

MINUTES OF THE TELECONFERENCE
OF THE PQRI PSD MASS BALANCE WORKING GROUP ON
30 MAY 2002

I. PARTICIPANTS

Terry Tougas (Boehringer Ingelheim), Chair
Myron Diener (Aventis)
Bill Doub (FDA)
Ken Furnkranz (FDA)
Martin Lavery (Aventis)
Lana Lyapustina (IPAC-RS)
Jolyon Mitchell (Trudell Medical)
Brian Rogers (FDA)
Helen Strickland (GlaxoSmithKline)
Yi Tsong (FDA)
Bruce Wyka (Schering-Plough)

II. OPENING

Dr. Tougas opened the meeting and welcomed the participants, especially the new statisticians provided by the PhRMA Statistics Expert Team, Dr. Diener and Ms. Strickland.

Dr. Mitchell proposed some revisions to the draft minutes of the 13 May meeting. Other Working Group members agreed to provide their comments on the draft minutes by Wednesday, 5 June.

Drs. Wyka and Mitchell informed the Working Group that they should be able to meet the target deadline (end of June) for the draft document outlining causes of CI MB failure.

III. ORGANIZATIONAL ISSUES

Dr. Mitchell reminded the participants that the European Pharmaceutical Aerosol Group (EPAG), of which he is a member, is planning to discuss and comment on the scientific issues outlined in this Working Group's Work Plan. As was discussed in a previous meeting and teleconference, the Work Plan has been approved by the PQRI Steering Committee and now is a public document. EPAG has asked Dr. Mitchell to make a presentation based on the Work Plan at the next EPAG meeting at the end of June. Dr. Mitchell noted that EPAG is a recognized body of experts in inhalation industry with significant expertise in the area of cascade impactors (CI), on which much of the Work Plan is focused.

The Working Group discussed and agreed that in general, presentations related to their PQRI work fall into three broad categories:

1. Discussions within each of the PQRI Member Organizations. These do not require specific oversight of PQRI committees because the organizations themselves are part of PQRI. Therefore, such presentations are the sole responsibility of the individuals making the presentation and no prior PQRI approval is required.

2. General presentations on PQRI work outside of PQRI. These do require the Working Group's review and approval; however, no further formal approval is required. The DPTC is included in this revision and approval process via email.
3. Presentations of specific PQRI results, findings and recommendations. These are limited to PQRI workshops and perhaps other fora, in which case explicit authorization of the PQRI Steering Committee is required.

Dr. Mitchell indicated that he plans to present slides to EPAG and would appreciate the Working Group's review of and comment on his draft slides. Dr. Mitchell stressed that no documents or drafts under development by the Working Group would be shared with EPAG. He requested that the Working Group provide their comments on the slides in a timely manner so he can incorporate all changes before the EPAG meeting. The Working Group members agreed to review and provide their input to Dr. Mitchell's presentation as soon as draft slides are available.

IV. DISUSSION OF PLANNED EXPERIMENT

Dr. Tougas reviewed the discussions at the 13 May meeting related to the design of an experiment planned for step 2 of the Work Plan. He reiterated that the experiment has two main objectives: (1) to compare the overall variability of a CI MB measurement to that of a DCU measurement, and (2) to quantify major contributions to the CI MB test variability. He also clarified that practically, the experiment would involve a series of measurements. In order to ensure that the above objectives are met through this series, the experimental design needs to be carefully discussed and planned with participation of both statisticians and analytical chemists familiar with CI operation and potential sources of variability.

In response to questions, Dr. Tougas further clarified that it is NOT the intention of this experiment to investigate how the CI MB measurement (from statistical perspective, average) is affected by such physical factors as temperature, humidity, flow rates, *etc.*, varied purposefully. Rather, the experiment is meant to quantify the real-life random variability (from statistical perspective, standard deviation) when the CI is operated in a standard way, according to best CI practices. Dr. Tougas listed some of the major contributors to the MB TEST variability: analyst, impactor, HPLC, day/time. Further, in order to minimize product-related variability, he suggested that a best-behaved product(s) be studied.

Participants briefly reviewed other factors that may contribute to the CI MB test uncertainty, such as number of actuations, specific product types, environmental conditions, *etc.* Dr. Tougas noted that the scope of the experiment will increase geometrically with the number of studied factors, and therefore it would be important to carefully design the experiment and develop a specific experimental protocol with participation of experienced statisticians.

Dr. Rogers suggested, and other Working Group members agreed, that the analysts involved in this experiment should be well trained specifically for CI testing. Dr. Rogers also proposed that only one analyst be involved, but the other participants pointed out that since

analyst-to-analyst variability is one of the main contributors to the MB test uncertainty, it is critical for this experiment to investigate this source of test variability.¹

In order to develop an experimental design addressing all critical factors adequately and practicably, Dr. Furnkranz proposed to hold a brain-storming discussion among interested chemists and statisticians. Dr. Diener, Ms. Strickland, Dr. Tougas and Mr. Wyka agreed to participate in such brain-storming. This discussion group will develop a concrete experimental design during a separate teleconference(s) and present the proposed design at the next teleconference of the full Working Group.

V. AGREED ACTIONS

- The Working Group members will provide comments on the draft minutes of the 13 May meeting by Wednesday, 5 June.
- Drs. Mitchell and Wyka will continue to prepare the document outlining causes of CI MB failures and will provide the next draft for the Working Group's review and comment at the end of June.
- The Working Group members will provide comments on Dr. Mitchell's slides for EPAG in a timely manner once the slides are available for review.
- A small discussion group will assess the requirements of the experimental design in a separate teleconference(s) and will present its proposed design at the next teleconference of the full Working Group.

VI. NEXT TELECONFERENCE/MEETINGS

The next teleconference of the PSD Mass Balance Working Group is scheduled for **Wednesday, 3 July at 10:00 AM (US EDT)/15:00 UK time.**

Minutes Finalized on 3 July 2002

¹ Following the teleconference, additional discussion occurred via email, as documented in the attached Exhibit A.

EXHIBIT A

Email 1

I needed to express my opinion a little more clearly than I was able during the Telecon.

I am not against gathering the data with the variables you mentioned. I know it seemed like that, but my purpose was to make sure that everyone understood my point about examining the analyst as an independent variable.

I will try to give you my opinion clearly and I won't object to this issue further.

I feel the examination of the analyst as an independent variable is extremely difficult at best for the following reasons:

1. I don't believe we will never get more than a couple qualified (however that may turn out to be defined, and the analysts must be qualified...) analysts in any one laboratory on a single cascade impactor under identical environmental and operating conditions (humidity, etc.). A meaningful result from this type of comparison will be very difficult to obtain.

As an aside, anyone reading this from industry can ask yourselves: How many PSD analysts are assigned to a particular drug product? I believe the answer is few (1 or 2) for various reasons, one of which is to minimize variability. I may be incorrect, so I am willing to listen to other's experience. The requirement for "numerous complicated manual operations, which require highly specialized analytical skills" dictates this conclusion. This is also my logic for stating the highest variability will obviously be in the analyst-to-analyst variability. This logic is implicit in the above quote from our working plan document.

In our data set, we may see the following results:

Within a laboratory, the analysts at each laboratory tested are highly variable. It is my opinion that that we can't draw any conclusion from this data. A lack of quality or equivalence will never prove inability to achieve this goal. Just because you haven't thought of the cause between a lack of equivalence doesn't mean it cannot be improved. It may be simply the difference in training, experience, ability, motivation, guidance, broken arm, whatever. Improvement in any of these causal factors will bring these analysts closer together in their results.

Within a laboratory, some sets of analysts will have high variability and some sets will have low variability. Again, no conclusion can be drawn since there is too much variability between laboratories. We will be unable to generalize for the purpose of a recommendation.

Within a laboratory, all sets of analysts will have low variability. This is the best case and will not really speak to the likelihood of having a high variability which is the default. I say this since there is considerable effort required to achieve low variability in this complex analytical method. I guess I am making an argument based upon entropy :).

These conclusions are all negative in their ability to provide useful information, other than the academic exercise in stating the results. This comparison is useless I feel.

Comparison of analysts between laboratories is, I feel, impossible to do meaningfully with an obtainable data set. There are too many confounding variables contributing to the PSD results and variability. Humidity, variance between different products, working conditions, training of the analysts, etc. These

variables will change from laboratory to laboratory and will not be easily separated from the variability due to purely the analyst to analyst variability which is what you are intending to establish or measure. The data set required to separate the other independent variables will be too large to be obtained from volunteers.

Email 2

I am not sure I fully agree with the assumption that for any one product only 1 or 2 analysts will be involved. For big selling product there may well be dozens of analysts involved (both in QC and in stability functions). While it is true we plan to minimize the number of operators and stacks etc, if you're making hundreds of batches a year and have significant stability protocols running, it's inevitable that more than 1 or 2 analysts will be involved.

I totally agree that there can be significant analyst to analyst variability. For that reason I believe that analyst to analyst variability must form a part of the total analysis of variability investigation. After all, compliance with the MB criteria is dependent on the sum of the variables, if analyst to analyst is large (and the magnitude is probably dependent on which particular drug product is being analyzed!) then it has to be assessed.

The actual experimental design therefore is complex and will need a high degree of replication to be able to assign variability, particularly if all the test labs are assessing different drug products. Such an experiment is very complex and labor intensive.

Email 3

I wanted to comment on the suggestion to stick with a single analyst. I disagree with this request. Having performed and published in the area of particle size measurement on different instruments, the very factors that the author of that request is trying to eliminate are those which can "make or break" a real-life comparison. Anyone who has ever worked on a method development and transfer knows that analyst to analyst variability must be included in the study. Otherwise, the data collected don't reflect the conditions that the compound will see in production.

We don't need another idealized study. I vote for keeping analyst to analyst variability. Without it, this becomes nothing more than an academic study.