Development challenges for hybrid applications of DPIs. Could IVIVC tools predict *in vivo* conditions? A case study with Elpenhaler® device.

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Introduction

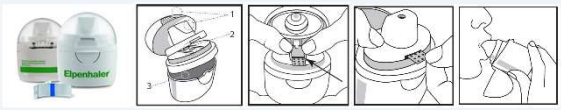
It is a common practice to combine various techniques in the effort to predict the clinical outcome of OIDPs. An official regulatory framework is not yet available, but efforts are made to unscramble the fate of the drugs in the respiratory tract. Prediction can be more risky when it comes to comparison of inhalers with different geometries and aerodynamic performance.

Aim

The development and comparison of DPI products are challenged with the use of two different versions of Elpenhaler devices that have entirely different principle of use from the reference product (blisters vs capsules). The challenge was the prediction of clinical similarity of these products by combining *in vitro* methodologies with computational models.

Materials and Methods

EH devices used for the specific studies were designed by Elpen Pharm.Co.Inc. and are part of the Elpenhaler® platform (Figure 1).



◄ Figure 1
EH description and brief IFU: (1) Mouthpiece and cap; (2) Drug supporting surface); (3) Storage case which houses the blister strips. The individual doses are packed in blister strips and the blister strip is attached on the supporting surface. The mouthpiece closes and the patient pulls away horizontally the embossed and protruding end of the strip to be detached. The dose is now ready to be inhaled. The patient breathes in from the mouth, according to the instructions.

A formulation of Tiotropium bromide (TIO) mixture with lactose monohydrate was used. Two EH devices, EHD1 and EHD2, EHD1 having higher turbulent kinetic energy than EHD2, and.Spiriva Handihaler (Boehringer Ingelheim) (HH) were studied. Devices' resistance (R): both EHs 0.056 √kPa min/L; HH 0.051 √kPa min/L, indicating that this minor difference will not have an impact to the PIF.

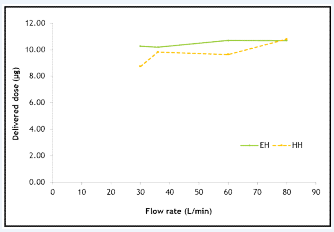
Next Generation Impactor (NGI) and Dose Uniformity Sampling Apparatus were used for the determination of the aerodynamic particle distribution (APSD) and the delivered dose (DD). The fractions collected were analysed by HPLC. **APSD, was determined by ELPEN at flow rates 30, 36, 60, 80 L/min using the USP IT and by Emmace Consulting AB at 46 L/min and 56 L/min, using oropharyngeal consortium mouth-throats (OPC-MT) of small (S), medium (M) and large (L) size**. The selection of the two latter flow rates was based on the equation: **PIFR50=1.82/R+21**, where PIFR50 (L/min) can be calculated for trained healthy volunteers (HV) from the device R [1]. PIFR50 for HH and EH is 57 and 53 L/min, corresponding to pressure drops of 8.4 kPa and 9.1 kPa, respectively. Hence **strong flow (56 L/min) should result in lung dose (LD) ratios best corresponding to anticipated flows in PK study on HV, whereas medium flow (46 L/min) may correspond better to a patient population. Simulations were run at PIFRs corresponding to the experimental NGI and lung dose (LD) flows on Mimetikos Preludium v1.1.7.**

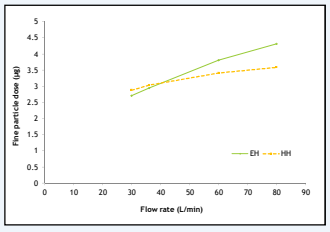
Bioequivalence (BE) studies to compare TIO delivered by EH and HH:
- **BE1:** An open label, 3-treatment, 3-period, 6-sequence, crossover, block randomized, single dose comparative bioavailability study, under fasting condition in 15 healthy, adult male and female subjects.
- **BE2:** An open label, 2-treatment, 2-period, 2-sequence, crossover, block randomized, single dose comparative BE study on 80 healthy male and female subjects, under fasting condition.
- **BE3:** An open label, 2-treatment, 2-stage, 2-period, 2-sequence, crossover, block randomized, single dose-comparative bioavailability study on 42 heathy male and female subjects, under fasting condition (24 HV were enrolled at the first study stage and 18 were enrolled at the second study stage).
- Washout period:14 days
- No charcoal
- Analytical method: HPLC-MS/MS.
- PK parameters: AUC_{0-72}, C_{max}, T_{max}, $t_{1/2}$ and K_{el}.

▼ Table 1
PK parameters and some demographic data of the 3 BE studies.

	BE1	BE2	BE3
EH device used	EHD1	EHD2	EHD1
Number of subjects analysed	14	80	39
Av. BMI (kg/m^2) and range	24.1 (18.6-29.8)	26.6 (18.9-29.9)	25.0 (20.5-29.8)
Av. Age (years)	29.8	45.1	39.0
FEV_1 (%)	85-125	86-117	85-127

Results





In vitro profiles of both EH devices, obtained with the USP throat, were similar and their average showed similarity within 25% of the HH, in the whole flow rate range (Figure 2).
It appeared that EH had slightly higher FPD values than HH at higher airflows and higher DD values at 30 and 60 L/min.

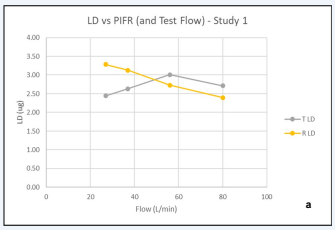
◄ Figure 2
Fine particle dose (FPD) and Delivered dose (DD) of TIO, as delivered in the NGI with a USP throat and DUSA respectively, from EH (average from both devices EHD1 and EHD2) and HH inhalers.

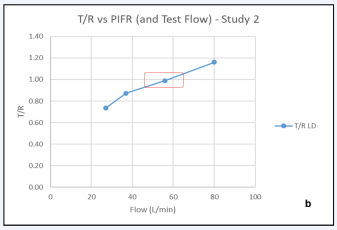
▼ Table 2
Experimental results for LD of EH and HH, using OPC-MT at medium M (46 L/min) and strong S (56 L/min) inhalation profiles.

	Test EHD1						Reference HH					
Inhalation profile	M	M	M	S	S	S	M	M	M	S	S	S
Throat	S	M	L	S	M	L	S	M	L	S	M	L
Mean LD (SD) (µg)	2.79 (0.33)	3.23 (0.32)	3.60 (0.56)	2.21 (0.40)	3.03 (0.63)	4.76 (0.28)	1.38 (0.21)	2.64 (0.54)	3.63 (0.33)	1.23 (0.29)	2.57 (0.26)	3.46 (0.66)
T/R (µg)	2.0	1.2	1.0	1.8	1.2	1.4	-	-	-	-	-	-
	Test EHD2						Reference HH					
Mean LD (SD) (µg)	2.54 (0.10)	3.29 (0.60)	4.07 (0.75)	2.31 (0.49)	3.94 (0.34)	4.79 (0.39)	1.29 (0.20)	2.72 (0.38)	3.83 (0.40)	1.36 (0.13)	3.14 (0.45)	3.85 (0.51)
T/R (µg)	2.0	1.2	1.1	1.7	1.2	1.2	-	-	-	-	-	-

The determination of the APSD with the use of anatomical throats (Table 2), revealed that LD from all inhalers increases as casts increase in size, indicating that subject anatomical characteristics will result in clinical variability. With M and L casts, the test to reference ratio (T/R) should be within 1 to 1.4, whereas with S casts T/R should be 1.7-2.0.
Results between EHD1 and EHD2 did not differ significantly.

The experimental *in vitro* results indicated *in vivo* similarity or superiority to the reference product.





Simulations of lung dose (LD) at PIFR at the various flow rates, using both EHD1 and EHD2, suggested that the flow dependency was not identical for HH and EH (Figure 3a), indicating that T/R ratios would vary depending on the actual inhalation effort. In an *in vivo* study with flows at 50-60 L/min, T/R ratio would be expected to result in a value close to 1 (Figure 3b).
The permissible flow range predicted to result in successful BE (assuming same PIFR for both products) is indicated by the red box (45-70 L/min).

◄ Figure 3
a) Simulated LD deposition of EH and HH versus PIFR and b) T/R ratio versus PIFR.

▼ Table 3
Test to Reference ratios (T/R), as calculated from the BE studies for TIO products EH and HH.

	BE1	BE2	BE3
EH device	EHD1	EHD2	EHD1
Cmax T/R	1.03 (0.85-1.24)	0.83 (0.77-0.89)	0.96 (0.87-1.05)
AUC_{0-72} T/R	1.15 (0.93-1.41)	0.89 (0.85-0.93)	1.02 (0.95-1.09)

Based on the actual *in vivo* results from the BE studies (Table 3), the T/R ratios observed were lower (in particular with EHD2) or similar to the predicted. This difference from the estimated values could be associated to variabilities of the body mass index (BMI) and physiology of the subjects or to the actual inhalation effort. For this latter case, it can be commented that the mean PIFR measured out of a total of 210 COPD patients (stages II-IV) was 60±11 L/min (34-95 L/min), indicating that the lowest PIFR value (in stage IV) was superior to the minimum PIFR required (30 L/min) for effective drug administration [2]. Hence, it can be observed that the predicted PIFR range for a successful BE is relevant to the patient population.

Conclusions

In vitro results were indicative of the clinical outcome in some cases, still the parameters affecting the outcome could not be totally predicted. Usually, the distribution in the lungs is overestimated, as the *in vivo* mouth-throat deposition is higher. By using anatomic models and patient simulated flow rates, a more accurate prediction can be made. The LD deposition pattern in correlation to the inhalation flow regime and the anatomical differences can be estimated.

Nevertheless, the biggest uncertainty remains the actual users and all their associated individualities. To this end, very good knowledge of the inhalers performance, adequate user training and very close monitoring of the clinical study could increase the probability of a successful result.

Acknowledgments

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References

[1] Delvadia R, Wei X, Longest W, Venitz J, Byron P: In *Vitro Tests for Aerosol Deposition. IV: Simulating Variations in Human Breath Profiles for Realistic DPI Testing*. J Aerosol Med Pulm Drug Deliv 2016;29(2):pp196-206.
[2] Zervas E, Petrocheilou K, Tsopa P, Evangeliou M N, Athanassiou A: *Peak inspiratory flow evaluation in different stages' COPD patients using In-Check method (INSPIRE STUDY)*. Presented at: *ERS International Congress, London*, UK, September 3-7, 2016; Eur Respir J. DOI: 10.1183/13993003.congress-2016.pa3962.