Specialized Trial Know-How

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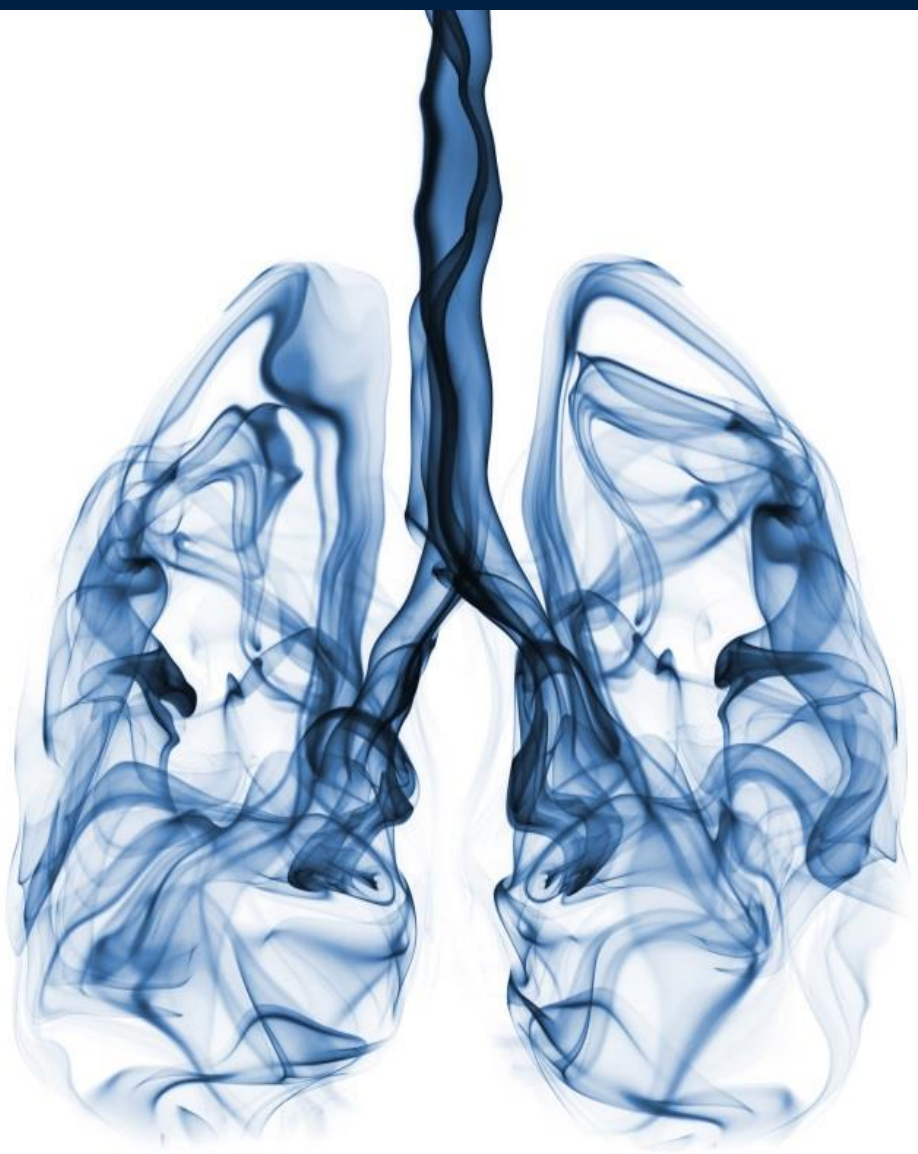
*Flow-Profile Measurements and Flow-Profile Studies | Technical and Subject Related Aspects*



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# Flow-Profile Measurements and Flow-Profile Studies | Technical and Subject Related Aspects

*by Simon Prentner, Dipl.-Ing. (FH)*

## Reasons for Flow Profile Studies

*The measurement of inhalation flow profiles of subjects inhaling through dry powder inhalers (DPIs) has been coming more and more into focus lately and is, for instance, currently requested by the EMA and FDA as part of the in-vivo device characterization process [1, 2, 3]. In order to thoroughly understand the technical and device specific aspects during inhalation, a comparison of flow profile measurements is considered necessary.*

*Please refer to [4] for detailed information about the requirements regarding inspiratory flow rates in clinical investigations, demands made by EU and FDA guidelines, the regulatory environment, statistical considerations and the results and benefits to be gained from such investigations.*

### *Flow-Profile Measurement and Evaluation System*

Based on the company's professional experience, Inamed has developed its own flow-profile measurement system. The main design feature of this system is to provide an inhalation situation that is as close as possible to real life for the subject, without influencing the device handling and inhaler properties.

The Inamed flow-profile measurement and evaluation system consists of a differential pressure transmitter linked to special measurement software installed on a laptop. This mobile unit permits on-site recording of flow profiles in a quick and uncomplicated manner.

The software used was developed and validated by Inamed according to ISPE GAMP®5 [5] guidelines regarding e.g. user specific requirements, risk analysis, validation plan, validation documentation and validation report. Hardware will be installed following the processes of design qualification, installation qualification and operation qualification (DQ, IQ, and OQ) for every flow-profile study individually and kept *frozen* during the respective study period.

## *Calculation of Inhalation Flow vs. Differential Pressure Ratio*

For several inhalation cycles, a flow/volume simulator generates a specific flow profile through a modified inhaler while mass flow rate and pressure drop are measured simultaneously. The acquired data result in a mean flow rate vs. differential pressure correlation curve and are stored within the software application for later flow-profile measurements off-site [Figure 1].

The entire procedure of measurement and analysis (evaluation) of flow profiles is detailed in several project specific Work Instructions prior to commencing the study.

With this set-up, measurements of a wide range of DPIs, including triggered devices, are possible.

In addition, with this method, the pressure drop, which is also a parameter proposed to be evaluated according to EMA guidelines, is part of the source data.

Alternatives to differential pressure measuring systems are e.g.:

- Water-gauge systems
- Windmill-type systems
- Temperature-gradient systems [TSI Mass Flowmeter]
- Acoustic systems [7]

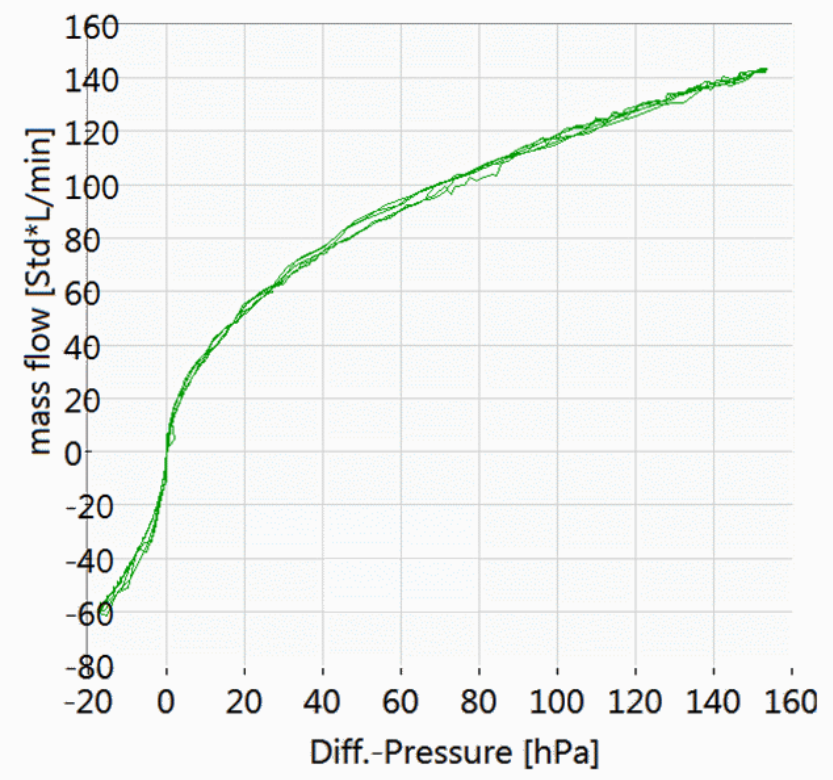


**Figure 1:** Data of several inhalations for correlation curve before building process

## *Inamed's Standardized Procedure*

By employing well-trained personnel in combination with the above mentioned measurement system, it is possible to evaluate the conduct of each inhalation maneuver immediately [Figure 2].

Criteria for *technically correct* inhalation maneuvers are the standard ones (such as 'no coughing during inhalation' or 'correct placement of mouthpiece') and specific ones as defined by the manufacturer/sponsor (such as 'inhalation performed as specified in the instructions for use').

> ***"Every single inhalation maneuver of every single subject is recorded, documented and evaluated in detail."***

Flow-profile measurements are recorded after the subject - patient or healthy volunteer - has been trained for the task. In between of every inhalation maneuver, sufficient time to recover is given to the subject. Recording will be completed when the required number of technically correct inhalations has been made.

Afterwards, all recordings will be checked by a second person for completeness and correctness and then released for evaluation (*technically evaluable*).

Instructions on how to proceed if, for example, the required number of evaluable flow-profile recordings has not been reached have to be defined in the investigational plan/study protocol.

Every single inhalation maneuver of every single subject is recorded, documented and evaluated in detail.

The obligatory parameter *peak inspiratory flow rate* (PIF) is often chosen as primary endpoint.

Various other parameters can serve as secondary endpoints, such as (total) inhaled volume, mean flow rate, time to reach PIF and/or inhalation time.

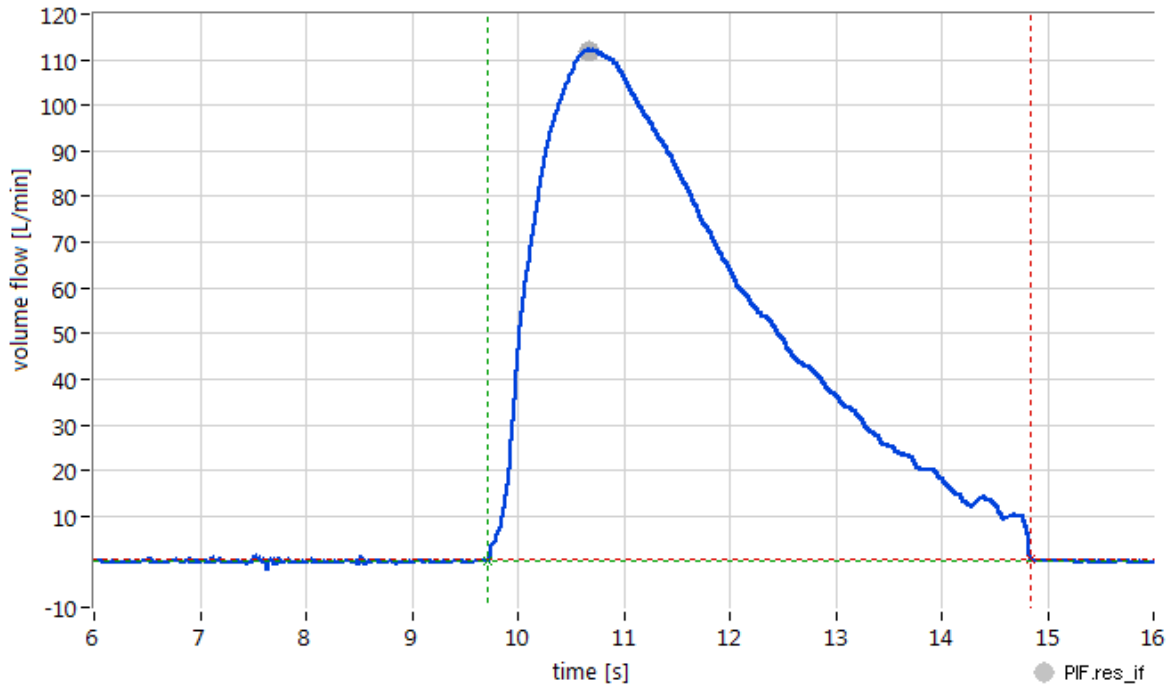


**Figure 2:** Inhalation curve of a tested DPI with volume flow versus time

## Points to be considered

Many details regarding the recording and evaluation of flow profiles have to be considered and defined prior to any measurement. Most importantly, technical aspects, the extent of training as well as the possibilities of evaluation of the flow profiles recorded have to be taken into account.

### *Technical Aspects*

It has to be decided which procedures to use to define the start and end points of any given inhalation. In the first place a quick and simple solution might be to determine the last zero value before and the first zero value after the PIF. More complex approaches consider for example a certain threshold, extrapolation or mean increase rate [Figure 3] as basis of calculation. Each procedure comes with its advantages and disadvantages and thereby possible influences on the results.

A minimum scanning rate has to be defined. For devices with trigger point a higher scanning rate is recommended. Inamed's long-standing experience shows that scanning rates between 5 and 20 ms seem to be good benchmark values.

In cases of an intra-device variation above 5%, the generation of individual correlation curves is advisable.

> ***"Each procedure comes with its advantages and disadvantages and thereby possible influences on the results."***

Some devices are used in combination with capsules enclosing the medication which have to be pierced before inhalation. Using the device with capsules will increase the flow resistance and inhalation time. Also the mass flow will fluctuate with a high signal-to-noise ratio because of rattling. Thus, in these cases, it is recommended to first conduct a feasibility study in order to collect data and to decide which study design is the most reasonable.

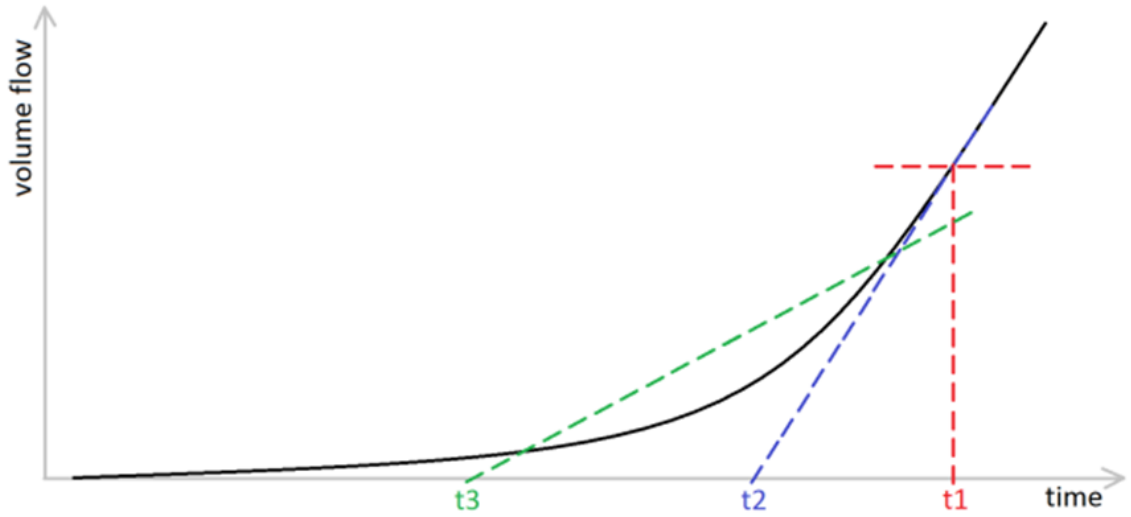


**Figure 3:** Start point options

## *Inhalation Maneuver Training*

Regarding the question of reproducibility, the limits of acceptable variability in inhalation maneuvers should be defined prior to study initiation.

On this issue, it needs to be taken into account that the ranges of variation likely differ between trained and untrained subjects, between healthy volunteers and patients and also depend on the type and severity of disease and the number of inhalations performed.

Therefore, a set of clear criteria should be defined for every inhalation to decide whether an inhalation has been performed correctly or not and to avoid the impression of cherry picking.

A proper inhalation should have an inhalation volume above 500 mL, an inhalation time longer than 1 second and a mean acceleration rate (start point to PIF) of more than 0.7 $L/s^2$ [6].

For ethical reasons, the training session and the measurements recorded should not exceed a predefined number of proper inhalations. In most cases three inhalations provide a good balance between a sufficient collection of statistical relevant data and a limited exertion of subjects. In addition, a reasonable rest period of at least 1 minute between every inhalation should be given to avoid exhaustion and to minimize variability.

Whenever possible, it is advisable that the training procedure and the actual recording of a flow-profile are as similar as possible and that a subject may not easily differentiate between them.

The intensity of assistance given is also crucial. When the assessment of handling, usability and user satisfaction is included as an additional parameter in a flow-profile study, training on a basic level as indicated in the instruction for use or based on a video prepared by the sponsor might be the best choice in order to come close to a real life situation. However, with this type of study it has to be kept in mind that the number of subjects to be recruited in order to obtain the required number of evaluable subjects might be higher because of non-evaluable data.

On the other hand, an intense training in an optimized and subject-oriented manner might be required when the inhalation procedure becomes more complicated (e.g. with triggered devices or unusual inhalation positions). Data gained by such a study design is most likely less variable but tends to be “optimized”.

## *Results and Benefits from Flow-Profile Studies*

The outcome of flow-profile studies typically demonstrates whether a wide variety of subjects of different ages presenting with airway obstructions of different nature and severity can operate the test DPI properly. Also it evidences the required minimal inhalation flow rate to ensure reliable device function (trigger release or actuation) and efficacious drug delivery to the lungs.

Similarities in flow rates indicate comparability, independently of the severity of pulmonary disease. The average inhaled volume measured demonstrates whether a sufficient lung deposition can be assumed.

***“Flow-profile studies come with several issues, are undefined in many details and need scientific advice.”***

Flow-profile studies come with several issues, are undefined in many details and need scientific advice. Therefore, it is essential to predefine important parameters and limits of the study in a comprehensible, clear and foresighted manner. Depending on fixed specifications, such as device type or target group the study design must be adapted.

## References


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## About the Author

Simon Prentner finished his studies of Microsystem Technology with focus on Biotechnology in the year 2008. After a scientific career in the field of research and development at a well-known institute, he joined the Inamed In-Vitro team in 2012.

Since then he has been the responsible Technical Service Manager for all inhalation flow profile studies regarding system development (including validation and qualification according to ISPE GAMP), quality control under GCP conditions and the associate partner for the Clinical Unit. Thus, he is Inamed's expert for inhalation flow profile studies and the contact person for sponsors and auditors.

## About Inamed

For nearly two decades now, Inamed has been supporting various companies in their pharmaceutical and medical device development activities by providing excellent CRO services. Inamed offers flexible, reliable, high-quality clinical research services, which cover mono-center and multicenter clinical trials with medicinal products from Phase I to Phase IV and clinical investigations with medical devices. Study conduct, data management, statistical and medical evaluation of study data as well as medical writing services complete Inamed's CRO services.

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