

MINUTES OF THE MEETING
OF THE PQRI PSD MASS BALANCE WORKING GROUP ON
29-30-31 JANUARY 2002

I. PARTICIPANTS

Terry Tougas (Boehringer Ingelheim), Chair
Ken Furnkranz (FDA)
Martin Lavery (Aventis)
Lana Lyapustina (IPAC-RS)
Jolyon Mitchell (Trudell Medical)
Guirag Poochikian (FDA), *30-31 January only*
Brian Rogers (FDA), *30-31 January only*
Bruce Wyka (Schering-Plough)
Kahkashan Zaidi (USP), *30-31 January only*

II. DISCUSSION

During the meetings, Working Group members:

- finalized and approved the minutes of the Working Group teleconferences on 30 November and 18 December 2001;
- reviewed results of the survey entitled "PQRI PSD MB basic agreements";
- developed the Working Group's hypotheses and a draft work plan;
- considered what data would be required for the Working Group's research and how it could be obtained;
- summarized the Working Group's issues and activities to date, for presentation at the PQRI Executive Workshop;
- considered whether a web-based chat room would be useful for this Working Group; and agreed that the current system of email communications is sufficient; and
- agreed on next steps.

The Working Group summarized its issues and activities to date as follows:

- *PQRI PSD Mass Balance WG:*
 - proposal for PSD MB research was approved by PQRI SC in July 2001
 - first teleconference in November 2001
 - to date, held three teleconferences and one face-to-face meeting
 - currently seven participants, including two from FDA and one from USP
 - prepared a document listing relevant definitions
 - prepared and conducted a survey concerning mass balance and PSD determination

- *Original Hypothesis for PSD MB WG:*
 - the original hypothesis questioned the 100±15% of the Label Claim mass balance specification in the two draft CMC Guidances for OINDP
 - now the Working Group is addressing both the mass balance requirement and what is appropriate to qualify a PSD test/cascade impactor run
- *Preliminary Work Plan for PSD MB WG:*
 - assess appropriate use of the mass balance measurement
 - propose means of establishing appropriate limits based on scientific rationale and data
 - draft “*Good Impactor Practices*”, which will address “good training”, “system suitability”, “investigational tree”
- *Why This Issue Is Complicated::*
 - a PSD determination involves numerous complicated manual operations that require very specific analytical skills
 - the multiplicity of error sources means that it is not easy to assign a failed mass balance measurement to a specific cause
 - aerosols are quasi-stable, dynamic systems, complicated dosage forms
 - there is no “standard” MDI or DPI to verify performance of a cascade impactor
 - impactors themselves are difficult to calibrate
 - a mass balance determination can only be made during the same test as the PSD measurement.

The particular points discussed during the meeting included the following:

Regarding Mass Balance Issues/Problems

- the variability of the PSD mass balance depends, among many other factors, on the absolute amount of drug per dose (*e.g.*, 100 µg vs. 1000 µg), the number of actuations per determination (*e.g.*, 1 vs. 10), exact impactor used, *etc.*;
- collecting the delivered dose off the cascade impactor is associated with a larger experimental uncertainty than collecting the same dose from a DCU apparatus;
- even though the mass balance may be affected by such product problems as wrong delivered dose or settling/creaming of the formulation, other tests will detect these problems more accurately; the mass balance determination are more often failed for a number of other, non-product related problems;
- in a DCU measurement, non-product related sources of variability are minimized, compared to the mass balance measurement;

- reporting the amount of drug on deposited stages in absolute amounts (as opposed to percent of total recovery) confounds the actual particle size distribution measurement with the total delivered dose measurement;
- the numerical value of a mass balance is obtained as an arithmetical sum of the amounts of drug deposited on individual stages; the amounts on individual stages cannot be combined physically to yield the total “mass balance”, in part because different dilutions are required for different stages, and because the PSD profile information would be lost;
- in addition to random uncertainties, CI measurements are associated with systematic uncertainties (bias), so the CI variability is not symmetrical around the target;
- there is a legal meaning to the term “specification”, which is different from that of “system suitability” or “run qualification”;
- any “odd” result is investigated by the company, but conducting an OOS (out-of-specification) investigation is legally different from an OOT (out-of-trend) investigation; and
- if the Working Group adopts the concept of re-testing upon failing the mass balance limits, it will be important to delineate a well-defined protocol for such re-testing.

Regarding the Work Plan

- the Working Group should address both the appropriate limits and the appropriate use (procedure and purpose) of the mass balance measurement;
- for conducting an experiment to compare DCU and PSD variances, it would be preferable to engage an FDA laboratory;
- it would be important to address both existing impactors and the Next Generation Pharmaceutical Impactor, or NGI (archival data generation for NGI will be completed by mid-2002); and
- appropriate MB limits could be established based on data mining, including FDA data mining.

As the next steps, the Working Group agreed to the following:

- prepare a draft work plan and discuss it at the next teleconference of the Working Group.

III. NEXT TELECONFERENCE/MEETING

The next teleconference of the PSD Mass Balance Working Group is scheduled for **Thursday, 14 February at 10:00 AM (US ET)/15:00 (UK)**.

The next face-to-face meeting is scheduled for **Monday, 13 May**.

IV. ADDRESSEES

PQRI PSD Mass Balance Working Group:

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Finalized on 13 May 2002