

Ventolin Diskus and Inspyrl Turbuhaler: An *In Vitro* Comparison

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ABSTRACT

Dose delivery (total emitted dose, or TED) from dry powder inhalers (DPIs), pulmonary deposition, and the biological effects depend on drug formulation and device and patient characteristics. The aim of this study was to measure, *in vitro*, the relationship between parameters of inhalation profiles recorded from patients, the TED and fine particle mass (FPM) of Diskus and Turbuhaler inhalers. Inhalation profiles (IPs) of 25 patients, a representative sample of a wide range of 1500 IPs generated by 10 stable asthmatics, 3 × 16 (mild/moderate/severe) COPD patients and 15 hospitalized patients with an exacerbation asthma or COPD, were selected for each device. These 25 IPs were input IPs for the Electronic Lung (a computer-driven inhalation simulator) to determine particle size distribution from Ventolin Diskus and Inspyrl Turbuhaler. The TED and FPM of Diskus and FPM of Turbuhaler were affected by the peak inspiratory flow (PIF) and not by slope of the pressure-time curve, inhaled volume and inhalation time. This flow-dependency was more marked at lower flows (PIF < 40 L/min). Both the TED and FPM of Diskus were significantly higher as compared to those of the Turbuhaler [mean (SD) TED_{diskus} (%label claim) 83.5 (13.9) vs. TED_{turbuhaler} (72.5 (11.1) ($p = 0.004$), FPM_{diskus} (%label claim) 36.8 (9.8) vs FPM_{turbuhaler} (28.7 (7.7) ($p < 0.05$)]. The TED and FPM of Diskus and FPM of Turbuhaler were affected by PIF, the flow-dependency being greater at PIF values below 40 L/min. Lower PIFs occurred more often when using Turbuhaler than Diskus, since Turbuhaler have a higher resistivity, requires substantially higher pressure in order to generate the same flow as Diskus. TED, dose consistency and the FPM were higher for Diskus as compared to Turbuhaler. The flow dependency of TED and FPM was substantially influenced by inhalation profiles when not only profiles of the usual outpatient population were included but also the real outliers from exacerbated patients.

Key words: dry powder inhaler, diskus, turbuhaler, electronic lung, fine particle mass

INTRODUCTION

THE EFFICACY of inhaled drugs to the lungs includes three steps: dose delivery from the inhaler (total emitted dose, or TED) that results in

a certain dose to patient, pulmonary deposition of the TED, and the biological effects of the dose.¹

The TED and aerosolisation of drugs delivered by dry powder inhalers (DPIs) depend on its formulation, device characteristics (e.g., resistance to

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airflow, or resistivity), airway characteristics and patient's inhalation technique.² The inspiratory effort generates a negative pressure drop in the mouth. The mouth-pressure versus time curve was defined as the inhalation profile (IP). When the resistivity is known, the pressure profile can be converted into a flow profile.³ Peak inspiratory flow (PIF),⁴ slope of pressure versus time,^{5,6} inhaled volume (Vi),^{1,7} and inhalation time (Ti)⁸ are variables of the inhalation profile which may influence the TED.

Conventionally, the *in vitro* methods testing the TED and the fine particle mass (FPM) (the amount of drugs in the respirable range, 0.5–5 μm^9) are based on impaction on the Cascade Impactor tested at *constant flows*. These measurements played an important role in the development and optimisation of inhalation devices. The relationship between *in vitro* and *in vivo* is still unclear. Most of the particle-size systems operate at constant and fixed flows (30, 60 and 90 L/min) typically from a pump, which do not mimic the actual patients' IP.

In the present study, two multidose dry powder inhalers (DPI) were compared *in vitro*; the Inspyrit Turbuhaler® (AstraZeneca, Sweden) contains 100 doses of 100 μg salbutamol (spherical pellets) stored in a reservoir dosing unit, and the Ventolin Diskus® (or Accuhaler®, GlaxoSmithKline, UK), which contains 60 individually sealed metered doses of 200 μg salbutamol plus a lactose carrier.

A selection of typical "real life" inhalation profiles of patients with asthma and COPD with a wide range of bronchial obstruction was imported in a computer-driven inhalation simulator, the Electronic Lung (GlaxoSmithKline Research and Development Ware, UK).¹⁰ The purpose of this study was to measure the effects of the inhalation profile variables on the TED and FPM. Furthermore, differences of TED and FPM between the two devices were also assessed.

MATERIALS AND METHODS

Study design

In two previous studies, inhalation profiles were recorded with the Inhalation Profile Recorder^{11,12} (GSK R&D Dept., Ware UK). In 10 stable asthma patients and three groups (mild, moderate and severe) of 16 COPD patients, 18 in-

halation profiles were recorded for each device during six sessions over 10 weeks. Also, 15 hospitalized patients participated in a randomized study of inhalation profiles through placebo devices.¹³ For each device, triplicate inhalation profiles were recorded during day 1–9 of admission and in stable phase.

Twenty-five inhalation profiles with a wide range of characteristics were selected for Diskus and twenty-five inhalation profiles were selected for Turbuhaler from the total of 3000 profiles collected in these studies and were the input for the Electronic Lung^{10,14} (GlaxoSmithKline R&D Dept., Ware UK), which enabled us to measure TED and the FPM.

Materials used

The study included the use of Ventolin Diskus inhaler, 200 μg /dose (GlaxoSmithKline, UK) and the Inspyrit Turbuhaler inhaler, 100 μg /dose (AstraZeneca, Sweden).

Inhalation profile

The inhalation profiles (pressure vs time) were recorded by a pressure transducer: the inhalation profile recorder¹¹ (GSK R&D Dept., Ware UK). The transducer measured pressures in the mouth-piece during the inhalation through a placebo Diskus and Turbuhaler. The variables of the inhalation profile recorder are pressure slope [Slope] (kPa/sec), peak pressure drop [PPD] (kPa), time to peak pressure drop: the time between the onset of the inhalation and the moment of reaching the PPD [Tp] (sec) (the start of the measuring time is the moment that the pressure passes the 0.2-kPa threshold), peak inspiratory flow [PIF] (L/min), inhaled volume [Vi] (L) and inhalation time [Ti] (sec). The relationship between PIF and PPD was calculated³ by $\text{PPD} = \text{PIF} \times R$, where R is the resistivity of the device [$R_{\text{diskus}} = 0.02133 \text{ (kPa)}^{0.5}(\text{L/min})^{-1}$ and $R_{\text{turbuhaler}} = 0.03223 \text{ (kPa)}^{0.5}(\text{L/min})^{-1}$].¹⁵

Electronic lung

The Electronic Lung is a computer-driven inhalation simulator^{14,16} (Fig. 1). *In vivo* IPS of patients were replicated. Next the mass and particle size distributions of drug delivered from a Ventolin Diskus and Turbuhaler were determined. The powder was drawn from the device into the metal sampling chamber by a computer-

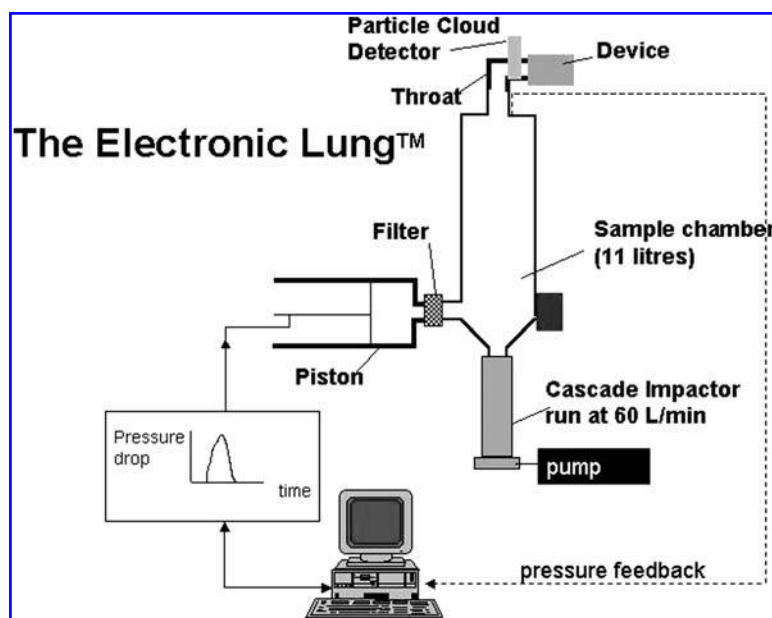


FIG. 1. The Electronic Lung.

driven piston, programmed by the IP. Then, the powder was extracted from the chamber by a second pump that was switched on after completion of the inhalation through an Anderson Cascade Impactor (Graseby Anderson Ltd, Orpington, UK) operating at 60 L/min. This was repeated 10 times to obtain a sufficient amount of drug for analyzing. The total emitted dose (TED) was the sum of the amounts of drug in the throat inlet, sampling chamber, and Cascade Impactor. The cumulative dose of the sampling chamber, throat, and the preseparator of the Cascade Impactor was labeled as coarse particle mass (CPM, $> 4.0 \mu\text{m}$). The accumulated amount of drug on stages 1–5 of the Cascade Impactor represented the fine particle mass (FPM, $0.76\text{--}4.0 \mu\text{m}$), whereas the particles on stages 6 and 7 plus the filter were termed very fine particle mass (VFPM, $< 0.76 \mu\text{m}$).

The throat, sampling chamber, preseparator, and all stages were washed out with a suitable solvent. The TED, CPM, FPM, and VFPM were determined by high-performance liquid chromatography (HPLC).

Statistical analysis

SPSS for windows version 9.0 was used for calculating means of the inhalation parameters. Data were expressed as mean \pm SD. A p value of < 0.05 was considered significant.

To select the inhalation profiles which had to be a representation of the range of the different profiles generated in the study, it was assumed that the profiles were adequately described by PIF, slope, V_i , and T_i . These parameters were plotted in a four dimensional hypercube design. Four center inhalation profiles were selected to give a representation of the middle range. Points were taken as extreme if they were below the 25th percentile or above the 75th percentile. As far as possible the 16 combinations of the four factors: PIF; slope; V_i and T_i (each at two levels) were used to select the inhalation profiles that correspond to these design points. For each device five extra plots in the lowest peak flow range were selected. These selection of inhalation profiles gave the widest span of the data (not only of the usual outpatient population, but also outliers from the extremes of disease severity during exacerbation).

Regression models were fitted (using JMP statistical software) for TED, FPM as percentage of label claim and FPM as percentage of TED with the natural logarithm of PIF as an explanatory variable. Device differences were also investigated, as was the effect of TED on FPM.

RESULTS

A total of 1500 inhalation profiles through each device was recorded from asthmatics and

COPD patients. For both Diskus and Turbuhaler, inhalation profiles of 25 patients were run with the Electronic Lung. The demographics of the patients from whom the selected inhalation profiles were taken, are shown in Table 1.

Inhalation profile variables

The mean inhalation profile variables are shown in Table 2. The PIF values of the Diskus were significantly higher as compared to Turbuhaler (mean [SD]: 100.1 [30.8] vs. 69.2 [19.3] L/min [$p < 0.001$]). The inhalation time of Turbuhaler was significantly longer as compared to Diskus (mean [SD] 3.3 [1.3] vs. 2.5 [1.1] sec [$p = 0.03$]).

Effect of inhalation profile variables on total emitted dose

Table 3 shows the Electronic Lung results (TED and FPM) for both devices.

Initially, the effect of PIF was assessed, since this is believed to be the most likely variable to influence the Electronic Lung results.

Figure 2 shows the relationship between TED and PIF. No significant correlation between PIF and TED was found for the Turbuhaler. Overall, the TED for Diskus was significantly higher than for Turbuhaler, but over a small increase in TED for Diskus, there appeared to be a slight flow dependency.

Effect of inhalation profile variables on fine particle mass

Figure 3 shows the FPM (percentage of label claim), plotted against PIF (L/min). There is a strong relationship between FPM and PIF, with FPM increasing as PIF increases. The rate of increase, however, appears to be greater when PIF is low.

Univariate regression models were fitted for TED as percentage of label claim, FPM as percentage of label claim, and FPM as percentage of TED with the Ln(PIF) as an explanatory variable.

Total emitted dose as percentage of label claim

$$\text{TED}_{\text{diskus}} = -54.6 + 30.4 \times \ln(\text{PIF}) \quad p = 3.14\text{E-}07 \quad r^2 = 0.57$$

$$\text{TED}_{\text{turbuhaler}} = 54.9 + 4.2 \times \ln(\text{PIF}) \quad p = 0.41 \quad r^2 = 0.57$$

Fine particle mass as percentage of label claim

Ln(PIF) and TED both had statistically significant effects on FPM (percentage label claim). There was no additional contribution of the device type once these effects were accounted for.

$$\text{FPM} = -49.4 + 0.32 \text{ TED} + 13.1 \ln(\text{PIF}) \quad p < 0.0001 \quad r^2 = 0.88$$

TABLE 1. PATIENT CHARACTERISTICS

Parameter	Diskus		Turbuhaler	
	Mean (SD)	Range	Mean (SD)	Range
Gender (M/F)	17/8		14/11	
Age (years)	66 (9.2)	34–75	66 (10.0)	38–75
FEV ₁ %pr (%)	63 (22.1)	24–106	66 (26.7)	16–105
FEV ₁ (L)	1.7 (0.7)	0.7–3.3	1.7 (0.8)	0.5–3.3
FEV ₁ /VC (%)	49 (12.9)	25–71	50 (16.6)	22–82
Reversibility (%)	8 (6.6)	2–30	6 (4.0)	0–17
Smoking: non/ex/current	7/13/5		3/17/5	
Device				
DPI	18		18	
pMDI	9		9	
pMDI + spacer	1		4	
nebulizer	1		0	

FEV₁ % pr, forced expiratory volume in 1 sec as percentage of predicted; FEV₁, forced expiratory volume in 1 sec; FEV₁/VC, FEV₁/vital capacity; reversibility, bronchodilator response of FEV₁ (%) related to the predicted value; device, device used by the patients in daily life.

TABLE 2. INHALATION PROFILE VARIABLES

Mean (SD) [range]	Diskus	Turbuhaler
PIF (L/min)	100.1 (30.8) [23.3–140.1]*	69.2 (19.3) [22.1–98.8]
Slope (kPa/sec)	13.2 (8.0) [1.0–38.2]	13.7 (9.0) [0.9–32.8]
Vi (L)	2.9 (1.1) [1.0–5.3]	2.8 (1.4) [1.0–6.1]
Ti (sec)	2.5 (1.1) [1.0–5.0]	3.3 (1.3) [1.1–5.8]*

Mean inhalation profile variable: PIF, peak inspiratory flow; Vi, inhaled volume; Ti, inhalation Time. * $p < 0.05$ differences between Diskus and Turbuhaler.

The effect of omitting the lowest PIF from the analysis

Recalculations of the fit without the lowest flows (PIF_{diskus} 23 L/min and PIF_{turbuhaler} 22 L/min) were performed.

TED _{diskus} (% label claim) = $-3.6 + 19.5 \times \ln(\text{PIF})$	$p = 0.002$	$r^2 = 0.51$
TED _{turbuhaler} (% label claim) = $123.4 - 11.8 \times \ln(\text{PIF})$	$p = 0.045$	$r^2 = 0.51$
FPM (% label claim) = $-48.6 + 0.32 \text{ TED} + 12.8 \times \ln(\text{PIF})$	$p < 0.0001$	$r^2 = 0.80$

The r-squared values for each of the two regression models are not significantly different, and there is no evidence that the model parameters change when the low flow data are omitted.

The residuals from these models have been plotted against the other inhalation profile variables (slope, Vi, and Ti). There was no indication for any other significant relationships.

Differences between the two devices

The Total Emitted Dose was significantly higher and marginally more variable overall for

Diskus than for Turbuhaler (83.5 [13.9] vs. 72.5 [11.1]% label claim, $p = 0.004$). There did not appear to be an effect due to device type at comparable inspiratory flows. The Turbuhaler having a higher resistivity, required substantially higher pressure, in order to generate the same flow at Diskus (Figs. 2 and 3).

DISCUSSION

The results of this study showed that the TED of Diskus was affected by the PIF, and no significant correlation between PIF and TED_{turbuhaler} was found. The FPM of Turbuhaler and Diskus were dependent of PIF and TED. These flow dependencies were more marked at the lower peak inspiratory flows (PIF < 40 L/min). Both the TED and FPM of Diskus were significantly higher as compared to Turbuhaler.

The aim of this study was to determine *in vitro* the drug delivery characteristics in respect of the delivered dose and particle size distribution of Diskus and Turbuhaler in asthma and COPD patients using real-life patient inhalation profiles. Inhalation profiles of these patients with a wide range of bronchial obstruction and inspiratory muscle function were replayed through the Electronic Lung: a computer-driven inhalation ma-

TABLE 3. ELECTRONIC LUNG RESULTS

Parameter	Ventolin Diskus		Inspyril Turbuhaler	
	Mean (SD)	Range	Mean (SD)	Range
Total emitted dose (% label claim)	83.5 (13.9)*	25.7–96.5	72.5 (11.1)	41.3–88.8
Total emitted dose (μg)	167.1 (27.8)*	51.3–193.0	72.5 (11.1)	41.3–88.8
Fine particle mass (% label claim)	36.8 (9.8)*	1.2–46.1	28.7 (7.7)	5.1–38.2
Fine particle mass (% TED)	42.7 (9.4)	4.7–51.3	39.4 (9.4)	10.5–50.0
Fine particle mass (μg)	73.7 (19.5)*	2.4–92.2	28.7 (7.7)	5.1–38.2

Total emitted dose as percentage of label claim; fine particle Mass as percentage of label claim and as percentage of the total emitted dose. * $p < 0.05$ differences between Diskus and Turbuhaler.

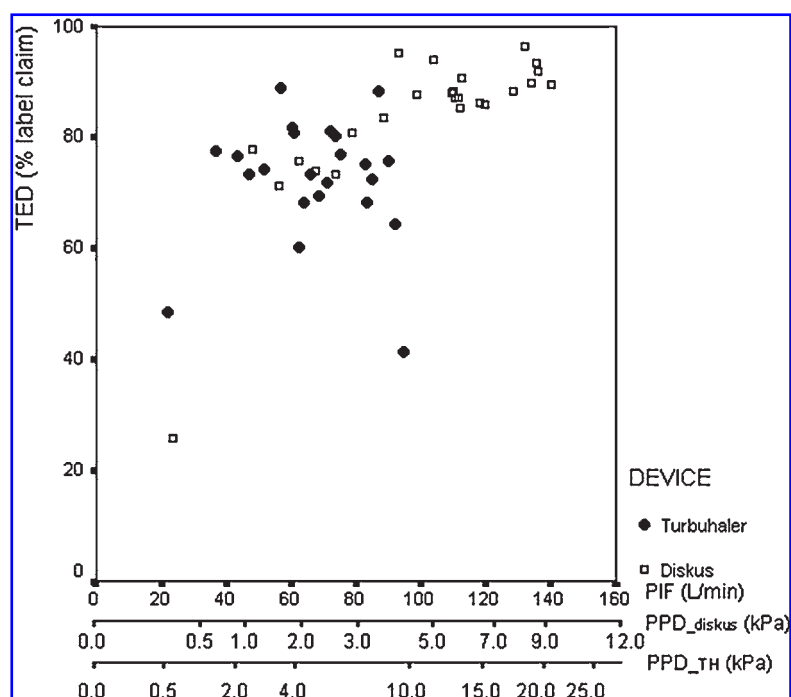


FIG. 2. The relationship between the total emitted dose (TED) as percentage of label claim and peak inspiratory flow (L/min). The relationship between TED and peak pressure drop (PPD; kPa) of Diskus and Turbuhaler were also shown.

noeuvre simulator. Conventional cascade impactors operate at constant flows, which is an unrealistic deviation from the actual flow patterns with respect to the drug release from the device. The airflow through a device during a patient's inhalation not only varies with time, but also between inhalations and patients. The Electronic Lung realistically simulates drug delivery, with real flow patterns.

The selected inhalation profiles for this *in vitro* comparison of Diskus and Turbuhaler showed significant lower PIF values and higher inhalation times for Turbuhaler. This was due to the different resistivities (resistance to airflow) of both devices. PIF decreases with increasing resistivity,¹⁷ which subsequently increases the total inhalation time.¹⁸

An appropriate and clinically efficient DPI should deliver a reliable, consistent dose and a large FPM, relatively independent of flow. The latter should possibly be generated with relatively low inspiratory pressures. In general, the TED for Inspyral Turbuhaler appeared to be significantly lower than that for Ventolin Diskus. This may be due to the fact that the PIF measurements were lower for Turbuhaler.

The present study showed that the TED_{diskus} is affected by PIF and is mainly due to one very

low result. Three relatively low TED_{turbuhaler} results did not fit well with a linear regression. There was also an indication that the dependency of TED on PIF of both devices was more marked at lower flows.

The relatively high variability of TED for Ventolin Diskus appeared to be a result of one low result. This suggests that the variation in drug particle release may decrease with increasing effort. After fitting separate regression models for each device, the residual variability for Ventolin Diskus was less than that for Inspyral Turbuhaler. This means that the Diskus provided a more consistent dose delivery.

The flow-dependent drug output (TED), consistency of the dose, and number of particles in the respirable range (FPM) may theoretically lead to a decreased clinical efficacy in patients who are not able to generate an adequate flow through Diskus or Turbuhaler.

Both devices were extensively studied, both *in vitro* and *in vivo*. Our data confirmed the results of two other studies, which found that a higher FPM of Fluticasone Diskus was delivered at 60 L/min as compared to 30 L/min.^{19,20} Also, other *in vitro* device evaluations showed that the TED and FPM of the Turbuhaler increase at higher PIF.^{11,20-22} However, in contrast to our results, a

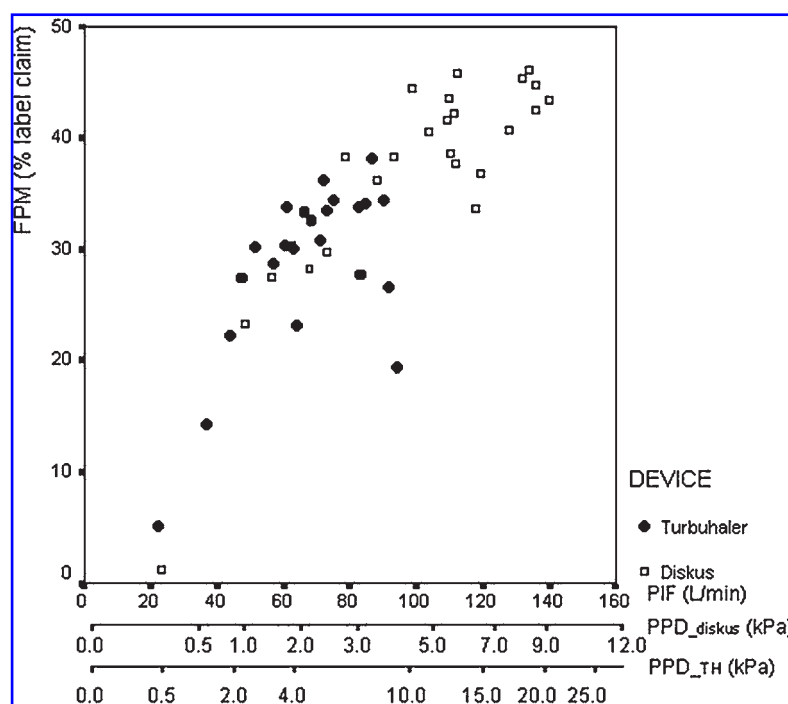


FIG. 3. The relationship between the fine particle mass (FPM) as percentage of label claim and peak inspiratory flow (L/min). The relationship between FPM and peak pressure drop (PPD; kPa) of Diskus and Turbuhaler were also shown.

consistent dose delivery and FPM, relatively independent of flow was described by several studies for Diskus.^{23,24} Since dose emission properties are specific for each drug-device product and the results of this study are only applicable for Ventolin Diskus and Inspiryl Turbuhaler, the conclusions may not be extrapolated for the different combinations. Another important reason for variation may be attributed to the unrealistic test conditions in those studies, that only used a fixed flow Cascade Impactor. Nevertheless, this was not the first study using the Electronic Lung methodology. Several studies used the Electronic lung methodology rather than a fixed flow rate cascade impactor, which all demonstrate that dose delivery from the Diskus is independent of flow.^{11,25} The reason that our data seem to contradict these studies could be that the data chosen for our evaluation was in the range of 21/25 the extremes of the 1500 inhalation profiles collected for each device. Only 4/25 were selected from the middle range. This resulted in a population of inhalation profiles which included not only profiles of the usual outpatient population but also the real outliers from patients at the extremes of disease severity. These profiles were also acquired from severely exacerbated patients

to whom a Diskus or Turbuhaler would normally not have been prescribed. So, the low profiles for Diskus and Turbuhaler were lower than collected in other studies. Recalculations of the fit without the lowest flows (PIF_{diskus} 23 L/min and $PIF_{\text{turbuhaler}}$ 22 L/min) were performed and there was evidence that these outliers influenced the overall results of TED. For TED turbuhaler the slope was actually negative when the low flow data were removed. This was presumably influenced by the lowest TED result belonging to the highest PIF. The regression models for FPM (%label claim) with and without the low flow data were also calculated, but there was no evidence that the model parameters change when the low flow data were omitted.

This study demonstrated that in practice, different devices are not operating at corresponding flows by patients. Patients are only able to generate a certain (maximal) inspiratory effort (pressure) irrespective of which inhaler they inhale through. The inherent resistivity of the given device will determine the flow achieved through the device (Figs. 2 and 3). Comparison of the performance of inhalation devices with different resistivities at the same PIF must be considered carefully, since a particular flow may relate to an

entirely different inspiratory effort in each device. Conventional *in vitro* measurements were usually performed with constant fixed flows of 30, 60 and 90 L/min. Nevertheless, the majority of patients inhaled with higher PIFs through the Diskus. So, the *in vitro* results in the PIF range 30–90 L/min are of high clinical relevance for Turbuhaler, but less for Diskus. Since the PIF is in general achieved *after* the release of the powder, the slope of the pressure profile (in kPa/sec) was also described as an important variable.^{5,6,11,26} Surprisingly, in the present study PIF seemed to influence the Electronic Lung results. There was no indication of a significant relationship with the other inhalation profile variables. However, it was shown for Diskus and Turbuhaler that peak inspiratory flow and slope correlate well in a wide range of patient groups.²⁷

In conclusion, the TED and FPM of Diskus and FPM of Turbuhaler for the salbutamol product were affected by PIF, the flow-dependency being greater at low PIF (<40 L/min). Lower PIFs occurred more often when using Turbuhaler than Diskus. Dose to patient (TED), dose consistency, and the mass of particles in the respirable range were higher for Diskus as compared to Turbuhaler. *In vitro* studies with a constant flow or with real-life flow profiles yield different results.

The flow dependency of TED and FPM of Diskus do not agree with other data published. This is likely to be due to the use of IPs, which include not only the usual clinical population but also the real outliers.

ACKNOWLEDGMENTS

We acknowledge the statistical support of M. Davies (GlaxoSmithKline R&D, Ware). This study was supported by GlaxoSmithKline Zeist, The Netherlands.

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Received on January 12, 2004
in final form, September 9, 2004

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