# Correlation between patient Handling Errors and *in vitro* Performance of Spiriva® Handihaler®

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## Introduction

Unlike the well-established oral route, assessing the link between *in vitro* parameters and *in vivo* action for orally inhaled and nasal products (OINDPs) can represent a major challenge. Lack of treatment adherence, incorrect breathing techniques and use of inhalers by patients, and variation in inhaler performance leads to some patients failing to reach the sufficient inhalation flow or volume that allows them to receive the needed dose from the Dry Powder Inhaler (DPI).

Several studies exist in which the prevalence of human error for each type of inhaler and each category are described.[1,2] However, the impact of these errors on the dose delivered to the patient remains unclear. Adapted *in vitro* measurements may help to better understand the importance and interactions between human handling errors and dose delivered to the lungs by the device.

## Methods

| Test parameter | Reproduced errors | *In vitro* parameters |
|---|---|---|
| 1 | Forcefully and deeply inhale through the device | Inhalation flows: 10 – 20 – 30 – 60 – 100 L/min<br>Inhalation volume: 2 and 4L |
| 2 | Not closing the device correctly | Device remains open during actuation |
| 3 | Double-piercing | Capsule pierced twice before actuation |
| 4 | Shake prior to use | Device shaken (up and down) before and after capsule piercing |
| 5 | Maintain the piercing button | Not releasing the piercing button during actuation |
| 6 | Incorrect inhaler position | DUSA positioned vertically (90° and -90°) during actuation |

## Conclusion

Our results shows the potential impact of patient nonadherence to the handling instructions presented in DPI leaflets. Although proper breathing techniques are important to achieve accurate and reproducible delivered dose, failure to meet specific items on the DPI handling checklist can lead to a drastic decrease in the device performance. A thorough *in vitro* simulation of handling errors might help patients and prescriber's understanding of the critical handling error to avoid when using their inhaler, improving handling technique, and ultimately impacting the chances of successfull outcome of the treatment.

**Failure to close the DPI until 'click' is heard** — **45%** of patients

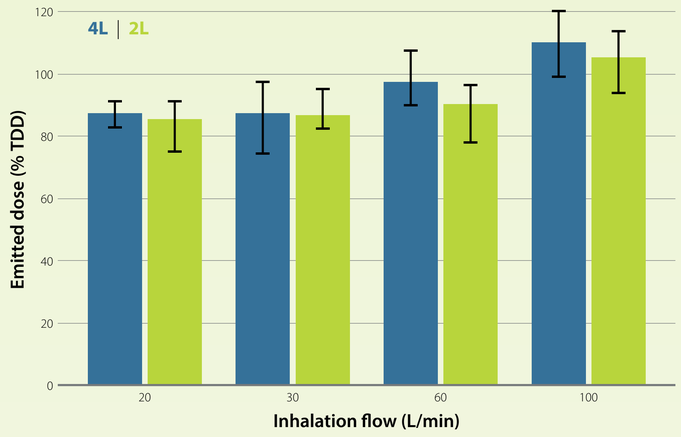
**Incorrect DPI position** — **44%** of patients

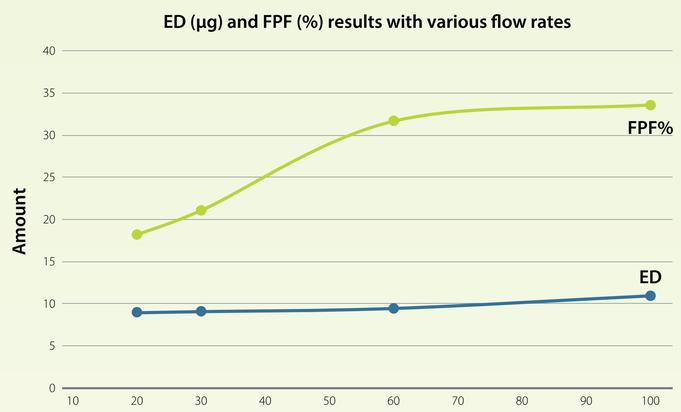
up to **85%** loss of emitted dose

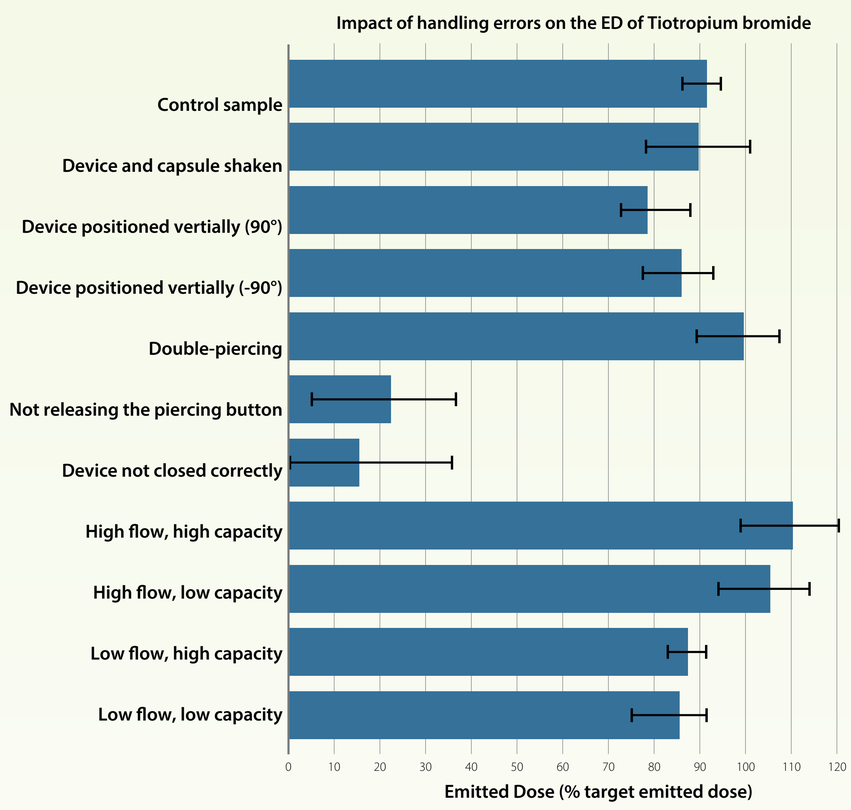
## Results and discussion

Insufficient inhalation effort is one of the main causes of patient's handling error, with up to 72% of Handihaler user not inhaling slowly and deeply enough to make the capsule vibrate.[3] In our study, the performance of the delivery system of DPIs is illustrated by the strong and stable dose delivered by the device, with at least 80% of the target delivered dose being emitted by the device when critical flow is achieved, for both 2 L and 4 L of air, highlighting the performance of the delivery system of DPIs when the lung capacity meets the device's requirements. Additional tests performed at 10 L/min have shown a dramatic fall of the DPI performance (<0.4 µg ED, data not shown), underlining the critical need to monitor seriously ill patients and children inhalation strength when using DPIs.

Interestingly, the increase of FPD results over the flow rate range does not correlate with the increased ED results, as FPD results are increased by 84% between the lowest and highest flow rates, compared to an increase of 23% of the ED over the same flow rate range. As the FPD results represent the amount of active pharmaceutical ingredient (API) contained in particles <5 µm and deposited into the lower respiratory tract, this further highlight the importance for the prescriber to assign appropriate devices adapted to the patient's pulmonary capacities.

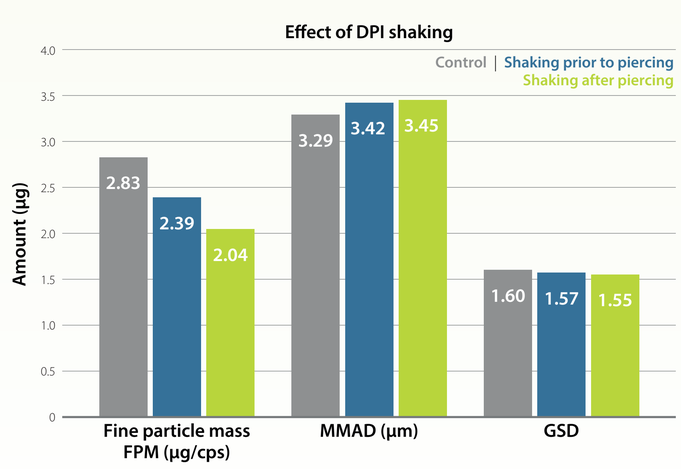



Among the different handling errors that were reproduced, 'Not releasing the pressed piercing button' and 'Device not closed correctly' are the ones that have shown a significant impact on the delivered dose. While these handling error can represent up to 45% and 44% of patients respectively[1] (25% and 12% respectively, for Handihaler[3]), the ED of these two handling errors was reduced from 91.5% of the TDD to 22.4% ($p<0.01$) and 15.5% ($p<0.01$) of the TDD, respectively. This represents a drastic decrease which can negatively impact the efficiency of the patient's treatment. The ED obtained from an upright (90°) position of the DUSA also shows 10% ($p=0.01$) decrease in the emitted dose, while the shaking of the device before use (5 "up and down" movements) and downward (-90°) actuations did not yield significantly different results than the control sample ($p>0.05$).

While the ED results between the control sample and the shaken device experiment were comparable, the effect of the capsule being shaken shows significant decrease in the amount of fine particles below 5 µm observed after a single "up and down" movement, potentially highlighting the role played by electrostatics in the performance of DPIs and the importance of patient compliance to device's instruction, in order to reach the adequate amount of fine particle dose delivered to the lungs in a reproducible manner and to maximize the chances of a successful outcome of the treatment.




**References**

**1** Lavorini F., Magnan A., Dubus J-C., Voshaar T., Corbetta L., Broeders M., Dekhuijzen R. Effect of incorrect use of dry powder inhalers on management of patients with asthma and COPD, Respiratory Medicine 2008, 102, (4), 593-604.

**2** Fröhlich, E. Biological Obstacles for Identifying *In Vitro-In Vivo* Correlations of Orally Inhaled Formulations. Pharmaceutics 2019, 11 (7), 316.

**3** Van Der Palen J, Eijsvogel MM, Kuipers BF, Schipper M, Vermue NA. Comparison of the Diskus inhaler and the Handihaler regarding preference and ease of use. J Aerosol Med. 2007 Spring;20(1):38-44.