Air Flow Meters Used at Testing of Inhalation Products – An Inter-Laboratory Comparison

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Summary

The aim of this inter-laboratory study, conducted by the European Pharmaceutical Aerosol Group (EPAG) Impactor sub-team, was to assess quantitatively the difference in the measurement of air flow between the various flow meters used for inhaler testing at several pharmaceutical companies. The study was organised as a round-robin in which one flow meter ('master') was sent around to ten different laboratories. At each laboratory, air flow was set to 20, 28.3, 40, 60 and 80 l/min (in triplicate) using the 'master' flow meter, whereby it was exchanged with the company laboratory flow meter and the air flow determined. It was found that the difference between the 'master' and a company flow meter at any of the five different flow rates was less than 2%. It can therefore be concluded that flow meters used are well suited for its purpose and 2% accuracy can be claimed.

Introduction

Air flow meters are used to set the volumetric flow rate when testing of pharmaceutical inhalation products [1, 2]. There are well established methods available in the pharmacopoeias that indicate how to use flow meters when testing inhalation products. Air flow rate is a critical experimental parameter when determining delivered dose as well as the fine particle dose when using impactors such as the Next Generation Pharmaceutical Impactor (NGI) or the Andersen 8-stage cascade impactor (ACI). Even though pharmacopoeias are very precise on which test equipment to use in these tests, including how to use them, the type of flow meter is not precisely defined and different companies use different types of flow meters. Furthermore, calibration of flow meters should be done in a GxP environment with instruments traceable to national standards. This means that there is a chance of differences between the flow rate setting both for inter-inhaler and intra-inhaler tests and between the different tests of inhalation products tested at various laboratories.

Company flow meter types vary in respect of type and brand. Furthermore, calibration is not standardized and is typically undertaken externally at a certified institute using national standards. Even then, one previous study involving a broad range of flow meters within one company indicated that as much as a 5% difference may exist between different flow meters used by that organization [3].

Given this background, a systematic study concerning flow meter calibration and associated measurement variance was conducted by the Impactor sub-team of the European Pharmaceutical Aerosol Group (EPAG). The aim of this study was to assess the difference between the various flow meters used at several pharmaceutical companies quantitatively.

Materials and methods

The study was organised as a round-robin in which one flow meter ('master') was sent around to ten different laboratories. These companies were located in five different European countries and Canada. At each laboratory, the air flow rate was set to nominal values of 20, 28.3, 40, 60 and 80 l/min (in triplicate) using the master, following which it was exchanged with the laboratory flow meter. The magnitude of the difference between the 'master' set air flow and the laboratory flow meter was then determined.

The experimental arrangement used is shown schematically in Figure 1. The set-up used was similar to that provided in the pharmacopoeias for dry powder inhaler testing, with the regulating valve set to provide critical flow. A TPK box (Copley Scientific, UK) was used to regulate the air flow through the system. The 'master' flow meter, the TPK box and tubing were supplied by EPAG and were sent as a standard set as round-robin equipment. Each company supplied its flow meter to be tested and the vacuum pump. At each test, atmospheric pressure, relative humidity (RH) and temperature were documented. The company flow meter reading as well as the three pressures from the TPK box were documented at each nominal flow setting.

The prime outcome of each measurement was the difference between master set flow rate and corresponding laboratory flow meter reading.

Before and after the round robin study, the master flow meter was sent for calibration at a certified institute in the UK (ASAP Calibration Services Ltd., Romsey, Hampshire, UK).

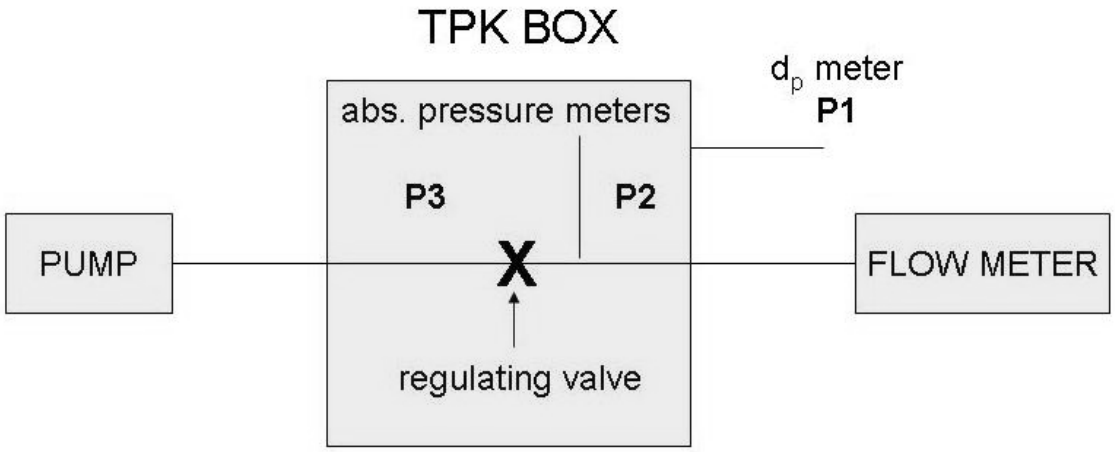

Figure 1. Schematic of the measurement system used by each company participating in the study with flow moving from right to left.

Results and Discussion

As a first validation step, the measured pressures P2 and P3 were checked and found to be both repeatable within each company and relatively similar between companies (the differential pressure, P1, was not required to be measured for this study). Furthermore, values of atmospheric pressure, temperature and relative humidity were found to be very similar in all tests, so that it was deemed that there was no need for further evaluation of these data (that would have been used to make corrections, if large deviations had been observed).

As the second validation step, the measurements of the 'master' flow meter by the certified institute confirmed that this flow meter had provided equivalent measurements for the duration of the study.

Key results from each laboratory (identified by number (#)) are summarized in Figure 2.

Comparison of measured flow as a percentage of the flow rate obtained by the 'master' flow meter is reported for five different flow rates. Importantly, since intra-measurement variability was found to be always less than 1%, this information was therefore excluded for the sake of clarity.

A small (≤ 2% deviation) was evident between company flow meter compared with the 'master' flow meter irrespective of nominal flow rate, except for laboratory #10, where the deviation at 20 l/min was close to 4%. As almost all of the observed deviations compared to the master flow meter are small, no clear trends could be discerned. It is noticeable that the relative deviation was often the same at all flow rates for one laboratory, indicative of a constant difference that might perhaps be attributed to the calibration accuracy of each flow meter.

A relatively small difference between the flow meters was seen, despite the inclusion of a broad range of flow meter types and the inclusion of laboratories located in many different countries. The small difference between the various flow meters including the master flow meter is indicative that the accuracy of flow rate setting for impactor measurements is good.

The study outcome also supports the finding that on the whole the measurement of flow rate across the industry for the various flow meters available is within good control.

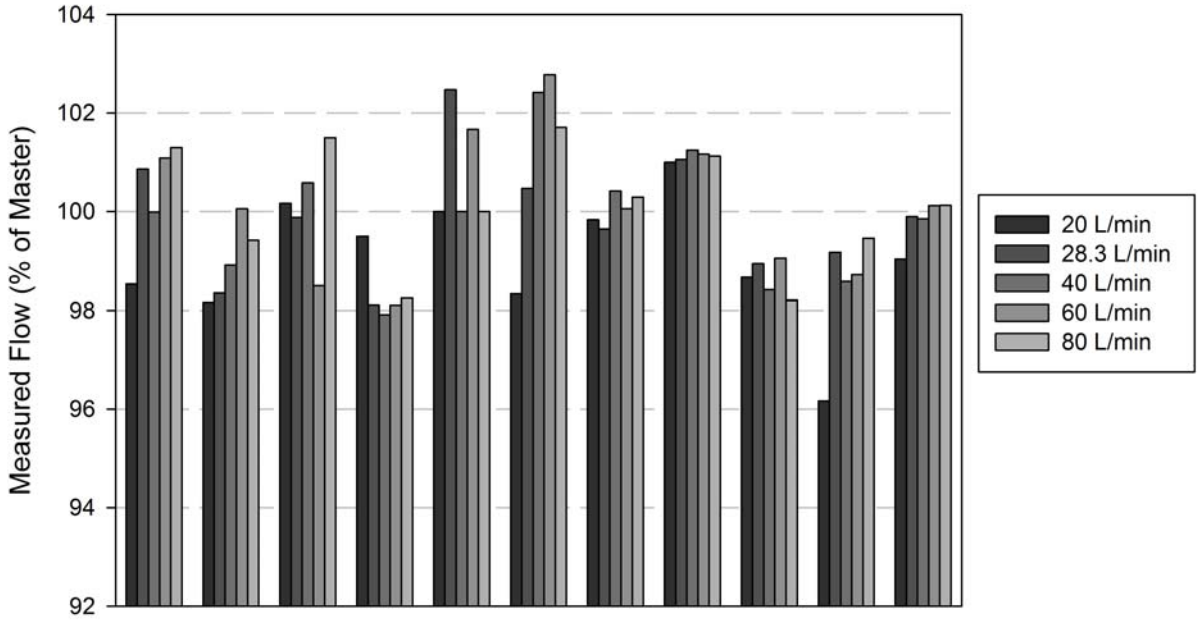

Figure 2. Mean Air Flow Rate Measured as Percentage of Set 'Master' Flow Rate for Each of the Ten Participating Laboratories at Different flow rates from 20 to 80 L/min.

The investigation also revealed some other useful information. In particular, during initial testing at two laboratories, unexpectedly large differences in flow compared to the master flow meter were reported. These deviations were subsequently investigated to establish cause. One deviation was attributed to a mistake in way the company flow meter had been tested in the round robin study. However, the second instance was slightly more complex in that the organization concerned did not apply the necessary correction factors for use in this application. This finding is of particular importance to remind users of these instruments not to accept the flow meter reading blindly, but to ensure that all proper procedures are followed both internally and also by external CROs and calibration services, when using and calibrating flow meters.

Conclusion

This inter-laboratory study has shown that if flow meters are used and calibrated correctly, flow setting between 20 and 80 L/min in the laboratory is accurate to within 2% of the reference value.

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References

1. European Pharmacopeia; Section 2.9.18 – Preparations for inhalation: aerodynamic assessment of fine particles. *European Pharmacopeia*: 5th Edn., Council of Europe, 67075 Strasbourg, France, 2005;2799-2811.
2. United States Pharmacopeial Convention; *USP 30-NF 25*; Chapter 601 – Physical tests and determinations: Aerosols. United States Pharmacopeia, Rockville, MD, USA., 2007; 220-240.
3. Wiktorsson, B and Asking, L,. Comparison between flow meters used to set flows in pharmaceutical inhaler testing. *Drug Delivery to the Lungs-XIII*, The Aerosol Society, London, UK, 2002:205-208.