Sustained Mechanical and Clinical Functionality of the Flexhaler™ Dry Powder Inhaler

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Abstract

Flexhaler™ is a multiple-dose, inspiratory flow-driven dry powder inhaler that is a newer version of Turbuhaler®, and is identical to the Symbicort Turbuhaler®. Sustained performance is of the utmost importance to ensure consistent drug delivery throughout the lifespan of the inhaler. We report functionality testing results of Flexhaler™ inhalers used in two large-scale 12-week studies of budesonide (Pulmicort®) and returned for testing. Functionality tests included measurement of airflow resistance and inspection of vital parts for the mechanical functionality of the inhaler, including visual inspection of the indicator wheel and function check of dose loading. In addition, delivered dose, particle size distribution, moisture content, and microbial counts were evaluated. Seven hundred sixteen out of 720 units were returned. Airflow resistance was not affected by the handling of the Flexhaler™ inhalers during use (prior to use, average airflow resistance: $67 \text{ Pa}^{0.5} \cdot \text{s} \cdot \text{L}^{-1}$; returned inhalers: 66 and $67 \text{ Pa}^{0.5} \cdot \text{s} \cdot \text{L}^{-1}$ in each study, respectively). The average dose delivered remained as intended after prolonged clinical use [95% (range 88–103%) vs. reference of 99% (range 93–104%) before issue]. Relative fine particle dose ($<5 \mu\text{m}$) after use was 107% (range 96–111%) of the reference value before issue. Moisture content in the inhaler desiccant was 3–25%, suggesting variability in storage conditions. Among the 28 inhalers randomly selected for microbiological testing there was no or very limited microbial growth. All 14 inhalers returned with functionality issues operated as intended and no reported functionality issues could be confirmed. Flexhaler™ inhalers operated as intended during these two clinical trials. These results should reassure both clinicians and patients with respect to the consistent quality of this unit for the delivery of dry powder formulations for inhalation.

Key words: Flexhaler™, Turbuhaler®, functionality, performance, delivered dose, particle size, microbiology

Introduction

FlexHALER™ IS A DRY POWDER INHALATION DEVICE used for the delivery of the corticosteroid Pulmicort® (budesonide) at doses of 90 and $180 \mu\text{g}$ for the maintenance treatment of asthma in adult and pediatric patients 6 years of age or older. Flexhaler™ was approved as Pulmicort® Flexhaler™ by the FDA on July 12, 2006, following evaluation in two randomized, double-blind, parallel-group, placebo-controlled 12-week trials studies in adults ≥ 18 years and children (6–17 years), respectively (SD-004-0620; SD-004-0726). Flexhaler™ is a version of Turbuhaler®, which is also used

for Symbicort Turbuhaler®. Pulmicort® Flexhaler™ is available in two strengths, 90 and $180 \mu\text{g}$. The Flexhaler™ has a tapered mouthpiece to facilitate correct mouthpiece positioning, a dose indicator to allow better tracking of drug use and contains lactose ($\sim 1 \text{ mg/actuation}$) to enhance dosing consistency.

With almost 20 years of clinical experience with the Turbuhaler® inhaler, it is regarded as easy to use by the vast majority of patients and physicians with minimal local side effects.^(1–5)

The Flexhaler™ inhaler is operated by physically rotating the dosing disc to allow drug to fill the dose-metering holes.

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As the patient inhales through the device, air passes through the dosing disc lifting the spheronised powder pellets, which disintegrate into their primary particles as they pass through the mouthpiece. The design of the inhaler prohibits the patient from inhaling multiple doses. To protect the drug from humidity during storage and during or immediately after inhalation, the FlexhalerTM inhaler contains an internal desiccant.

Given the repeated use over time, sustained performance of all the components of these units is of the utmost importance to ensure consistent drug delivery throughout their life span. However, to date there have been no reports of systematic evaluations of the sustained functionality of dry powder inhalers following "real-world" clinical use. As already mentioned, the efficacy of budesonide (Pulmicort[®]) delivered via FlexhalerTM was recently evaluated in two large-scale, international studies (SD-004-0620; SD-004-0726), and this controlled setting provided an opportunity to evaluate the postdelivery functionality of the FlexhalerTM inhalers following their routine clinical use by patients.

Here we report the results of functionality (e.g., air flow resistance and visual inspection of the dose indicator), delivered dose, fine particle fraction, moisture in spheronized powder and in desiccant, and microbiologic contamination testing of 716 FlexhalerTM inhalers returned by the study investigators after use and an additional 14 inhalers returned by patients during these studies with reported functionality problems.

Methods

Inhaler sample

FlexhalerTM inhalers used by patients taking part in two large-scale 12-week studies (SD-004-0620; SD-004-0726) designed to evaluate the efficacy and safety of budesonide (Pulmicort[®]) and returned after use from the study centres were evaluated for overall functionality and performance. In addition, FlexhalerTM inhalers returned by patients themselves with reports of functionality problems were included in this evaluation.

Three batches of FlexhalerTM inhalers were issued for one clinical study (pediatrics) and six batches were issued for the second study (adults). Approximately 1500 inhalers containing active drug per study were issued. For both studies, only those inhalers used by patients for the 4-week period between visits 4 and 5 (collected at visit 5) and the 4-week period between visits 5 and 6 (collected at visit 6) were required to be returned. Reference values for each batch with respect to functionality and performance were obtained for random samples within each batch prior to release for clinical use. For each batch, 3 inhalers were tested for functionality, 10 inhalers for delivered dose, 2 inhalers for aerodynamic particle size distribution, 5 for water/moisture content in inhaler desiccant, 2 for water/moisture content in spheronized powder, and 10 for microbiological condition.

Functionality testing

Functionality tests included measurement of airflow resistance and inspection of vital parts for the mechanical func-

tionality of the inhaler, including visual inspection of the indicator wheel and function check of dose loading.

Delivered-dose testing

Given that the typical median inhalation flow rate achieved by patients using FlexhalerTM is around 60–70 L/min, a flow rate of 60 L/min was used to determine the delivered dose. For the reference testing, 10 inhalers per batch and three doses (first, middle, and end dose) per inhaler were analyzed.

The doses from each of the returned inhalers were withdrawn onto a glass filter, dissolved in methanol, and then analysed by UV-spectroscopy.

Particle size distribution

Particle size measurement was conducted using an Andersen cascade impactor at a flow rate of 60 L/min. For the reference testing, two inhalers were tested from each batch. For FlexhalerTM 180 µg, the first four doses and the last four doses of each inhaler were tested, while for FlexhalerTM 90 µg, the first eight doses and the last eight doses of each inhaler were tested. The chemical analysis of the fine particle dose was then performed using liquid chromatography with internal standard methodology. The relative fine particle dose was defined as the particles <5 µm in diameter. For the returned inhalers, either four or eight doses were tested, depending on the product strength.

Moisture content in inhaler desiccant and spheronised powder

The weight of the inhaler desiccant was measured both before and after drying to determine the amount of water in the desiccant. The amount of moisture in the spheronized powder was measured using volumetric titration according to Karl Fischer (USP<921>, method 1a, direct titration).

Microbiological testing

The total aerobic count, as well as the total moulds and yeasts, per inhaler were determined (USP<61>, plate method).

Test allocation

Basic functionality and delivered dose testing was conducted for all returned inhalers. For practical reasons not all inhalers underwent particle size distribution, moisture content, and microbiological testing. Instead, subsets of returned inhalers were randomly allocated to these remaining tests.

Inhalers returned by patients themselves with reported functionality problems were investigated according to the reported functionality issue within 1 month of return. Thus, where investigation of the primary issue required removal of the mouthpiece, delivered-dose testing was not subsequently conducted.

Results

Following completion of two large-scale studies designed to evaluate the clinical efficacy of budesonide delivered via FlexhalerTM, 716 out of 720 inhalers used between visits 4 and

6 were returned from the centers by the investigators (in total throughout both studies 3099 inhalers were used). Both studies were of 12 weeks' duration. The first study (SD-004-0620) involved 621 randomized subjects with asthma assigned to one of five treatment groups. Approximately 35% of subjects were male and the overall mean age was 40 years (range 18–80 years). Most subjects were Caucasian (64%), with Asian subjects comprising 29% of the population; 450 subjects (72%) were from the United States and 171 subjects (28%) were from Asia. The second study (SD-004-0726) comprised a total of 516 randomized subjects with mild asthma assigned to one of five treatment groups. Here, the mean age was 12 years (range 6–17 years), with 45% ($n = 232$) of subjects between the ages of 6 and 11 years and 55% ($n = 284$) between the ages of 12 and 17 years. In this study approximately 65% of subjects were male; Caucasian and Asian subjects accounted for 52 and 33% of the population, respectively, while 66% were from the United States and 33% were from Asia. The mean number of doses taken in each study was not recorded.

Functionality

A total of 688 of the 716 returned inhalers underwent functionality testing; the remaining 28 inhalers underwent microbiology testing.

Airflow resistance. Prior to use, the average airflow resistance of the Flexhaler™ inhalers used in the clinical studies was $67 \text{ Pa}^{0.5} \cdot \text{s} \cdot \text{L}^{-1}$. The returned inhalers were tested for airflow resistance and yielded an average airflow resistance of 66 and $67 \text{ Pa}^{0.5} \cdot \text{s} \cdot \text{L}^{-1}$ [relative standard deviation (RSD) 2.2% and 2.2% respectively] in the two studies, indicating that airflow resistance was not affected by the handling of the inhalers during use.

Visual inspection of the components. There was no damage to any mouthpiece or cover in any of the returned inhalers and the mouthpieces could be easily rotated in all cases. The indicator wheel and the operating unit worked

correctly for all returned inhalers. No other mechanical wear of significance to the functionality of the inhalers were observed.

Delivered dose testing

A total of 688 returned inhalers were tested. There was negligible difference in terms of delivered dose (average per cent of the nominal delivered dose) between returned Flexhaler™ inhalers and reference values determined prior to use in the clinical studies (Table 1).

Reference testing prior to use in the clinical studies determined an average delivered dose of 99% (range 93–104%; RSD 9.2%). The average delivered dose by returned inhalers across both studies was 95% of the labeled dose value (range 88–103%; RSD 12.2%).

Particle size distribution

A total of 144 of the returned inhalers were tested. The relative fine particle dose for the returned inhalers at a flow rate of 60 L/min was 107% (range 96–111%) of the reference value obtained prior to use in the clinical studies (Fig. 1). This difference was considered to be negligible, and was not regarded as clinically important.

Moisture content in desiccant and spheronised powder of Flexhaler™

A total of 88 returned inhalers were tested.

Spheronized powder. The amount of water in the spheronized powder was, in general, only slightly higher compared with the reference data (Table 2). Returned inhalers from the two studies had an average water content of 4.9 and 4.4% by weight compared with reference values of 4.7 and 4.2%, respectively.

Inhaler desiccant. The amount of water found in the inhaler desiccant after 30 months storage at 25°C at a relative humidity of 60% was approximately 6%, according to sta-

TABLE 1. DOSE DELIVERED BY FLEXHALER™ INHALERS BEFORE USE AND ON RETURN BY PARTICIPANTS IN ONE OF TWO LARGE-SCALE CLINICAL STUDIES

		Reference delivered dose (average % of nominal delivered dose; RSD)	Post use delivered dose (average % of nominal delivered dose; RSD)
Study 1	Batch		
	1	96 (10.6)	93 (12.9)
	2	93 (10.3)	88 (13.4)
Study 2	3	96 (9.9)	91 (10.9)
	Batch		
	1	98 (9.4)	92 (11.2)
	2	104 (6.0)	97 (11.9)
	3	98 (9.2)	94 (12.3)
	4	103 (8.8)	101 (13.8)
	5	104 (8.9)	103 (12.7)
Cross-study average	6	101 (9.4)	100 (11.1)
		99 (9.2)	95 (12.2)

RSD, relative standard deviation.

FIG. 1. Relative fine particle dose (%) compared to prerelease reference values for Flexhaler™ inhalers used in two large-scale clinical studies.

bility data in the registration file. In the returned inhalers the amount of water in the inhaler desiccant ranged from 3 to 25% of dry desiccant, indicating that they had been used and suggesting variability in adherence to storage instructions (Table 2).

Microbiological testing

A total of 28 randomly selected returned inhalers were subjected to microbiological testing. No more than 60 colony-forming units/g for aerobic micro-organisms (these included *Staphylococcus* sp., *Micrococcus* sp., and spore-forming bacteria), molds and yeasts were identified in any tested inhaler.

The results indicated no or only very limited microbial growth, and the microbial status of the tested inhalers was judged to be acceptable. No pathogenic micro-organisms were detected in any inhaler.

Inhalers returned with functionality issues

A total of 14 inhalers were returned with reports of possible functionality issues—this corresponds to 0.4% of all issued inhalers, including those containing placebo [a total of approximately 3900 inhalers (active and placebo) were issued]. These inhalers were not decontaminated prior to testing. Upon examination, all the inhalers were shown to op-

TABLE 2. AMOUNT OF WATER IN SPHERONIZED POWDER AND DESSICANT IN FLEXHALER™ INHALERS BEFORE USE AND ON RETURN BY PARTICIPANTS IN ONE OF TWO LARGE-SCALE CLINICAL STUDIES

	Spheronized particles		Desiccant
	Reference water content (% by weight)	Post use water content (% by weight)	Post use water content (% by weight; range)
Study 1 Batch			
1	4.7	4.7	10.5 (3.6–20.3)
2	4.8	5.0	10.7 (3.0–17.2)
3	4.7	5.0	6.5 (2.9–16.3)
Study 2 Batch			
1	4.3	4.3	9.0 (3.6–16.8)
2	4.2	4.5	11.3 (5.3–25.3)
3	4.3	4.5	7.8 (4.0–11.6)
4	4.3	4.3	10.1 (3.7–22.2)
5	4.2	4.5	11.0 (6.1–15.6)
6	4.2	4.5	12.9 (6.5–22.8)

TABLE 3. FUNCTIONALITY TESTING OF FLEXHALER™ INHALERS (90 AND 180 µG DOSES) RETURNED BY PARTICIPANTS IN ONE OF TWO LARGE-SCALE CLINICAL STUDIES WITH REPORTED FUNCTIONALITY ISSUES

<i>Inhaler</i>	<i>Dose/pack size</i>	<i>Reported issue</i>	<i>Result</i>	<i>Delivered dose (% of nominal delivered dose; RSD)</i>
1	180/120	Unable to activate/counter did not move	The inhaler showed normal operation Powder deposition in the mouthpiece indicated several doses had been withdrawn	Not tested
2	180/120	Inhaler did not click during dose loading	The dose indicator, the dose loading, and the rotation of the mouthpiece operated normally	109 (7)
3	180/120	Dose not felt during inhalation	The dose indicator, the dose loading, and the rotation of the mouthpiece operated normally	106 (6)
4	180/120	Counter did not move	The dose indicator, the dose loading, and the rotation of the mouthpiece operated normally	104 (8)
5	180/120	Inhaler malfunctioned	The dose indicator, the dose loading, and the rotation of the mouthpiece operated normally	101 (8)
6	180/120	Patient had used 124 doses but the dose counter displayed 30 doses left	Powder deposition in the mouthpiece confirmed several doses had been withdrawn The dose indicator, the dose loading, and the rotation of the mouthpiece operated normally	Not tested
7	180/60	Dose not felt during inhalation and the counter did not move	The dose indicator, the dose loading, and the rotation of the mouthpiece operated normally	101 (9)
8	180/60	Counter display was incorrect	The dose indicator, the dose loading, and the rotation of the mouthpiece operated normally	101 (7)
9	180/60	A taste was reported after several doses	Powder deposition in the mouthpiece confirmed several doses had been withdrawn The dose indicator, the dose loading, and the rotation of the mouthpiece operated normally A faint smell of spices was suggesting the inhaler may have been stored with strong smelling spices	Not tested
10	180/60	A taste was reported after several doses (reported by the same patient as for inhaler #9)	Powder deposition in the mouthpiece confirmed several doses had been withdrawn The dose indicator, the dose loading, and the rotation of the mouthpiece operated normally A faint smell of spices was suggesting the inhaler may have been stored with strong smelling spices	Not tested
11	180/120	Inhaler malfunctioned	The dose indicator, the dose loading, and the rotation of the mouthpiece operated normally	89 (5)
12	90/60	Inhaler malfunctioned	Powder deposition in the mouthpiece confirmed several doses had been withdrawn The dose indicator, the dose loading, and the rotation of the mouthpiece operated normally	Not tested

(continued)

TABLE 3. FUNCTIONALITY TESTING OF FLEXHALER™ INHALERS (90 AND 180 µG DOSES) RETURNED BY PARTICIPANTS
IN ONE OF TWO LARGE-SCALE CLINICAL STUDIES WITH REPORTED FUNCTIONALITY ISSUES (CONT'D)

<i>Inhaler</i>	<i>Dose/pack size</i>	<i>Reported issue</i>	<i>Result</i>	<i>Delivered dose (% of nominal delivered dose; RSD)</i>
13	90/60	Inhaler should have been empty	Powder deposition in the mouthpiece confirmed several doses had been withdrawn The dose indicator, the dose loading, and the rotation of the mouthpiece operated normally The dose indicator showed approximately five doses remaining	Not tested
14	90/60	Inhaler should have 60 doses left	Powder deposition in the mouthpiece confirmed several doses had been withdrawn The dose indicator, the dose loading, and the rotation of the mouthpiece operated normally	Not tested

RSD, relative standard deviation.

erate as intended, and no reported functionality issues could be confirmed. The issues and results of functionality testing are summarized in Table 3.

Discussion

The results of the functionality and performance testing reported here have shown that the Flexhaler™ inhaler operated as intended during two separate large-scale clinical trials. All parts of the returned inhalers remained intact.

Our data have shown that the dose delivered by the returned inhalers remained as intended even after a prolonged period of clinical use. The average delivered dose level was slightly lower and the average relative standard deviation was higher for the returned inhalers compared with the reference data obtained prior to release for clinical use. The average delivered dose ranged from 88% to 103% between batches of returned inhalers compared with a range of 93 to 104% prior to issue. Applying the regulatory agreed bioequivalence interval, 80–125% on the present *in vitro* data indicates that the performance of the Flexhaler™ inhalers before and after patient use was similar. Thus, the observed small differences in delivered dose can be considered negligible and are not likely to be clinically relevant.

The delivered fine particle dose ($<5\ \mu\text{m}$ aerodynamic diameter) has been shown to correlate with the degree of lung deposition, which ultimately determines the clinical efficacy.^(6,7) In the present study, the fine particle dose delivered by the returned inhalers was approximately 107% of that of the reference values (range 96–111%) and such a small difference in aerosol properties can, as discussed above, be considered negligible for the clinical outcome. Dry powder drug formulations may be sensitive to humidity. Exposure to high humidity levels may result in drug degradation during storage and particle clumping during use, but the amount of moisture in the spheronised powder was generally only slightly elevated compared with that prior to release for clinical use. The amount of water in the inhaler desiccant ranged from 3 to 25%, suggesting wide variability in adherence to recommended storage conditions. Variability in ambient humidity across the country in which the studies were performed may have contributed to the observed variability. However, even in inhalers with water content in the desiccant of 25%, 40% of the water absorbing capacity remains and the humidity inside the inhaler is approximately 40% relative humidity.⁽⁸⁾ Evidence for a good performance of Turbuhaler® in a humid environment is supported by a study performed in Queensland in Australia.⁽⁹⁾ In the study, salbutamol was given either via pMDI or Turbuhaler®, and no difference in clinical effect between the two devices could be observed. The humid conditions did not affect drug characteristics. In the present study, evidenced by the delivered dose and fine particle dose data on the returned inhalers, the observed range in water content in the desiccant was still below the point where the desiccant ceases to function.

Different manufactures of dry powder inhalers have solved the problem of humidity protection in different ways and each inhaler system should be evaluated on its own properties, as generalizations across the group of dry powder inhalers cannot be made. Thus, it has been shown that another dry powder inhaler, Diskus™, which uses prefilled blisters, is sensitive to environmental humidity while

stored.⁽¹⁰⁾ The fine particle dose, as well as lung deposition, for Diskus™ decreased to half of its initial value while Turbuhaler® was unaffected by a storage at 40°C/75% relative humidity.⁽¹⁰⁾

Microbiological testing indicated no or very limited growth and the microbial status of the inhalers were regarded as acceptable. Finally, none of the reported functionality issues for the 14 inhalers returned during the two studies could be confirmed on testing. All inhalers were shown to operate as intended.

No comparable reports of the functionality of other dry powder or pressurised metered-dose inhalers have been reported. One report of a systematic study of functionality and acceptability of a new insulin injection pen has recently been reported⁽¹¹⁾ suggesting an increasing awareness of the need to ensure quality control of drug delivery devices in the clinical trial setting.

To our knowledge this is the first report of a systemic evaluation of dry powder inhaler functionality and performance and should reassure both clinicians and patients with respect to the consistent quality and accuracy of Flexhaler™ during drug delivery.

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Author Disclosure Statement

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