

MINUTES OF THE TELECONFERENCE
OF THE PQRI PSD MASS BALANCE WORKING GROUP ON
MONDAY, 30 NOVEMBER 2001

I. PARTICIPANTS

Terry Tougas (Boehringer Ingelheim), Chair
Ken Furnkranz (CDER/FDA)
Martin Lavery (Aventis)
Lana Lyapustina (IPAC-RS)
Jolyon Mitchell (Trudell Medical)
Lee Nagao (IPAC-RS)
Dennis O'Connor (Boehringer Ingelheim)
Brian Rogers (CDER/FDA)
Bruce Wyka (Schering-Plough)
Kahkashan Zaidi (USP)

II. OPENING

Dr. Tougas welcomed the participants. He explained the objectives of the teleconference as follows: (i) to review background information on cascade impactor (CI) operation; (ii) to agree on objectives of the PSD Mass Balance Working Group; (iii) to identify main elements of a Work Plan; (iv) to discuss need for additional expertise; and (v) to agree on next steps. Working Group members approved the proposed agenda.

The participants approved the minutes of the previous teleconference of the PSD Mass Balance Working Group on 19 November 2001.

The Working Group Chair confirmed that all participants have received from Ms. Sylvia Gantt a document entitled "Guidance for Working Groups of PQRI", which outlines the expectations and procedures for PQRI Working Groups.

III. DISCUSSION

Background Information on CI Operation

The Working Group Chair reviewed the following questions, which were circulated to all Working Group members in preparation for the teleconference:

- How many of the Group members have actually done or observed a cascade impactor (CI) determination? Would it be useful to go through the operation to gain perspective?
- If we view Mass Balance (MB) as a potential system suitability check, should the objective be expanded to consider best approach to system suitability for CI?

- In the context of system suitability, what does the mass balance confirm relative to the determination of the particle size distribution? (*e.g.*, in HPLC a resolution criterion confirms separation, an RSD criterion confirms precision...)
- For a CI determination, when should system suitability be confirmed? Each day? Each run? or should MB and/or some other performance check be part of the calibration/qualification of an individual impactor?

Prior to the teleconference, several Working Group members provided written answers and comments via email. During the teleconference, Drs. Lavery, Mitchell, Tougas, and Wyka reiterated that they have extensive knowledge of the CI operation; Drs. Furnkranz and Zaidi explained that they have been exposed to it only to a limited degree.

To review the CI operation, the Working Group Chair had invited Mr. Dennis O'Connor to give a brief presentation. Mr. O'Connor, an expert on cascade impactors and PSD measurements, explained the following (as supplemented with comments from Drs. Mitchell, Tougas, and Wyka):

CI Description

A cascade impactor is a stainless steel device set up as a tower with several "pie" plates stacked up vertically one above the other. Each plate has holes; the hole size decreases from the upper to the lower plates. Behind each plate with holes is a solid plate, which collects the particles depositing at each stage. For dry powder aerosols, collection plates are coated with a suitable material to ensure the capture of impacted particles. For MDI aerosols, no coating is typically necessary because the formulation itself contains surfactants and other ingredients that help prevent the bouncing-off of deposited particles.

O-rings provide a seal between subsequent stages. An air flow through the entire device is established by drawing a vacuum on the lowest stage. The larger particles are captured near the top of the impactor, and the smaller particles, near the bottom.

Below the bottom plate is the backup filter capturing those particles that have not deposited in the earlier stages. Above the top stage is the inlet adaptor that allows one to connect an inhaler device to the cascade impactor. Typically, a USP inlet is used, which is a stainless steel "pipe" with a 90° bend to mimic the geometry of the human throat; other types of inlet may also be used. To the end of an inlet, a mouthpiece adaptor is attached.

PSD and MB Determination

To perform a PSD measurement, the cascade impactor has to be built from the bottom up. The outlet nipple is connected to a vacuum pump, which creates the flow of air through the impactor. The flow rate is verified to make sure it is within validated limits. An inhaler is attached to the CI's mouthpiece adaptor and actuated. The aerosol is swept into the cascade impactor and separated by aerodynamic particle size.

The CI is disassembled, starting from the top down. The inlet, stages, and filter are taken apart. The drug deposited on each collection stage, inlet and filter is extracted with appropriate solvent. The collected supernatant is analyzed by HPLC. The amounts

of drug deposited on each stage, the inlet and filter are determined. If required by the method validation, the inside walls of the cascade impactor are also extracted and the amount of drug is determined by HPLC. (The amount of drug deposited on the walls depends on the particular drug, and typically is in the 1-2% range. For certain drugs, wall losses could be greater, up to 5-10%).

Prior to use, the HPLC system is subject to its own system suitability check to ensure that the HPLC apparatus is operating properly. Each HPLC analysis may take up to 5-10 hours.

The cascade impactor is cleaned and re-built for next use. For the next PSD determination, the cycle is repeated, starting with the calibration of the flow, actuation of the drug, disassembly and subsequent analysis. Typically, only 2-5 CI determinations could be performed per day.

Drs. Mitchell, Tougas, Wyka and Mr. O'Connor commented that in practice, many variations of the above description could be encountered.

Dr. Rogers inquired how good of a seal is made between the inlet adaptor and the first plate. Mr. O'Connor responded that the seal is typically good, and that if that seal, or any other CI seal, is poor, the flow rate measurement at the beginning of a PSD run would indicate the abnormal flow rate, so that the leak could be detected and corrected prior to the PSD determination. He also added that each O-ring is inspected prior to the CI assembly, and defective or worn-out O-rings are replaced. Dr. Mitchell further clarified that the leaks at the top of a cascade impactor are less critical for the correct PSD determination than the leaks near the bottom. He also pointed out that since there is no vacuum near the top of a cascade impactor, the quality of the seal there is even less important, because the absence of a significant pressure differential near the top minimizes the possibility of leakage.

Dr. Rogers requested that the others comment on the quality of the inlet-to-CI seal if the CI were to be operated under vacuum. Drs. Mitchell and Tougas noted that cascade impactors are never used that way, but if there was a need for a tighter seal at that juncture, it could be achieved. Dr. Mitchell pointed out that the Next Generation Impactor (NGI), among other improvements over the typical CI, has an improved inlet seal. Dr. Rogers asked Dr. Mitchell and others to speculate on how the seal might be improved between the inlet adapter and the body of the Andersen Cascade Impactor. Dr. Mitchell reiterated that this concern is not encountered in practice; however, to offer advice on the posed hypothetical situation, he suggested use of a silicone-type sealant, or teflon tape; however he stressed that extra caution should be exercised when resorting to such auxiliary sealants, so as to make sure that the sealing material does not get in the flow of particles and does not interfere with the proper particle size separation, as documented in method validation.

Dr. Tougas suggested that Dr. Rogers contact the experts of the Working Group off-line to discuss his question about the sealing of an Andersen CI inlet port, and that the Working Group return to the agreed agenda for the present teleconference.

Dr. Mitchell concluded the above discussion by saying that PSD mass balance by itself is not a good indicator of the particle size distribution because of potential leakage problems. Depending on the exact location of the leak, the total mass balance may or may not be related to the quality of the particle size distribution.

Role of Mass Balance

The participants turned to the discussion of the Working Group's objectives and a Work Plan, and considered the following first questions posed in the agenda:

What is appropriate use of PSD mass balance, product specification or system suitability (or other)? Does the decision "Specification vs. System Suitability" require additional research?

All industry participants agreed that the appropriate use of the mass balance is as a system suitability test, because invalid mass balance indicates problems with the testing system (improper CI setup, or leakage, or errors in extracting the drug from the plates, or spills in transferring the extracted drug solutions to the HPLC, etc.).

Dr. Rogers replied that the answer to the above questions depends on what is called "system suitability". He stated that the cascade impactor should not be disassembled between the mass balance and the PSD determination. The Working Group members strongly supported the recommendation that the CI be NOT disassembled or otherwise disturbed between the mass balance and the PSD determination, and stressed that for the mass balance to have any relevance, both measurements ought to be determined from the same PSD run.

Another issue that Dr. Rogers described as a reason for using mass balance as a specification rather than the system suitability check is that mass balance is less sensitive to problems than PSD acceptance criteria. For example, a mass balance determination will not necessarily detect leakage in the CI seals, since any leaks will be of air entering the device, and no drug substance will be lost from the CI into the laboratory, except through analyst error during the CI determination or HPLC. However, other participants argued that precisely because mass balance is less sensitive to the quality of the particle size distribution, it should NOT be used as a product specification.

Dr. Rogers clarified that in his opinion, the mass balance determination is necessary to assure that the actuations from the tested inhaler provided the expected mass into the CI and thus the PSD determination is representative of the formulation. One participant mentioned that there have been published studies demonstrating that the PSD determination is not necessarily linked to the total mass balance.

Dr. Zaidi asked that Dr. Rogers provide a clarification on the Agency's thinking in regard to mass balance. Dr. Rogers replied that according to his understanding and instructions he received, his function as a Working Group member is to provide scientifically sound opinions and not to provide interpretations of the Agency policy. He also commented that he did not have any input in the draft CMC Guidances containing the mass balance requirement.

Dr. Rogers repeated that he believes the mass balance specification is necessary to ensure that the inhaler delivers the correct dose. The other participants remarked that a cascade impactor is not equipped to test for delivered dose uniformity, and that delivered dose is properly controlled by a separate test specifically designed for that purpose.

Dr. Rogers further explained that in his view, the mass balance specification is necessary to detect settling or creaming of a suspension formulation. According to Dr. Rogers, settling or creaming of a suspension formulation may cause the mass of drug substance deposited on the critical stages of a CI to be within specifications when the actual formulation sampled in the metering chamber (owing to creaming or settling) is not representative of the bulk formulation.

Dr. Rogers repeated that it is required that the mass emitted into the CI be representative of the bulk formulation, and in his view the mass balance in conjunction with the particle size distribution is the only way to establish this relationship. Drs. Wyka, Tougas and other participants replied that the effect of settling or creaming is studied during development, leading to instructions for appropriate shaking of the product prior to use; and that a suspension formulation would be shaken and re-suspended prior to a PSD test. They further noted that if abnormal settling or creaming is a problem, it would be more readily detected by other tests, such as dose uniformity. They also pointed out that the acceptance criteria for the particle size distribution are more sensitive to an incorrect dose than the overall mass balance.

Working Group members suggested that for clarity, Dr. Rogers present all possible reasons in writing and forward them to the Working Group for discussion. However, Dr. Rogers explained that he had been instructed not to get involved in the Working Group's discussions but to participate only as an observer, except when scientifically unsound opinions or data were being considered. Other participants remarked however, that PQRI was designed as a forum where all parties, including FDA, can have scientific and technical discussions as equal partners on matters related to the Agency's Guidances. They also commented that since the primary objective of the Working Group is to provide recommendations on the mass balance requirement in the current draft Guidances, it is impossible to even start addressing this topic without a clear understanding of the Agency's reasons for such a requirement.

Dr. Rogers replied that he will discuss this issue internally with his superior and may provide clarifications to the Working Group at the next teleconference.

IV. AGREED ACTIONS

- The next teleconference will be held on Tuesday, 18 December, at 10:00 AM EST.

V. NEXT TELECONFERENCE/MEETINGS

The next teleconference of the PSD Mass Balance Working Group is scheduled for **Tuesday, 18 December at 10:00 AM (US EST)/15:00 GMT.**

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

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PQRI
PSD MASS BALANCE WORKING GROUP

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Jeffrey Blumenstein (Pfizer)
Robert Dana (PDA)
Shawn Dressman (USP)
Devinder Gill (FDA)
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Waseem Malick (Hoffman-LaRoche)
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Finalized and approved on 30 January 2002