



Product Quality Research Institute

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Ms. Helen Winkle, Director  
Office of Pharmaceutical Sciences  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Dear Ms. Winkle:

The Product Quality Research Institute (PQRI) is pleased to submit for FDA's consideration the attached text related to Cascade Impactor Mass Balance which represents the culmination of the PQRI Mass Balance Working Group's efforts over nearly a five year period. This submission constitutes one of the final deliverables of the Working Group and is offered for the Agency's consideration and proposed inclusion in the appropriate draft guidances for industry.

The PQRI Mass Balance Working Group was established in 2001 to address a specification included in two FDA Draft CMC Guidances for Industry; one for metered dose inhalers and dry powder inhalers; and one for nasal spray and inhalation solution, suspension and spray drug products issued by the Agency in 1998 and 1999, respectively. The specification recommended fixed limits on the total amount of drug recovered from the stages and accessories of the cascade impactor (CI) - so called "mass balance" (MB) - when the drug product was tested for aerodynamic particle size distribution using a CI. Previous public comments regarding this specification had indicated that an MB measured by a CI strongly depends on factors not related to product quality, such as the skill and flawless performance of the human analyst, the exact condition of the CI and associated equipment during the test, environmental parameters, and so on. For these reason, it was argued, the MB should not be treated as a product specification, especially not with the pre-set narrow limits stated in the Draft Guidances.

The PQRI MB Working Group, which included participants from the Agency, industry, USP and academia, had planned to investigate this issue through data and literature surveys and scientific reasoning. Over the course of the first two years, some of its planned deliverables were completed, including a paper on "good cascade impactor practices" and "mass balance failure investigation tree", published in a peer-reviewed scientific journal (see

references below). Other deliverables, however, could not be accomplished for reasons beyond the Working Group's control. For example, collection of relevant data was stalled due to (1) the requirement by some members of the group that such data refer to marketed products; and (2) concerns over potential proprietary and regulatory implications of compiling data on marketed products.

Nevertheless, the Working Group agreed, by the end of 2004, to develop recommendations for appropriate use of MB based on statistical simulations. After several months of discussion, a possible method for treating MB was developed in early 2005; however the Working Group encountered an impasse when some of its FDA members withdrew themselves from the PQRI process. At the direction of the DPTC and Steering Committee (SC), the Working Group reconvened in late 2005 in order to present its two emerged positions to the DPTC and to consider potential ways forward. Based on that meeting, it was agreed, with the DPTC and SC approval, that the respective representatives of the Working Group would publish their technical positions in peer-reviewed journals in order to document the developed views and to allow further discussion of the MB issue by the broader scientific community. In addition, it was agreed that those members of the Working Group who continued their participation would propose specific language for potential inclusion in pertinent FDA guidances.

The attached text represents such language being proposed to the Agency on behalf of the current Mass Balance Working Group for potential inclusion in an appropriate FDA guidance or guidances, in line with the Quality-by-Design paradigm. This text has been approved both by the DPTC (from the technical perspective) and by the Steering Committee (from the strategic perspective). This submission completes the Mass Balance Working Group's deliverables to the Agency.

We look forward to FDA's response to this submission and welcome any questions or clarifications which may assist you in your review. Please do not hesitate to contact me (203-798-5701) if I may assist you further in this regard.

Respectfully submitted,



Gordon Hansen  
Chair, PQRI Steering Committee

cc: Bruce Wyka, Chair, Mass Balance Working Group  
Terry Tougas, Chair, Drug Product Technical Committee

#### REFERENCES:

FDA. 1998. Draft guidance: Metered dose inhaler (MDI) and dry powder inhaler (DPI) drug products chemistry, manufacturing and controls documentation. Docket 98D-0997.

FDA 1999. Draft Guidance: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products Chemistry, Manufacturing, and Controls Documentation. Docket No. 99D-1454.

PQRI MB WG Work Plan. 2002. Establishment of the Appropriate Use of the Particle Size Distribution Mass Balance Determined by Cascade Impactor for Orally Inhaled and Nasal Drug Products (<http://www.pqri.org/commworking/minutes/pdfs/dptc/psdmbwg/workplan02.pdf>).

Christopher, D., P. Curry, B. Doub, K. Furnkranz, M. Lavery, K. Lin, S. Lyapustina, J. Mitchell, B. Rogers, H. Strickland, T. Tougas, Y. Tsong, and B. Wyka. 2003. Considerations for the development and practice of cascade impaction testing including a mass balance failure investigation tree. *J. Aerosol Med.* 16:235-247.

J. Mitchell. 2003. Regarding the Development and Practice of Cascade Impaction Testing, Including a Mass Balance Failure Investigation Tree. . *J. Aerosol Med.* Vol. 16, No. 4: 433-433.

1 PQRI PSD Mass Balance Working Group  
2 Final Dated 11 May 2006

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4 Mass Balance Proposal for FDA Guidance Document  
5

6 The total mass of drug recovered from all stages and accessories of an impactor  
7 is useful in assessing the validity of an aerodynamic particle size distribution  
8 (APSD) determination. For this assessment, the result for the recovered mass  
9 can be expressed on a per actuation basis as either a percent of the claimed  
10 delivery which represents the target delivered dose (DD) from the mouthpiece or  
11 as a percent of the target APSD mass recovery (henceforth referred to as mass  
12 balance). The target APSD mass balance can be distinct from the claimed  
13 delivery to compensate for differences between the APSD and DD  
14 methodologies, e.g., non-recovery of stage wall losses in the APSD  
15 determination, the number of actuations used, an analytical bias, etc. The mass  
16 balance results should be consistent with the expected range of DD results for  
17 the product, taking into account the number of actuations used for the APSD  
18 determination relative to the DD determinations and the demonstrated  
19 differences in the method variability, if any. These factors are useful in  
20 establishing a typical range for the APSD mass balance that can be used when  
21 assessing the results for a test. The determination of the mass balance is not  
22 considered as a test of the inhaler in itself. Due to the nature and complexity of  
23 APSD determinations via cascade impaction testing, and the likelihood of  
24 analytical or instrument error, the test should be repeated when an APSD mass  
25 balance result falls outside the expected range.