To the Editor:

We are currently evaluating in our laboratories the drug delivery performance of a series of novel, marketed, dry powder inhaler systems. These studies include a consideration of both "user friendliness", and potential problems associated with non compliance with user instructions.

In a recent study, demonstrating similar clinical efficacy for delivery of β₂-agonists from the unit dose Diskhaler and multidose Turbuhaler devices, Brown et al. [1] commented that, prior to verbal instruction, there was a trend towards better compliance with the written package insert for Diskhaler than with Turbuhaler. In the latter case, noncompliance was principally associated with the loading angle, although a case of exhalation into the device was noted.

The Turbuhaler drug reservoir nominally provides 200×500 µg doses of terbutaline sulphate, as visible aggregates, which break up following fluidation in the inhaled air stream to give particles of respirable size. However, when exposed to moist air, deaggregation is less efficient [2, 3]. For this reason, the device contains a desiccant, and the package insert cautions against storage with the cap off, and exhalation into the device.

To examine the potential effect of not replacing the cap effectively, Turbuhalers were stored at 30°C and 75% relative humidity, for up to 60 days, five with their caps secured and five with their caps off. A second series of five devices was stored for up to 24 h with caps off. At various intervals, devices were assessed for emitted dose and respirable fraction of terbutaline sulphate by collecting single shots, three replicates per device, into Apparatus A of the BP 1988 (Appendix XVIIIC). This is a twin-stage liquid impinger (simple glass model of the lungs), which estimates the respirable fraction as 0.5-6.4 µm mass median aerodynamic diameter, at an airflow rate of 60 l·min⁻¹ [4, 5]. This flow rate is relevant to Turbuhaler evaluation, since our studies with a cohort of 32 patients [6] showed them capable of achieving similar mean peak inspiratory flow (PIF) values through the device; (asthma severity, mean PIF/1·min⁻¹ (sd): mild, 62 (13) n=9; moderate, 72 (22) n=14; severe 56 (17) n=7).

Overall, the emitted drug dose remained consistent, and independent of storage condition; the overall mean value for the three replicate shots from each device at each assessment point was 427 µg (sd 78 µg) equivalent to 85% (sd 16%) nominal.

To allow statistical comparison, respirable fractions were normalized by calculation as percentage emitted dose. Prior to storage, the three groups of five devices delivered equivalent respirable fractions; (means: 58%, "Caps on": 57 and 52%, "Caps off", F=1.9, p=0.19) and this was maintained when the product was stored with the cap secured after 60 days, (mean 60%, t₉₋₀=0.51). However, as shown in figure 1, a marked deterioration in respirable fraction occurs after 0.5-1 h exposure to humidity, the mean respirable fraction falling by half from 54 to 27%. This low value, representing a reduction to ~23% of the nominal dose, was maintained over the 60 day storage period.

These findings indicate that there is a potential for ineffective delivery if the device cap is left off inadvertently for short periods, or is not properly secured between doses, thus confirming the data sheet warning, which should be reinforced by verbal instruction.

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Fig. 1. - Effect of storage at 30°C and 75% RH on the respirable fraction of terbutaline sulphate emitted from turbuhaler devices. •: mean per data set; ○: device mean (3 doses).
References

From the authors:
Meakin et al. have examined the problems created by storing Turbuhalers uncapped, in an atmosphere of 75% relative humidity, for up to 60 days. Their studies simply demonstrate that a relative humidity of 75% will saturate the desiccant within the Turbuhaler, and this will result in inefficient delivery of drug from the device. The manufacturers of the Turbuhaler do, of course, recommend that the cap should be replaced immediately after it is used, on every occasion.

The statement by Meakin et al. that the Turbuhaler is less efficient when it is used in an atmosphere of high relative humidity is correct, but this does not have any relevance to their experiments. The efficiency of the Turbuhaler in a highly humid atmospheres is due to the air which is entrained through the device, and its effect on disaggregation of the particles already in the dosing chamber. It is nothing to do with the desiccant within the device. The efficiency of all dry powder inhalers is decreased when they are used in atmospheres of high relative humidity. This is not a phenomenon which is peculiar to the Turbuhaler.

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CORRESPONDENCE

Influence of in vivo prednisolone on increased in vitro O_{2}-generation by neutrophils in emphysema

To the Editor:

We read with interest, the paper by Rehakeme et al. [1], implicating a role for neutrophil oxidants in the pathogenesis of emphysema, and the potential beneficial effects of steroids. We believe that the paper raises several issues requiring further consideration. The authors reported that neutrophils from patients with emphysema, upon stimulation, produced more superoxide radical than cells from healthy control subjects. It was noted that all patients included in this study were receiving β-agonists, anticholinergics, methyloxanthines, or a combination of all three. The authors state that the literature suggests that these agents are inhibitory to neutrophil superoxide generation [2, 3], which would strengthen their conclusions.

We would like to raise two issues; firstly, the articles cited describe studies of the agents in vitro, without any evidence of their effects in vivo, which may be quite different. For example, we have shown previously that the non-steroidal anti-inflammatory drug, indomethacin, had no effect on neutrophil function in vitro, but in vivo had a marked inhibitory effect on chemotaxis of neutrophils from normal subjects, when administered over a period of 2 weeks. This suggested an effect on the differentiating neutrophil in the bone marrow, rather than on the mature blood cell [4]. Thus, in vitro findings cannot with confidence always be ascribed to in vivo circumstances, without assessment of the agents in vivo.

Secondly, the literature is not even clear about the effect of bronchodilator agents on neutrophil functions in vitro. The authors cited two publications showing a suppression of superoxide production by these drugs. Other writers, however, have shown a bimodal effect of theophylline on neutrophil superoxide generation [5], with stimulation of superoxide release at low levels (therapeutic levels), and inhibition at higher levels. This is thought to be due to two classes of adenosine receptors, A_{1} receptors of high