, 2003). Therefore, it is recommended that the procedure in GCIP be used prescriptively to investigate CI measurement failures.

Points Requiring Further Discussion

1. Target MB Range of $\pm 15\%$ Emitted Dose

Additional discussion required regarding exceptions to the target MB range of $\pm 15\%$ emitted dose (e.g. see discussion below for Single Actuation Determination). Specifically, can a sponsor argue for wider limits based on scientific evidence and supported by data?

2. Justification for Recentering

Additional discussion on the mechanisms causing net systematic bias are required. Also, compensating bias(es) that reduce the overall loss in the CI MB should be described in the rationale for recentering the target mass balance.

3. Repeat Measurements

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151 The decision to repeat measurements on the current unit or a new unit, after the GCIP failure
152 mode analysis (Figure 1), requires clarification by the working group.

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155 4. Single Actuation Determination

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157 In general, the precision for a cascade impactor (CI) measurement improves with increasing
158 number of inhaler actuations into the CI system, primarily because fewer stages are subject to
159 mass collections that are close to or below the limit of detection/quantitation (LOD/Q). In the
160 latter instance, the mass/stage affected would be recorded as zero, even though a very small mass
161 of active below the LOD/Q may have been present on each of these stages. This principle should
162 therefore drive the setting of the widest limits for a MB determination for single actuation tests.
163 However, the limits could also be broadened, but by a slightly lesser degree for a two actuation
164 determination and so on. This type of exception may have to be argued by the manufacturer of
165 the inhaler product on a formulation-by-formulation basis, as high unit dose formulations will be
166 less susceptible to the problem than low unit dose products. Also, clarification is required for the
167 treatment of data above the LOD but below the LOQ.

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169 Mass balance obtained with single actuation determinations has been addressed in Nasal Spray
170 and Inhalation Solution, Suspension, and Spray Drug Products, CMC Documentation Guidance
171 for Industry, CDER/FDA, 2002, as follows:

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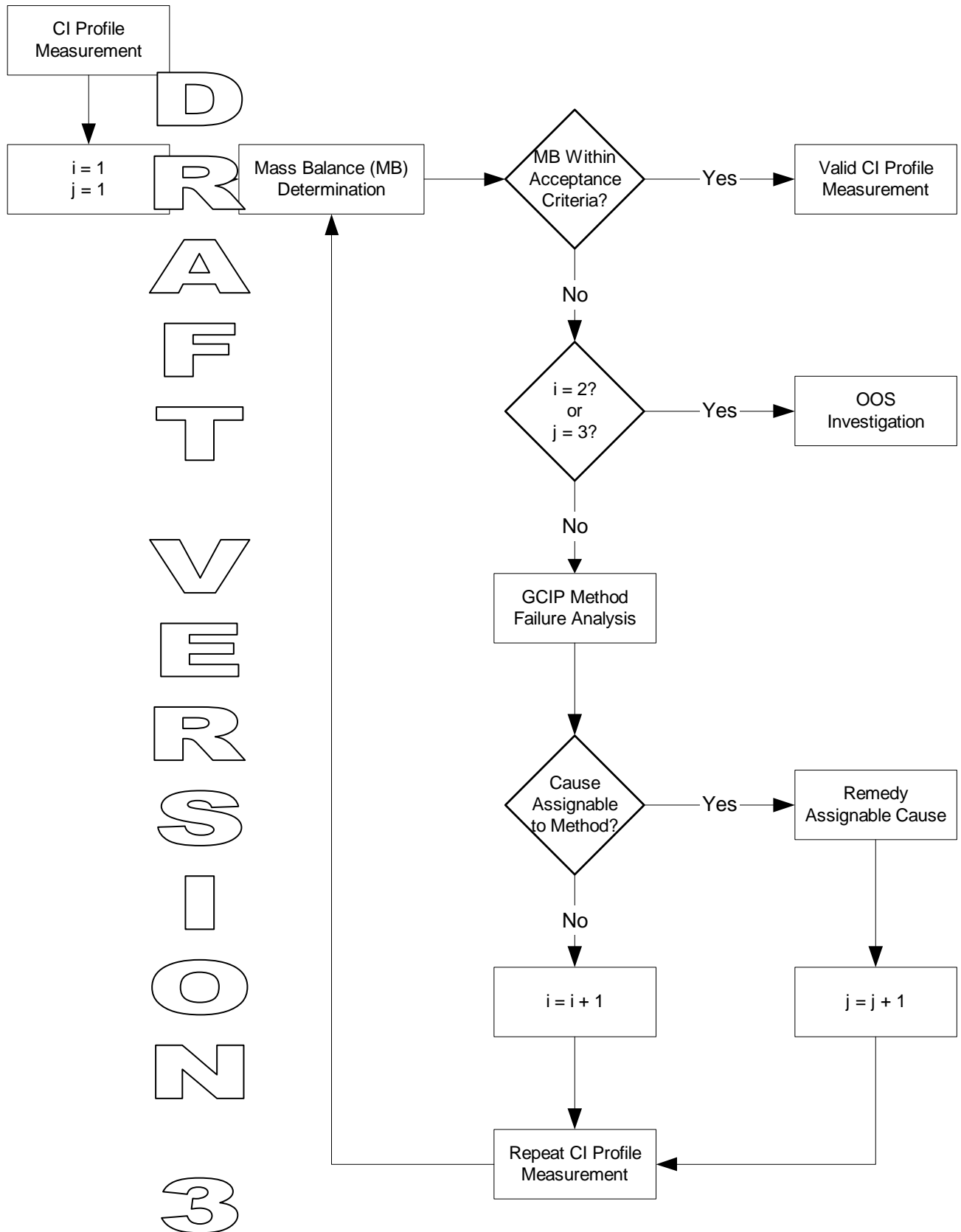
173 *If the procedure is based on a single actuation determination, then the range can be*
174 *broadened to reflect the limits allowed for an individual actuation.*

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176 Wally Adams may be able to provide additional information on considerations for single
177 actuation determinations.

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Figure 1: Mass Balance Investigation Process Diagram