

**MINUTES OF THE TELECONFERENCE**  
**OF THE PQRI PSD MASS BALANCE WORKING GROUP ON**  
**18 DECEMBER 2001**

**I. PARTICIPANTS**

Terry Tougas (Boehringer Ingelheim), Chair  
Mary Devlin Capizzi (IPAC-RS)  
Ken Furnkranz (FDA) (until call was interrupted)  
Sylvia Gantt (PQRI)  
Lana Lyapustina (IPAC-RS)  
Jolyon Mitchell (Trudell Medical)  
Lee Nagao (IPAC-RS)  
Guirag Poochikian (FDA)  
Brian Rogers (CDER/FDA)  
Bruce Wyka (Schering-Plough)  
Kahkashan Zaidi (USP)

**II. OPENING**

Dr. Tougas welcomed the participants. He reviewed the objectives of the teleconference as stated in the proposed agenda: (i) to review basic definitions; (ii) to review basic agreements; (iii) to discuss the draft Work Plan; and (iv) to agree on next steps. Dr. Tougas suggested that the goal of the teleconference would be to start a discussion on the mentioned documents rather than to finalize them.

In response to a question, Dr. Lyapustina clarified that all Working Group members except Dr. Lavery and Ms. Miran are present.

**III. DISCUSSION**

**Role of Individual Participants**

Dr. Tougas proposed to discuss some process issues before turning to the main part of the agenda. He acknowledged that the previous teleconference, on 30 November, was difficult due to technical problems with telephone connections, and due to some misunderstanding of the role of PQRI Working Group participants. He reiterated that the purpose of PQRI is to develop consensus recommendations based on good science that would provide scientific basis and support for Agency's regulatory documents. Therefore, each PQRI participant is encouraged to contribute to the deliberations of the Working Group in their capacity as individual scientists, with the understanding that their views will not be taken as official positions of the organization that the individuals are affiliated with.

Dr. Tougas emphasized that each participant should feel free to put forth positions, supported by good science, while being respectful of the opinion of others. Dr. Tougas encouraged all Working Group members to listen to each other carefully, and if they disagree, disagree respectfully. He also reminded that any disagreement should be directed at scientific

positions and not at individuals. Dr. Tougas concluded by saying that each participant is, and should feel, an equal and important part of the overall process.

**Process for Commenting on and Finalizing Minutes**

Dr. Tougas reviewed the proposed process for revising and finalizing the minutes of the Working Group's teleconferences as outlined in a recent email. Dr. Tougas suggested that the first draft of the minutes be issued for a 7-day review and comment period, after which he would reconcile all comments in a revised draft, to be issued for a further review. The minutes would be finalized at a next teleconference or meeting of the Working Group.

Dr. Mitchell supported the proposed process, but requested that the review and commenting period be extended to 10-14 days. Dr. Zaidi asked that a 2-week review period be allowed, as she has to circulate draft minutes and other documents to the USP Aerosol Expert Committee for comment.

Participants agreed that the commenting period for the draft minutes should be two weeks from the date of issue. Any received comments will be circulated to the full Working Group for consideration. One participant asked whether comments should be provided in a particular format, *e.g.*, as specific re-wording or as general comments. Dr. Tougas explained that no specific format is required, however, specific wording for suggested revisions would be more helpful than general comments.

Dr. Tougas invited the Working Group members to consider whether in the minutes, individual speakers should be identified by name or by their affiliation. He mentioned that the attribution of remarks is necessary for clarity, and that complete anonymity would be confusing. Participants agreed that it is more appropriate to refer to individuals by name rather than organizational affiliation, because the views expressed during the teleconference may not necessarily represent the official position of the respective organization.

Dr. Rogers inquired whether the revised draft of the minutes would be subject to further review before finalizing. Dr. Tougas and Ms. Capizzi clarified that this is the case, and that after the revised draft has been prepared and reconciled by Dr. Tougas, it will be issued for further review and comment. The minutes will be formally approved and finalized at the teleconference or meeting that follow the issuance of the draft minutes.

Dr. Rogers suggested that any unresolved issues with the minutes be discussed in writing via email rather than during teleconferences. Other participants agreed that teleconference time should not be spent in detailed discussions of minutes of past teleconferences, and that all issues should be resolved via email, if possible.

With respect to the minutes of the 30 November teleconference, Dr. Tougas proposed that a revised draft be issued shortly, and that those minutes be finalized at the upcoming meeting of the Working Group in January 2002. Participants agreed with this approach.

**Basic Definitions, Basic Agreements and Draft Work Plan**

Dr. Tougas drew attention of the participants to the compilation of PSD-related definitions prepared by Drs. Tougas, Mitchell and Wyka, circulated to all members of the Working Group and DPTC prior to the teleconference. He noted that the definitions were drawn from authoritative sources such as ICH guidelines, FDA Guidances, and USP general

chapters. Dr. Tougas encouraged Working Group members to review these basic definitions off-line.

Next, Dr. Tougas introduced a questionnaire entitled "PQRI PSD MB basic agreements" (see the attachment) and a draft Work Plan, both of which were circulated to all members of the Working Group and DPTC prior to the teleconference. Dr. Tougas explained that the questionnaire was prepared to provide a framework for a structured discussion on the mass balance issue. The ultimate goal, however, is to develop a specific Work Plan based on this discussion.

Dr. Tougas recognized that it would be impossible to work through the entire questionnaire during this teleconference, but he invited the Working Group members to at least start a discussion of the questions posed. Dr. Zaidi noted that she had circulated the questionnaire to the USP Aerosol Expert Committee (AEC). Dr. Mitchell commented that it would be important to have the input of the USP AEC. Dr. Tougas and the other participants agreed that the target date for collecting all responses should be mid-to-late January, in advance of the Working Group's meeting. Dr. Mitchell further suggested that a compilation of all responses be prepared and circulated to the Working Group for consideration prior to the January meeting.

#### ***Questions 1 and 2: Specification vs. System Suitability***

Dr. Tougas reviewed the first two questions in the questionnaire (see the attachment) and noted that the intent was to distinguish the definition of terms "specification" and "system suitability"; the former being a comment on the product, and the latter, a comment on the method. Dr. Tougas noted that the difference is most obvious when one considers the consequences of failing a system suitability test as opposed to failing a specification. A failing system suitability leads to correcting the problem and repeating the test. A failing specification, on the other hand, leads to an OOS investigation and rejection of the batch.

Mr. Wyka pointed out that according to the USP definition, "system" in "system suitability", includes a standard. Thus, the combination "instrument + standard + analyst" constitutes the "system"; and a system suitability test is intended to demonstrate whether this "system" is capable of making a correct judgement on a sample.

Dr. Tougas agreed that the classical definition of the "system suitability" is part of the problem when one talks about PSD mass balance. In the conventional understanding of the term, a check of the system suitability should be done PRIOR to testing a sample, and it should involve not the sample being tested but a SEPARATE, standard sample. By contrast, in a PSD determination, the sample being tested has to be simultaneously part of the system suitability test, because of the inherent setup of a PSD experiment. As discussed in the previous (30 November) teleconference, for the MB to be valid, it has to be performed in the same run as the PSD determination itself, because each run (be it conducted for a PSD or a MB measurement), involves a disassembly and re-assembly of the cascade impactor. Thus, the MB "system suitability" test has to be concurrent with the actual test, unlike for classical system suitability tests.

Dr. Poochikian congratulated the authors of the questionnaire and characterized it as interesting and thought-provoking. He then suggested that since there is a disconnect between

the classical definition of the “system suitability” and the way the term is used for the PSD MB, the term “system suitability” be used in quotation marks until a better term is found.

Mr. Wyka agreed that a better term is needed to describe the function and purpose of the PSD MB and suggested “run qualification” as one possibility. An MB within validated limits would confirm that appropriate mass has been captured for a PSD determination, and thus the run would be “qualified”. He invited the other group members to consider this and other possible terms, as well as consequences of not meeting the MB requirement, and the process for establishing the MB limits.

Dr. Rogers pointed out that additional tests are needed for verification of the “system suitability” besides the mass balance. He expressed hope that the group will not view mass balance as the only way for validating a CI run.

Dr. Tougas agreed that other tests may be necessary for a complete system suitability verification. For example, a simple shot weight test, in conjunction with PSD MB, may be used to ensure that a PSD run is “qualified”.

Dr. Rogers suggested that there also should be a test to verify that there are no CI leaks exceeding a certain level. Dr. Tougas asked Dr. Rogers to elaborate on his question, since the sealing O-rings either hold or fail. Dr. Rogers clarified that he is concerned about defects in O-rings that are not readily apparent, such as wet spots or minor defects that may affect the quality of seals.

#### **Origin of Guidance’s MB Specification Requirement**

Dr. Poochikian explained that the concept of the MB as a specification was introduced in the draft CMC Guidances because there has been data, submitted by several different companies on several different products, where the mass balance is significantly deviating from the label claim (LC) in either direction, while the dose content uniformity (DCU) data for the same products and same batches is very close to 100% LC.

Dr. Tougas suggested that perhaps the problem is in defining mass balance in terms of the label claim rather than the delivered dose, since not all of the labeled content amount may be recovered without loss in a PSD experiment. However, Dr. Poochikian reminded participants that the DCU for the same batch may be close to 100% while the MB may be significantly off target. Moreover, the MB deviation may occur in either direction (too high or too low). The direction of the deviation would be consistent within each product, though.

Dr. Rogers asked if anybody knew why an MB could be so different from the DCU results. Dr. Mitchell offered one possible explanation - wall losses, which could amount to up to 5%. He admitted that he could not see how an MB could be consistently HIGHER than the label claim. Dr. Poochikian concurred that up to 5 % loss could be unavoidable, but the problem products he was referring to exhibited up to 20-30% deviation in certain cases.

Drs. Poochikian, Tougas and other participants agreed, however, that it is difficult to discuss and analyze these cases without knowing the specifics.

#### **Questions 3 and 4: MB Diagnostics**

Dr. Tougas reviewed the possible reasons for an MB failure as outlined in question 4 of the “basic agreements” document (see the attachment). He commented that it is important to

understand and agree on what the MB is an indicator of. Dr. Mitchell agreed with the listed four possible causes of the MB failure (i - iv), but proposed to clarify the definition of an "abnormal dose". Dr. Mitchell pointed out that some reasons for an "abnormal dose" may have nothing to do with the quality of the product, but may be due to "system"-type failures, such as misfiring, or lack of proper shaking, or lack of proper priming.

Mr. Wyka in addition pointed out the need to harmonize the MB limits with the DCU limits, because an "abnormal" dose by the Guidances' PSD MB standard (outside the 85-115% interval) may well be a "normal" dose within the appropriate DCU limits.

Dr. Tougas agreed that the harmonization of limits is important, and further noted that in a PSD run, the noise component is much larger, *i.e.*, in a DCU test there are far fewer sources of variance (and error) than in a PSD test. For example, the HPLC component alone is comprised of only one HPLC run for a DCU test, while multiple HPLC runs for a single PSD test have to be performed. Thus, one cannot expect the same precision for the PSD MB measurement as for the DCU measurement.

Dr. Rogers asked for a clarification of reason (i) in question 4, "*CI is not operating properly.*" He indicated that it is not obvious how a CI could be operating improperly in such a way that the MB falls outside validated limits. Dr. Mitchell offered one possible example: if the collection plates are misaligned due to an incorrect assembly, there may be a higher than usual loss to the walls leading to a low MB.

Dr. Poochikian asked for a clarification of the term "validated limits". Dr. Tougas replied that these are understood in the usual "system suitability" sense, *i.e.*, the limits that are characteristic of the particular tests system when it is operating normally, as established in validation studies. Dr. Poochikian, however, wondered whether in question 4 the term refers to the numerical limits on the mass balance (*e.g.* 85-115% as in the draft Guidances) or whether they involve a range of many different parameters, such as holes, sizes, *etc.* Dr. Tougas confirmed that in the questionnaire, "validated limits" refer to specific numerical values recommended for PSD MB, such as 85-115%, or 90-110%, or 80-120%. Mr. Wyka reminded participants that the specific limits depend on many parameters and the particular procedure. For example, they will depend on how many actuations are used per test, and whether the walls are washed or not. Dr. Poochikian confirmed his understanding that the validated limits for an MB should be obtained under standardized conditions and according to the specific procedure in question. Dr. Tougas noted that this is similar, for example, to setting resolution criteria for HPLC.

Due to time limitations, participants agreed to discuss the remaining questions via email and at the face-to-face meeting. Working Group members agreed to provide completed responses to the questionnaire in advance of the meeting so that the Secretariat may prepare and circulate for discussion a compilation of all responses.

#### **IV. AGREED ACTIONS**

Working Group members agreed to:

- complete the questionnaire on basic agreements and forward their responses and other comments to the Secretariat for circulation to the full Group no later than mid-to-late January 2002 (questionnaire attached below);

- review the basic definitions circulated prior to the teleconference; and
- consider the draft Work Plan circulated prior to the teleconference and be prepared to discuss it at the face-to-face meeting on 30-31 January 2001.

The Secretariat was directed to:

- issue minutes of all teleconferences and meetings as a draft subject to a two-week review and commenting period, after which a revised draft will be prepared and circulated for additional review and final approval; and
- compile all responses and comments to the questionnaire on basic agreements and forward the compilation in advance of the 30-31 January meeting to the Working Group for consideration.

## **V. NEXT TELECONFERENCE/MEETINGS**

There will be no additional teleconferences held prior to the face-to-face meeting of the Working Group at the end of January.

The all-PQRI Executive Training Workshop is scheduled for **Tuesday-Wednesday, 29-30 January in Rockville, MD.**

The first face-to-face meeting of the Working Group is scheduled for **Wednesday, 30 January 2002, 1:30 PM- 5:00 PM (US EST)** and **Thursday, 31 January, 9:00 AM – 1:00 PM (US EST) in Washington, DC.**

## **VI. ADDRESSEES**

### PQRI PSD Mass Balance Working Group:

Ken Furnkranz (CDER/FDA)  
Martin Lavery (Aventis)  
Deborah Miran (GPhA)  
Jolyon Mitchell (Trudell Medical)

Brian Rogers (CDER/FDA)  
Terry Tougas (BI),  
Bruce Wyka (Schering-Plough)  
Kahkashan Zaidi (USP)

### PQRI Drug Product Technical Committee:

Larry Augsburger (AAPS)  
Jeffrey Blumenstein (Pfizer)  
Robert Dana (PDA)  
Shawn Dressman (USP)  
Devinder Gill (FDA)  
Sid Goldstein (Duramed)

Waseem Malick (Hoffman-LaRoche)  
Chris Moreton (GenPharm)  
Guirag Poochikian (FDA)  
Richard Poska (Abbot Laboratories)  
Rajendra Uppoor (FDA)

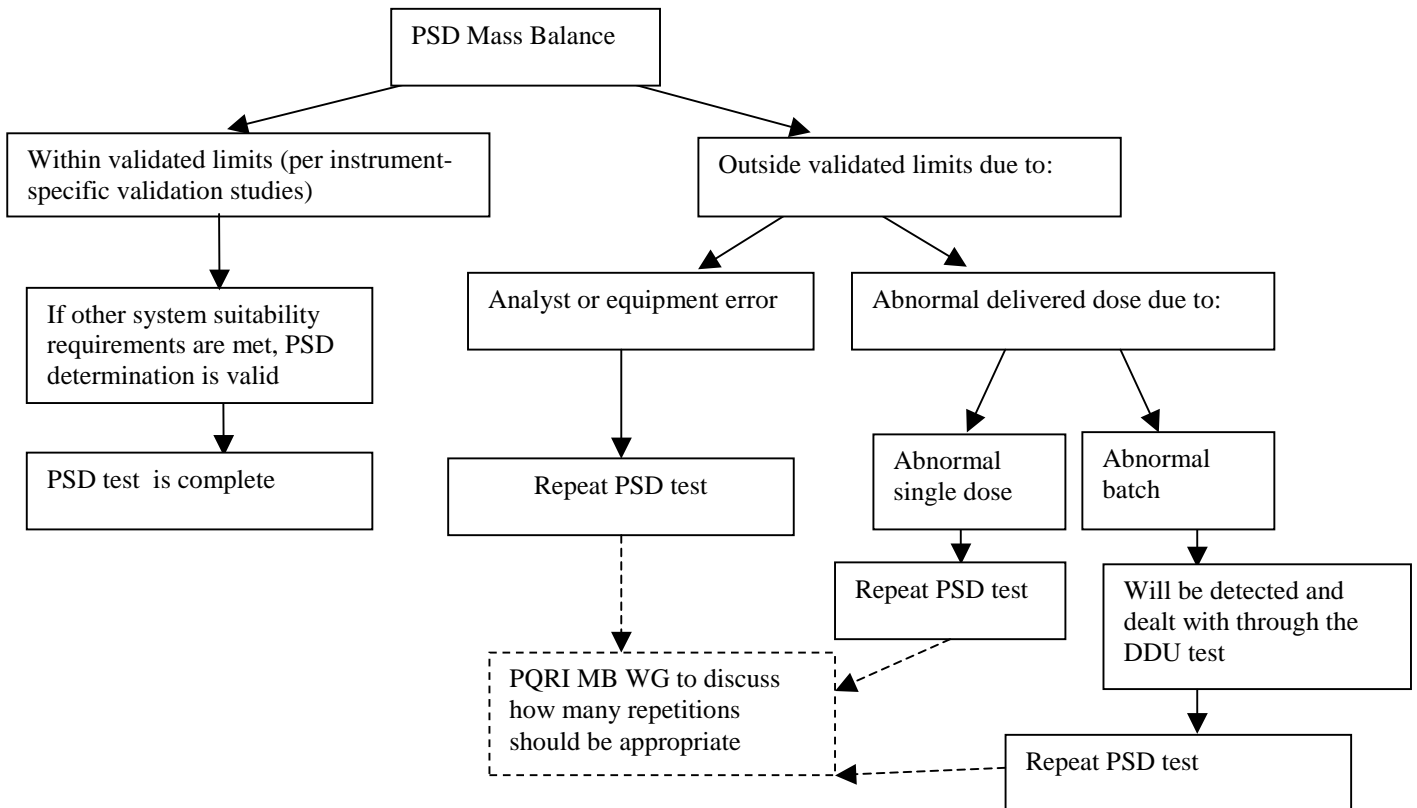
*Copy:* Sylvia Gantt (PQRI)

*Finalized and approved on 30 January 2002*

- (1). A failed specification should lead to investigation of the batch (OOS investigation), and if the failure is confirmed, rejection of the batch.
- Agree
  - Disagree because
- (2). A failed system suitability requirement should lead to investigation of the cause of system failure, correction of the identified cause, and repeat of the testing.
- Agree
  - Disagree because
- (3). A PSD mass balance that falls within validated limits confirms that the results of the PSD run could be trusted, provided other system suitability requirements are met.
- Agree
  - Disagree because
- (4). A PSD mass balance that falls outside validated limits indicates one or more of the following:
- (i) CI is not operating properly; and/or
  - (ii) analyst made an error (*e.g.*, spilled the extract); and/or
  - (iii) HPLC is not operating properly; and/or
  - (iv) an abnormal dose was delivered into CI.
- Agree
  - Disagree because
- (5). A PSD mass balance that falls outside validated limits indicates that the results of the PSD run could NOT be trusted.
- Agree
  - Disagree because
- (6). If a metric is used to decide whether test results could be trusted or not, this metric is called a system suitability requirement.
- Agree
  - Disagree because
- (7). MB system suitability determination should be performed in the same run as the PSD determination (*i.e.*, the CI should not be disassembled between the MB and PSD determinations).
- Agree
  - Disagree because
- (8). MB limits should be established in validation studies, as these limits are system-specific.
- Agree
  - Disagree because
- (9). From the causes above, (i) –(iii) have no relationship to the quality of the batch. Therefore, if MB is failed due to (i)-(iii), PSD test should be repeated.
- Agree
  - Disagree because

- (10). From the causes above, cause (iv) should fail the batch if this abnormal dose measurement is reflective of the quality of the batch.
- Agree
  - Disagree because
- (11). PSD test is not equipped to test delivered dose uniformity of the batch or even dose uniformity within a single inhaler.
- Agree
  - Disagree because
- (12). A dose uniformity test specifically designed to control dose uniformity of the batch will detect, with pre-established high confidence, a problem with batch dose uniformity, should such problem occur.
- Agree
  - Disagree because
- (13). A failing MB measurement does not necessarily mean that delivered dose of the batch is abnormal.
- Agree
  - Disagree because
- (14). An abnormal dose could be due to lack of proper shaking of the tested inhaler, valve malfunction, or other causes, which could indicate a problem affecting the batch or the problem limited to a single dose.
- Agree
  - Disagree because
- (15). If an abnormal dose indicates a problem affecting the batch, that problem will be detected by the appropriately designed DDU test.
- Agree
  - Disagree because
- (16). If an abnormal dose indicates a problem limited to a single dose, the PSD test should be repeated.
- Agree
  - Disagree because
- (17). When PSD specification is expressed in absolute amounts of drug found on stages or groups of stages, the PSD and MB measurement are confounded. For well designed limits/criteria it is NOT possible to pass the PSD limits one and fail MB limits.
- Agree
  - Disagree because
- (18). The purpose of PSD release test is to confirm that the batch with high confidence has acceptable distribution of particle sizes.
- Agree
  - Disagree because

- (19). The relative amounts (%) of particles of different sizes is controlled by the PSD test.
- Agree
  - Disagree because
- (20). The absolute amounts of particles of different sizes is controlled through the combination of DDU test and % amounts confirmed in the PSD test.
- Agree
  - Disagree because
- (21). I agree/disagree with the following scenarios and conclusions.
- Scenario A: PSD% on all stages are within limits. MB within limits. – Conclusion: PSD system (CI+analyst+HPLC) is operating properly. PSD specifications are met.
- Scenario B: PSD% on all stages within limits. MB outside validated limits. – Conclusion: some of aerosol was lost, or the inhaler misfired, thus the test was not performed properly. Repeat the PSD test.
- Scenario C: PSD% on some or all stages outside limits. MB within limits. – Conclusion: If other system suitability tests are also within limits, PSD test was performed properly. Particles size distribution is outside specifications. Initiate an OOS investigation.
- Scenario D: PSD% on some or all stages outside limits. MB outside limits. – Conclusion: some of aerosol was lost, or the inhaler misfired, thus the test was not performed properly. Repeat the PSD test.
- Agree
  - Disagree because
- (22). I agree/disagree with the following flowchart:
- Agree
  - Disagree because



(23). Based on the preceding analysis, the meaning and appropriate purpose of the PSD Mass Balance is as a system suitability test.

Agree

Disagree because