Uniformity of delivered dose from the first to last dose of the BF Spiromax® inhaler in the laboratory and under 'real-world' conditions

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Summary

Budesonide/formoterol Spiromax® ([BF Spiromax], Teva Pharmaceuticals) is a dry-powder inhaler delivering budesonide and formoterol for the treatment of asthma and COPD. BF Spiromax has been developed in low strength, middle strength and high strength formulations (80 µg/4.5 µg, 160 µg/4.5 µg and 320 µg/9 µg of budesonide/formoterol per inhalation, respectively).

Dose consistency was evaluated using uniformity of delivered dose (UDD) assessments. UDD was tested using low, medium and high strength inhalers. Doses from different stages of the BF Spiromax lifespan were collected using a Dose Uniformity Sampling Apparatus. To simulate real-world conditions, inhalers were subjected to natural knocks/vibrations and temperature/humidity variations. Inhalers were assessed at the beginning, middle and end of their lifespan and UDD measured over a ≤90 day period until the last labelled dose. Five simulation schemes were assessed using low, medium and high strength BF Spiromax with variations in the number of inhalations twice daily.

The BF Spiromax devices delivered consistent doses throughout inhaler lifetime. Delivered doses increased in proportion with the labelled doses for each strength. Using real-world simulations, for all five schemes, UDD was also consistent throughout inhaler lifetime. Dosing regimen had no impact on UDD for each BF Spiromax formulation.

All three strengths of BF Spiromax delivered consistent doses throughout their lifetimes and over five real-world dose and schedule regimens.

Introduction

Combination therapy with budesonide and formoterol fumarate (BF) is commonly used to treat asthma and chronic obstructive pulmonary disease. BF Spiromax® (Teva Pharmaceuticals) is a novel, inhalation-driven, multi-dose, dry powder inhaler (DPI) designed to administer this treatment. Three formulations of BF Spiromax have been developed: low strength (120 inhalations, each delivering 80 µg budesonide and 4.5 µg formoterol), middle strength (120 inhalations, 160 µg budesonide and 4.5 µg formoterol per inhalation), and high strength (60 inhalations, 320 µg budesonide and 9 µg formoterol per inhalation). To ensure patients always receive an appropriate dose, it is important for inhalation devices to demonstrate a consistent delivered dose and fine particle mass from the first to the last dose. The EU Pharmacopeia compendial procedure specifies that 9 out of 10 dry-powder inhaler doses are within +/- 25% of the specified dose and that outliers should be within +/- 35%.[1]

During the development of an inhaler device, performance is first evaluated in the laboratory. This includes assessments of dose consistency. However, laboratory conditions differ considerably from the real world, where inhalers are used across a range of temperature and humidity, subjected to a variety of knocks/vibrations and used over a long period of time. Consequently, in addition to laboratory testing, the development process must include assessment under conditions designed to simulate use by patients.

We report results of two studies: the first was a laboratory study designed to measure the uniformity of delivered dose (UDD) throughout the lifetime of the BF Spiromax inhaler (as an indication of dose consistency) from the first dose until the last labelled dose. The second study investigated the dose consistency (as UDD) of BF Spiromax under conditions simulating 'real-world' inhaler handling and dosing regimens.

Methods

UDD over product lifetime

BF Spiromax devices were used according to the information for patients with respect to storage, orientation, and minimum dosing interval. Three different BF Spiromax inhalers were investigated: low strength (120 inhalations, each delivering 80 µg budesonide and 4.5 µg formoterol); middle strength (120 inhalations, each delivering 160 µg budesonide and 4.5 µg formoterol); and high strength (60 inhalations, each delivering 320 µg budesonide and 9 µg formoterol). The devices were not cleaned throughout their lifetime (from beginning of life [BOL] to end of life [EOL]). Inhalers were selected from three batches of low strength BF Spiromax (n = 42), three batches of the middle strength product (n = 42) and three batches of high strength BF Spiromax (n = 42).

To assess UDD over the device lifetime a fixed flow rate of 62.5 L/min, representing a 4 kPa pressure drop over the device (Q) was applied to achieve an inhalation volume of 4 L. Ten doses from different stages of the BF Spiromax lifetime were collected separately using Dose Uniformity Sampling Apparatus (DUSA). Three doses were collected from the first discharges of the device (BOL), four doses were taken midway through the inhaler lifetime (middle of life [MOL]) and three doses from the end of the inhaler's lifetime including the last labelled

dose (EOL). After 4 L of air had been drawn through the device, the collected doses of budesonide and formoterol were recovered and analysed using validated high performance liquid chromatography (HPLC).

Real-world simulations

Real-world conditions were simulated by analysts carrying inhalers with them during working day hours, dispensing doses according to specified schemes and cleaning the inhaler mouthpiece weekly with a dry cloth in accordance with the patient leaflet. Five different simulation schemes were designed to test inhalers up to their last labelled doses, as summarised in Table 1.

Table 1. Study simulation schemes

Scheme	Inhaler Strength	Dosing Regimen	Duration	Number of Inhalers	UDD Assessments
A	Low	One inhalation twice daily	72 days	6 (3 from each of 2 batches)	Day 1–2 (3 doses) Day 36–37 (4 doses) Day 71–72 (3 doses)
B	Low	Four inhalations twice daily	21 days	6 (3 from each of 2 batches)	Day 1 (3 doses) Day 10 (4 doses) Day 21 (3 doses)
C	High	One inhalation twice daily	32 days	6 (3 from each of 2 batches)	Day 1–4 (3 doses) Day 15–18 (4 doses) Day 29–32 (3 doses)
D	High	Two inhalations twice daily	16 days	6 (3 from each of 2 batches)	Day 1 (3 doses) Day 8 (4 doses) Day 15–16 (3 doses)
E	Middle	One inhalation twice daily	90 days	9 (3 from each of 3 batches)	Day 1–2 (3 doses) Day 45–48 (4 doses) Day 87–90 (3 doses)

Within each scheme, inhaler doses were collected for UDD analysis. For UDD assessments, doses were collected into a DUSA at a pressure drop of 4 kPa over the device. After 4 L of air were drawn through the device, collected drug substances were recovered and analysed using a validated HPLC. Results obtained from the same inhaler batches under laboratory conditions (25ºC, 60% relative humidity) over a single day were used for comparison.

Results

UDD over product lifetime

The BF Spiromax devices delivered consistent doses of budesonide and formoterol throughout their lifetime (Figures 1 and 2). Importantly, mean doses for the lifetime of each formulation were similar to the labelled doses (Table 2). Although there was a trend for BOL doses to be slightly lower than MOL and EOL, all doses were within +/- 15% of the labelled quantity (low strength doses ranged between 90.7 and 108.0% of the labelled dose for budesonide and 87.6–101.1% for formoterol; middle strength ranges were 92.4–108.5% and 94.8–109.9%; high strength ranges were 92.7–104.8% and 96.8–110.2%).

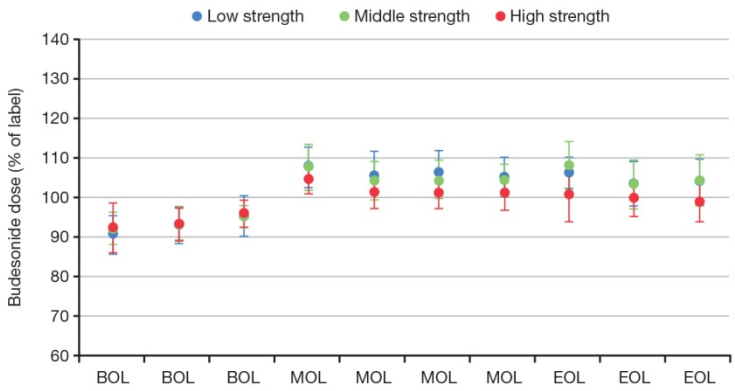

Figure 1. Delivered dose (DD) of budesonide by low, middle and high strength BF Spiromax inhalers at beginning [BOL], middle [MOL] and end [EOL] of the lifetime of each device. Error bars represent standard deviation. Data are presented as percentage of the labelled dose.

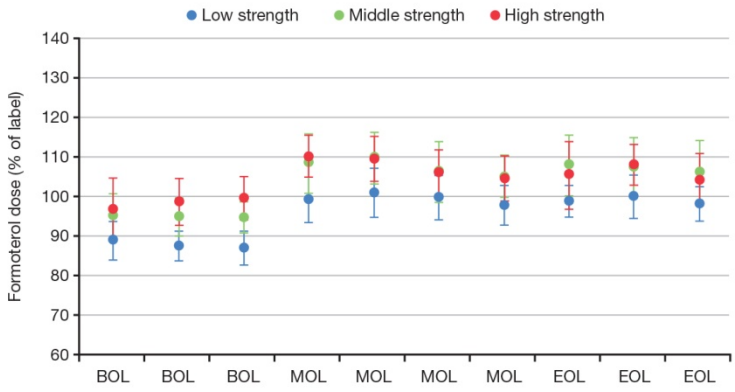

Figure 2. Delivered dose (DD) of formoterol by low, middle and high strength BF Spiromax inhalers at beginning [BOL], middle [MOL] and end [EOL] of the lifetime of each device. Error bars represent standard deviation. Data are presented as percentage of the labelled dose.

Table 2. Delivered doses of budesonide and formoterol: device lifetime mean, calculated for each formulation from all of the data shown in Figures 1 & 2 (three doses at beginning of life, four doses at middle of life and three doses at end of life). Standard deviations are shown in parentheses.

	Low Strength	Middle Strength	High Strength
Budesonide, µg	82 (5)	163 (9)	317 (12)
Formoterol, µg	4.3 (0.3)	4.7 (0.3)	9.4 (0.4)

Real-world simulations

UDD data for budesonide and formoterol under 'real-world' conditions (expressed as delivered dose [% of labelled dose]) across simulation schemes A–E are shown in Figure 3. For all three inhaler strengths, delivered doses were consistent throughout the lifetime. There was no difference in UDD data between single-inhalation/day and multiple-inhalation/day regimens (Figure 3).

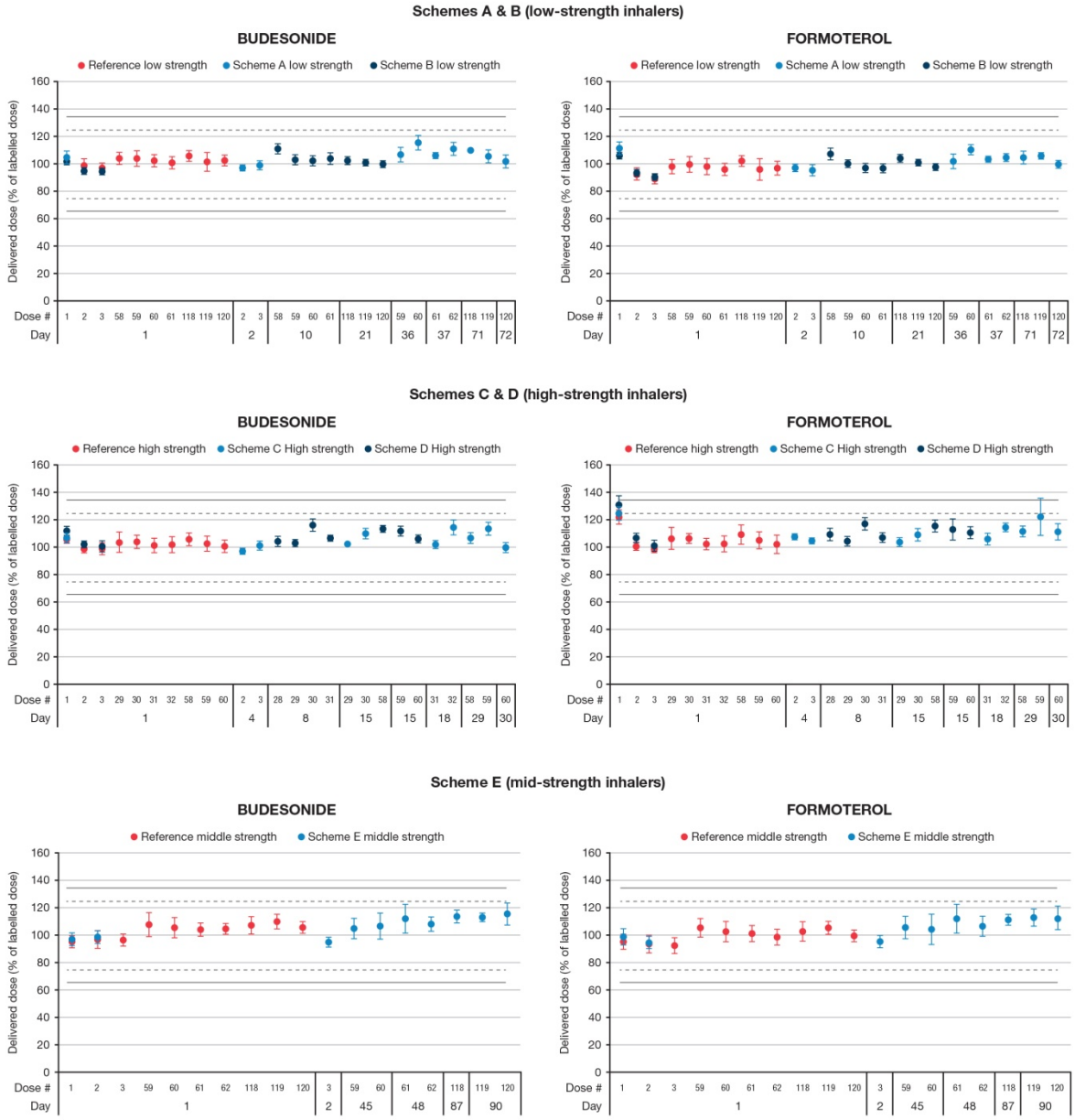

Figure 3. Doses delivered by BF Spiromax: low strength inhaler (simulation schemes A & B), high strength inhaler (simulation schemes C & D and middle strength inhaler (simulation scheme E). Data are presented as percentage of the labelled dose.

Conclusions

BF Spiromax delivers doses of budesonide and formoterol that are consistent with the labelled quantity and meet requirements for delivered dose uniformity. These findings apply to the whole inhaler lifetime and to all three BF Spiromax formulations. Consistency in dosing of all three strengths was also demonstrated in real-world conditions supporting that results obtained from laboratory testing of the device are representative of its real-world performance.

Reference

1. Preparations for inhalation (01/2012:671). In: European Pharmacopoeia, 8th Edition. Council of Europe, 2013.