

IMPROVEMENTS IN CLINICAL DEVELOPMENT PROGRAMS BY DOSE ESTIMATION IN RESPIRATORY CLINICAL TRIALS

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Introduction

Success rates for marketing authorization of new drugs in clinical development are estimated at 16 % overall. Many factors influence the probability of success, but correct dosage is one of the most important influences. Dose optimization is an important approach to streamlining costs and timelines, while improving safety.

Inamed Research proposes solutions to optimize the design of clinical trials and focuses here on respiratory clinical trials.

Results

Intrabronchial dose can vary from 25 mg to 110 mg causing wide variability in outcomes (Fig. 1).

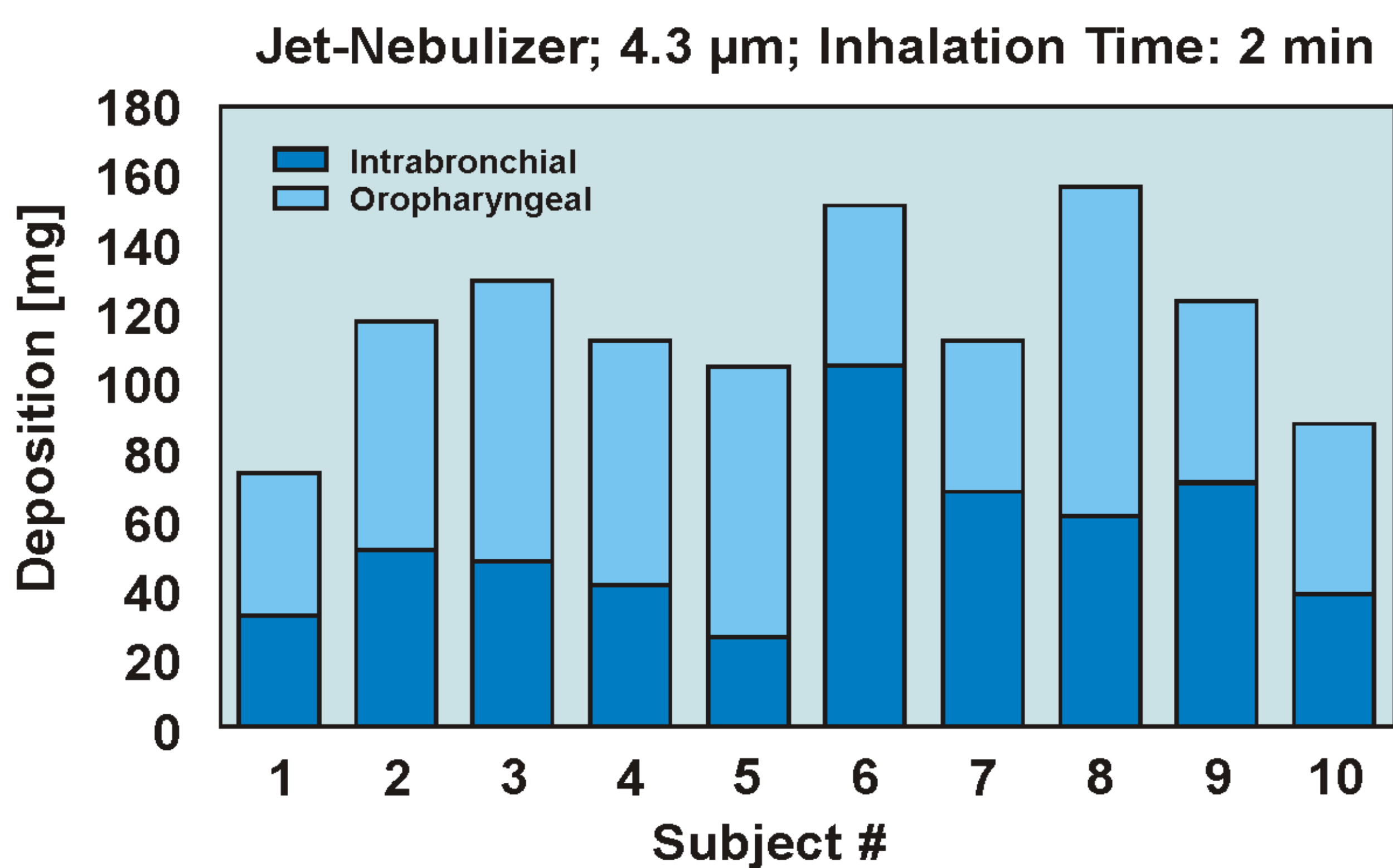


Figure 1; Radioactive measurement of intra-bronchial deposition by use of a Jet-Nebulizer. Dose varies widely between 25 mg (Subject #5) and 110 mg (Subject #6).

Source: D. Köhler et. al.

Is the lack of a “positive signal” actually related to an inadequate dose delivery? Are adverse events related to the study medication or to unexpected overdosing? Knowledge of intra-individual dosing into the lungs and/or reduced variability is essential in clinical trials with inhaled drugs.

Dose estimation in clinical trials can be achieved by two different methods:

- ◆ Reduction of variability by use of a controlled inhalation with a special inhalation device (see Fig. 2)
- ◆ Registration of the inhalation profile (flow and volume) and subsequent deposition calculation (see Fig. 3)

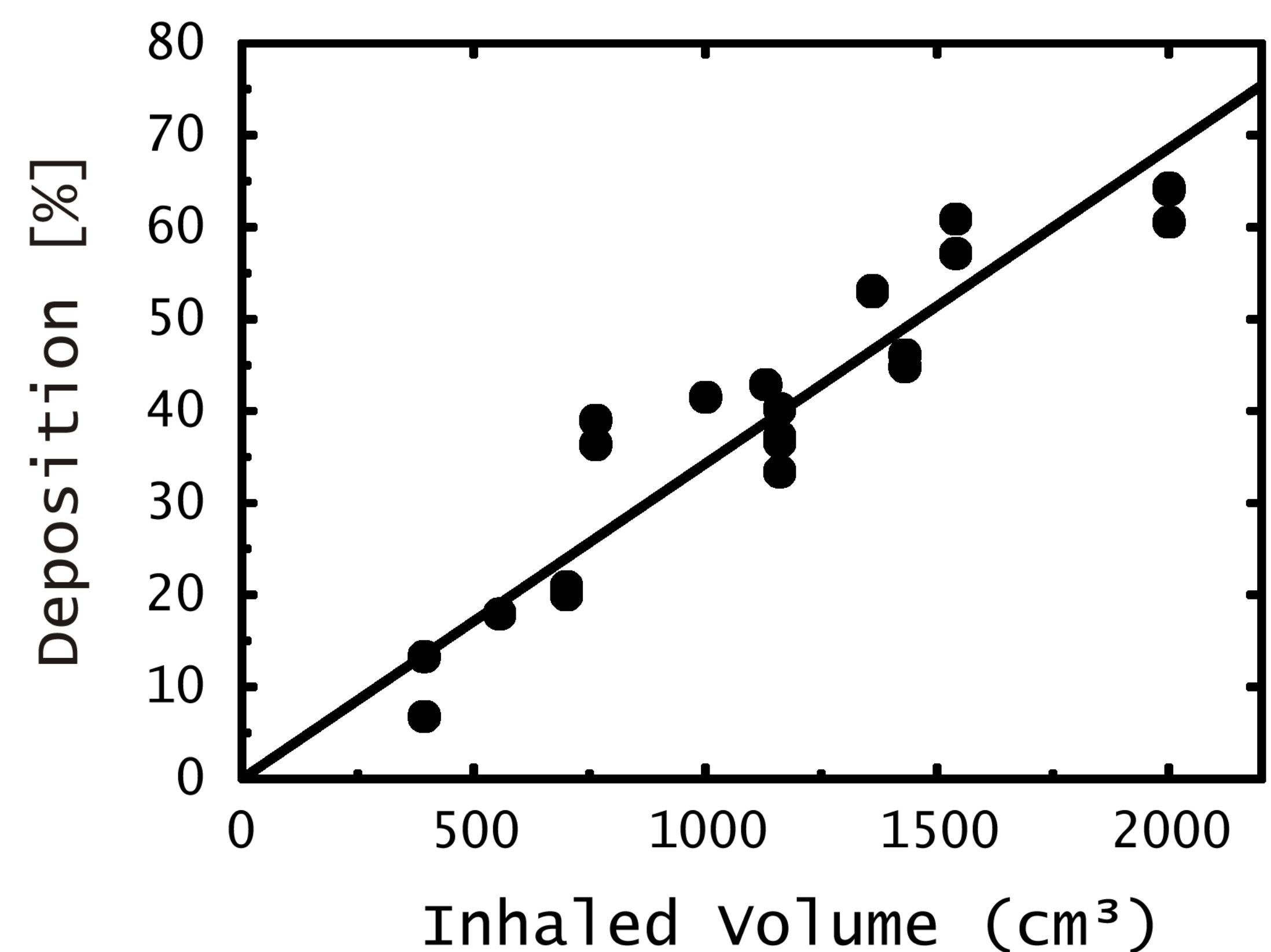


Figure 3; Function of lung deposition in healthy subjects versus inhaled volume. Inhalation technique determines % deposition, i.e. dosage delivered

Source: P. Brand et. al.: Total Deposition of Therapeutic Particle During Spontaneous and Controlled Inhalations; Journal of Pharmaceutical Sciences, Vol. 89, 724 -731 (2000).

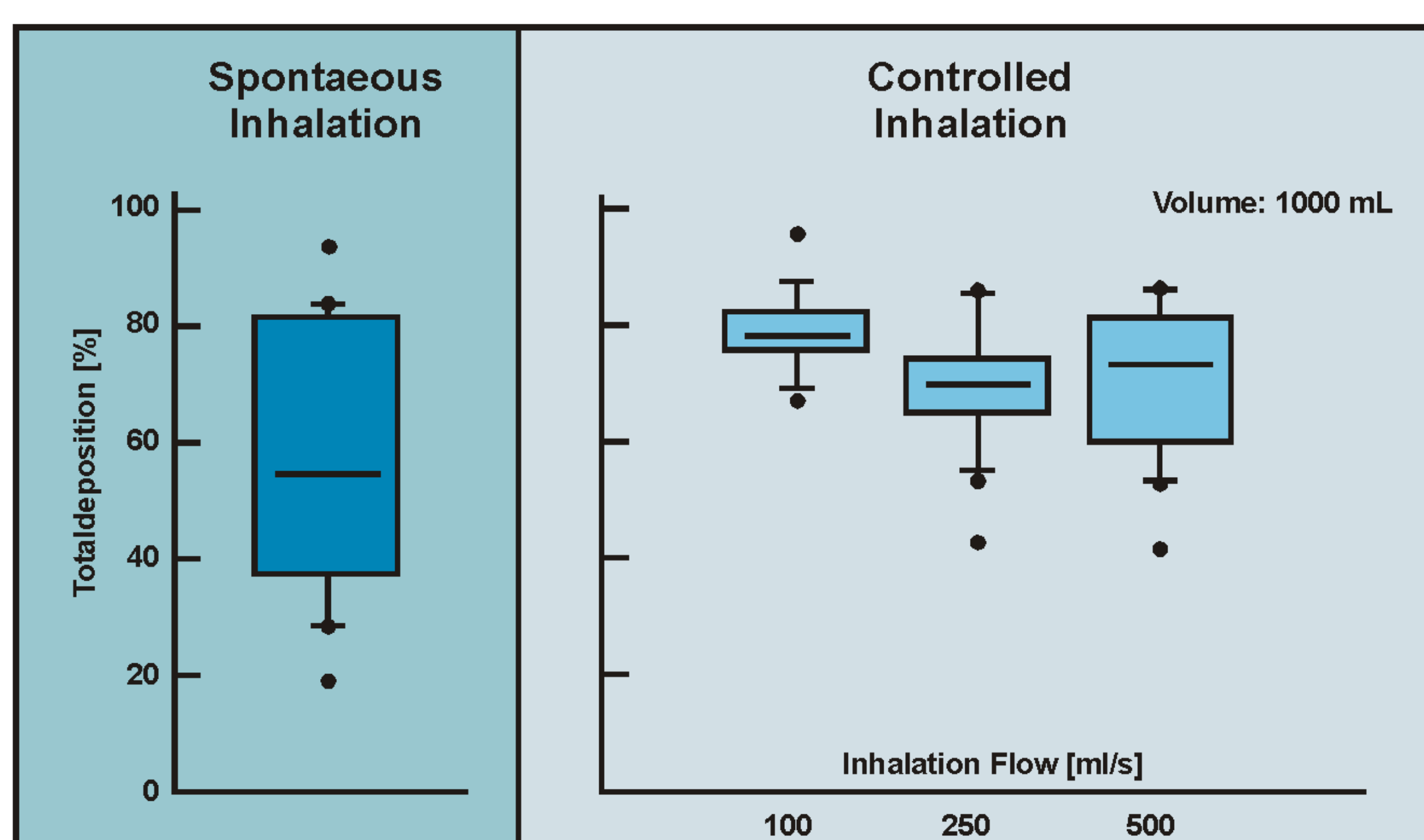
Methods

Inamed has developed a good inhalation approach for use in clinical trials to optimize inhalation. Reduction of variability is the basis for effective inhalation trials with reduced number of subjects, and therefore reduction in time and cost.

Inamed has developed an innovative and validated method for estimating deposited dose. We have tested this algorithm for deposition calculation by comparison to the main results of one of our clinical trials to illustrate its utility. This method is optimal for clinical trials with commercial inhalation devices like MDIs or DPIs.

Conclusions

Compared to other routes of administration for drugs (e.g. oral, iv) the inhalation of drugs has numerous advantages. However, in clinical trials variability of inhaled dosing leads to an increase in the number of required subjects to show the same effects as in other routes of administration. Optimization of dosing and knowledge of individual deposition into the lungs of the subjects is a valid method to achieve better results.



18 Patients; Different lung diseases; Particle size 3 µm (MMAD) [Brand, P. et. al. J Pharm Sci 6/2000]

Figure 2; Spontaneous inhalation pattern shows high variability in total deposition. Variability is significantly reduced by use of a controlled and slow inhalation.