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Dose counter performance of mometasone furoate/formoterol inhalers in subjects with asthma or COPD

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Received 8 November 2010; accepted 23 January 2011

Available online 12 March 2011

KEYWORDS

Dose counter;
Inhaler;
Accuracy;
Mometasone
furoate/formoterol;
Dulera;
Asthma

Summary

Background: Consistent delivery of medication to treat asthma and chronic obstructive pulmonary disease (COPD) is critical for disease control. Dose tracking may eliminate the possibility of sub-therapeutic dosing. This study evaluated the overall performance, including accuracy and ruggedness, of the mometasone furoate/formoterol (MF/F) metered-dose inhaler (MDI) with an integrated numerical dose-counting mechanism in adolescent and adult subjects (aged ≥ 12 y) with persistent asthma or COPD.

Methods: In a phase III, open-label, single-arm, multicenter study, subjects demonstrating at least 90% compliance with MF/F during the screening period received twice daily MF/F MDI 100/10 μg with the integrated dose counter for 4 weeks. Accuracy and ruggedness of the dose counter were assessed by the overall discrepancy rate of subject-recorded actuations versus subject-recorded dose counter readings. Discrepancy rates for Counterstrip™, a manual counting method, were evaluated for reference. Compliance and ergonomic safety were also assessed.

Results: The 233 subjects who used $\geq 90\%$ of labeled actuations were included in the primary analysis. Of 26,317 total actuations, 33 dose counter discrepancies occurred (rate = 0.13/100 actuations), of which 13 were due to undercounting. In comparison, the Counterstrip discrepancy rate was 10-fold higher (1.34/100 actuations). Compliance with medication use, Counterstrip use, and e-diary recordings were all high ($>98\%$). No new repetitive strain injuries or exacerbations of preexisting ergonomic injuries of the finger, hand, or arm were reported.

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Conclusions: The MF/F MDI dose counter was accurate and rugged in subjects with asthma or COPD. No new repetitive strain injuries or exacerbations of existing ergonomic injuries were associated with inhaler use.

Clinical trial registration number: ClinicalTrials.gov identifier = NCT00604500

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Introduction

According to national and international asthma and chronic obstructive pulmonary disease (COPD) guidelines, the main goal of treatment is to maintain disease control, primarily measured by the severity of symptoms, airflow obstruction, and the frequency of exacerbations.^{1–3} In addition, these treatment guidelines stress the importance of appropriate and consistent medication delivery in asthma and COPD management. Medication for controlling asthma and COPD is principally delivered by pressurized metered-dose inhalers (MDIs) or dry powder inhalers (DPIs) to allow for high lung deposition with minimal systemic adverse effects. Studies have shown that when correctly used, there are no differences in clinical outcomes between MDIs and DPIs.^{4,5} However, when misused, both MDIs and DPIs contribute to a decrease in asthma or COPD stability.^{6–8}

Even when inhalers are well designed and used correctly, consistent medication delivery (particularly with MDIs, which require 2 inhalations per dose) may be limited by the patient's inability to recall if they have taken their full prescribed dose. Such inconsistent asthma medication use can have serious clinical implications by contributing to an increased risk of exacerbations and poor outcomes.^{9–13} Another barrier to consistent and optimal therapeutic delivery is the inability of patients to know when their inhaler is empty.¹⁴ To help patients keep better track of their dosing and promote consistent usage, manufacturers have begun to incorporate dose counters into their inhalation delivery devices. A reliable dose counter can help patients track their medication use, determine when to replace their inhaler, and prevent them from actuating their inhaler beyond the labeled number of doses. In 2003, the US Food and Drug Administration (FDA) released a guidance document for industry on integrating dose counters into MDIs. Although this guidance allows for both numerical counters and dose indicators, including those that convey only end-of-use information, the FDA recommends that all dose counter mechanisms be evaluated for accuracy, ruggedness, and ergonomics.¹⁵ For numerical counting mechanisms, accuracy relates to the ability of the dose counter to decrement 1 unit upon patient actuation. Ruggedness requires that the counter performs accurately upon multiple actuations (ie, over the life of the inhaler) under real-world handling conditions. Ergonomics indicates that the integration of the dose counter into the MDI delivery device is user-friendly and does not present any safety or ergonomic handling issues.

Mometasone furoate/formoterol (MF/F) is a recently developed inhaled corticosteroid (ICS) and long-acting β_2 -agonist (LABA) combination delivered via a hydrofluoroalkane-pressurized MDI (Dulera[®], Merck & Co., Whitehouse Station, NJ) that has been approved by the FDA for the treatment of asthma. MF/F MDI is also currently under investigation for the treatment of COPD.

The primary objective of this study was to evaluate the overall performance of the MF/F MDI with an integrated numerical dose-counting mechanism in terms of accuracy and ruggedness in adolescent and adult patients with asthma or COPD. Other objectives were to assess subject adherence and safety (including ergonomics). Accuracy and ruggedness were assessed by determining the overall dose counter discrepancy rate (comparison of subject-recorded number of actuations to subject-recorded dose counter readings), quartile discrepancy rates (discrepancy changes over time), discrepancy size (magnitude of discrepancy), and end-of-use agreement (discrepancy at end of inhaler life). Dose counter discrepancies were also compared with discrepancies observed with Counterstrip[™] (a non-mechanical numerical counter affixed to the MDI). Compliance was monitored throughout the study to confirm the primary assessment results. Ergonomics were assessed through inhaler usability metrics and monitoring of repetitive strain injuries.

Methods

Study design

This was a phase III, open-label, single-arm, multicenter study conducted in the United States. The study was conducted in accordance with principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies. Written informed consent was obtained from all subjects. The study duration was a maximum of 7 weeks and included 3 phases (Fig. 1). Phase 1 was a familiarization period (lasting up to 1 week) during which subjects were trained and became acquainted with the use of a placebo MDI matching the MF/F MDI without a dose counter, a Counterstrip, and an electronic diary (e-diary). Subjects remained on their prescribed asthma or COPD treatment during this phase. Also during this phase, medical history (including history of repetitive strain injury [RSI]) was taken and routine laboratory tests were conducted to determine study eligibility. Phase 2 was a 2-week screening period during which subjects discontinued their previously prescribed asthma or COPD treatment and received MF/F MDI 100/10 μg without the dose counter (administered as 2 inhalations of MF/F 50/5 μg) twice daily (BID) and approximately 12 h apart, to confirm acceptable MDI dosing technique, stable asthma control, and at least 90% compliance with use of the e-diary, Counterstrip, and study medication. Subjects who did not meet the 90% compliance cut-off were discontinued, and the reasons for non-compliance (ie, e-diary, Counterstrip, study medication, and/or MDI technique) were evaluated (Table 1). RSI history was also reassessed during this phase to confirm subject eligibility. Phase 3 was a 4-week treatment period during which subjects received MF/F MDI 100/10 μg (administered as 2 actuations of MF/F

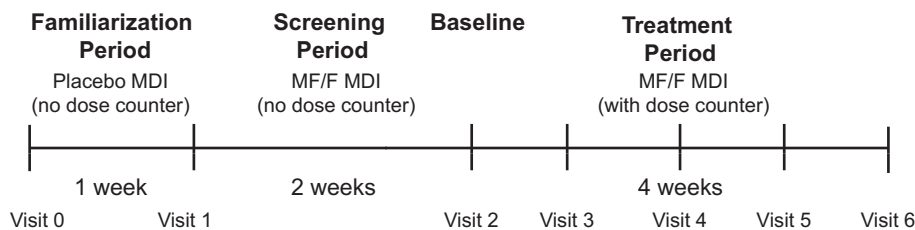


Figure 1 Study design. MDI = metered-dose inhaler; MF/F = mometasone furoate/formoterol.

50/5 µg) BID with an integrated dose counter. During the treatment period, subjects returned to the study center weekly for evaluation of their MDI dosing technique; the use of their study medication, e-diary, Counterstrip; and their RSI assessment. At these weekly visits, the investigator recorded the number of actuations displayed on the physical dose counter and the physical Counterstrip for the purpose of comparing them to the number of subject-recorded actuations in the e-diary and to the prescribed number of actuations (Fig. 2).

Subjects

Subjects included in the study were ≥12 years of age, of either sex and of any race, with at least a 12-month history of persistent asthma or COPD. Additional inclusion criteria required asthma subjects to have a forced expiratory volume in 1 s (FEV₁) ≥70% and COPD subjects to have a FEV₁ ≥50% and a pre-bronchodilator FEV₁/forced vital capacity ratio ≤0.70 at screening. Asthma subjects must have been using a low-dose ICS with or without a LABA or medium-dose ICS without a LABA for at least 12 weeks before screening and must have had a stable dosing regimen for at least 2 weeks before screening. There were no prestudy ICS requirements for

COPD subjects. All subjects had to demonstrate ≥90% compliance with e-diary completion, Counterstrip use, and study medication use during the 2-week screening period without the dose counter. Subjects were excluded if they were unable to adequately use the MDI without the dose counter or had a recent or current RSI or ergonomic injury (eg, tenosynovitis, tendinosis) of the finger, hand, or arm that, in the judgment of the investigator, could have prevented the subject from effectively participating in the full duration of the study.

Accuracy and ruggedness assessments

With each actuation, MDI use was recorded automatically by the dose counter and manually on the Counterstrip (Fig. 3). Actuations related to the initial priming of the MDI, performed under the supervision of the study personnel, were not included in the dose counter discrepancy evaluation. Subjects were required to enter the dose counter and Counterstrip values into their e-diary, both before and after each of the 2 actuations that comprised 1 dose, during each prescribed BID dosing session. Subjects also recorded whether or not the actuation was inhaled and the actual date/time of inhalation for comparison with the e-diary’s automated date/time stamp. The e-diary prompted the subject to contact the study center if the actuation was not inhaled or if the dose counter or Counterstrip e-diary values were not consistent with either the number of recorded actuations or the number of prescribed actuations. There

Table 1 Non-compliance-related reasons for screen failures and discontinuations.^a

Reason	Screen Failures (n = 56)
MDI technique	1
Non-compliance	
e-diary	27
Study medication	12
Counterstrip usage	7
Other ^b	28
Treatment period discontinuations (n = 11)	
Non-compliance	
e-diary	2
Study medication	2
Counterstrip usage	0
Other ^b	7

^a This table reflects a breakdown of the documented reasons for non-compliance related to subject screen failures and discontinuations. As subjects may have met more than one reason for non-compliance, these numbers do not match those for subject disposition.

^b Documented reasons related to non-specific subject error or non-compliance.

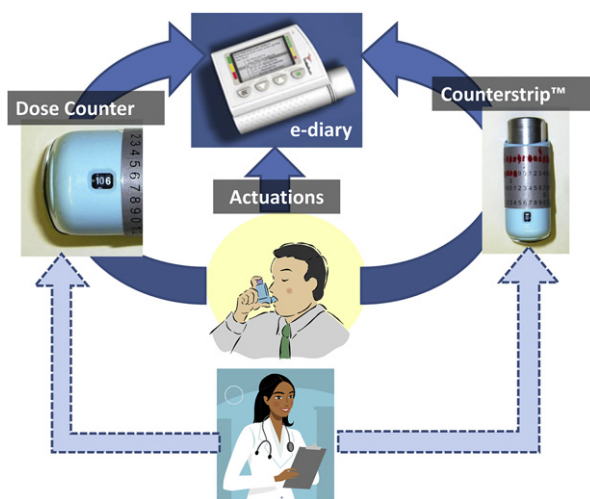


Figure 2 Integrated approach to identifying true dose counter discrepancies.

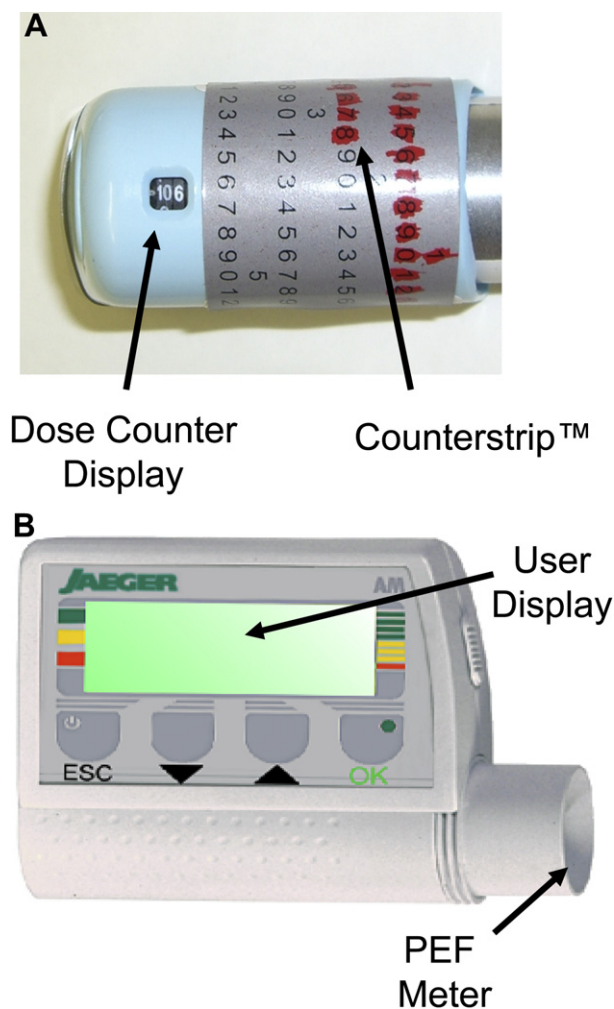


Figure 3 Recording devices used. (A) MF/F MDI with integrated dose counter and affixed Counterstrip and (B) e-diary with integrated peak expiratory flow (PEF) meter.

were 2 ways to account for nonprescribed actuations and/or inhalations made by the subject: (1) subjects were permitted to record nonprescribed actuations and/or inhalations associated with inadvertent/accidental actuations or test sprays (that may have occurred at any time) in a nonstandard e-diary session and (2) study centers were permitted to use an investigator mode to enter actuations and/or inhalations that the subject reported but did not enter into the e-diary (unrecorded actuations).

Compliance assessments

To support the primary study objective of evaluating dose counter performance, subject compliance with MDI technique, use of medication, Counterstrip, and e-diary were closely monitored. At each weekly visit, the subject demonstrated his/her ability to use the MDI, Counterstrip, and e-diary as directed. An e-diary report was printed which contained a compliance score for study medication, Counterstrip, and e-diary use based on the previous week. The investigators were also instructed to carefully review the subject's e-diary recordings including an evaluation of: any missing or incomplete e-diary sessions, extra e-diary sessions

(ie, inadvertent actuations), incomplete dosing sessions (ie, <2 inhalations), dose counter readings that did not decrement by 1 unit per actuation, Counterstrip readings that did not increment by 1 unit per actuation, subject's last e-diary dose counter and Counterstrip recordings in comparison with the investigator-observed actual dose counter and actual Counterstrip readings, and subject's total number of actuations versus the prescribed number of actuations. Study-specific electronic data collection tools were used by the study center to document non-compliance with each of these study procedures.

Ergonomic assessments

Inhaler usability assessments included an evaluation of missing e-diary data, failed doses, and need for further instruction on use of the MF/F MDI dose counter. The quality and design of the MF/F MDI dose counter were also assessed through separate subject satisfaction assessments (manuscript submitted). Ergonomic safety was reported separately from other adverse events before dispensing the MF/F MDI dose counter and after using MF/F MDI dose counter for up to 4 weeks and included an assessment of RSI of the finger, hand, or arm.

Safety assessments

Safety assessments included rescue medication use, symptom scores, peak expiratory flow (PEF) measurements, and adverse events. The e-diary/PEF meter was used to monitor subject safety throughout the course of the study as follows: (1) the spirometry component of the e-diary was used to measure PEF twice daily during the prescribed BID e-diary session; (2) use of rescue medication (short-acting β_2 -agonist or oral corticosteroid) was captured in the e-diary; (3) asthma or COPD symptoms were assessed through subject responses to questionnaires captured in the e-diary; and (4) the e-diary was programmed to alert the subject if PEF fell below his/her established stability limit, rescue medication use exceeded the amount allowed by the study, or there were other signs of asthma or COPD worsening. Adverse events were also monitored.

Accuracy and ruggedness analysis

The accuracy and ruggedness of the MF/F MDI dose counter were primarily assessed by the discrepancy rate over the life of the inhaler (120 labeled actuations) for subjects who used at least 90% of the labeled number of actuations during the treatment period (Completer Population). Dose counter discrepancy rates were calculated as the difference between the subject-recorded number of actuations versus the subject-recorded dose counter readings per 100 actuations. For comparative purposes, the dose counter discrepancy rate was also computed for all subjects who used the MF/F MDI dose counter, regardless of compliance or duration of use (Treatment Period Population). Discrepancies were classified as Undercounting (dose counter did not count down upon actuation [spray, not count] or dose counter counted upward without a known actuation [count up, unknown spray]) or Overcounting (dose counter

counted down without an actuation [count, not spray] or with an unknown spray [count, unknown spray]).

To fully characterize dose counter accuracy and ruggedness, quartile discrepancy rates (discrepancy rates between weekly site visits), discrepancy size (magnitude of discrepancy), and end-of-use agreement (discrepancy at end of inhaler life) were also evaluated. For comparative purposes, Counterstrip discrepancy rates were calculated as the subject-recorded number of actuations versus the subject-recorded Counterstrip readings per 100 actuations.

Dose counter accuracy check

A Dose Counter Accuracy Check (DCAC) was performed at every scheduled visit to identify suspected dose counter discrepancies.¹⁶ The DCAC is an algorithm that applied a predefined set of criteria to the subject's e-diary data accrued since the last weekly visit to identify a suspected dose counter discrepancy. Each time the DCAC was performed, it compared the change in dose counter value with 3 other indices of actuations: total recorded actuations, the Counterstrip, and prescribed actuations. The DCAC indicated the possibility of a true dose counter discrepancy and the need for further investigation, including an *in vitro* analysis consisting of a prespecified root cause analysis plan with visual, dimensional, and functional testing of the MDI and its components.

Anomalies

The total error rate (anomaly rate) was estimated from the e-diary count sequence for the purpose of comparison to the dose counter discrepancy rate identified by the DCAC. The dose counter anomaly rate was computed as the total number of differences between the expected and actual e-diary recorded dose counter values (ie, every actuation in the e-diary that the dose counter did not decrement by 1 unit). Dose counter anomalies may arise from a true malfunction of the dose counter or subject error (reading or data entry errors) and subject non-compliance with recording actuations (not recording actuations or recording actuations that were not performed). The rate of subject error and non-compliance with the dose counter was calculated by subtracting the dose counter discrepancy rate from the dose counter anomaly rate. This estimate of subject error/non-compliance rate was used to validate the utility of the DCAC and its ability to discriminate between subject error/non-compliance and "true" dose counter discrepancies. Calculation of the dose counter subject error/non-compliance rate also allows for a direct comparison to the Counterstrip discrepancy rate because, as a non-mechanical counter, its count sequence differences are due only to subject error or non-compliance. Documented subject error or non-compliance was not included in the final dose counter discrepancy calculations.

Statistics

The study was designed with a target sample size of 240 subjects. For this sample size, assuming a 1% discrepancy rate, the 95% CI would be 0.885–1.115%. In addition, approximately 25% of the subjects were to be 65 years or older. For all assessments, only descriptive statistics were performed. Based on the study objectives, there were no

prespecified hypotheses and no formal comparisons between treatment groups were conducted.

Results

Demographics and baseline characteristics

To ensure a thorough evaluation of the dose counter over its intended lifespan, the clinical protocol stipulated that the primary data analysis include subjects who used $\geq 90\%$ of the labeled actuations during the treatment period (Completer Population). Of the 272 subjects who used the MF/F MDI with dose counter (Treatment Period Population), 233 subjects were in the Completer Population (Fig. 4). In the Completer Population, most of the subjects were white women; 25% were ≥ 65 years of age and 81% had persistent asthma (Table 2). Demographic characteristics of the Treatment Period Population were comparable to those of the Completer Population.

Dose counter discrepancies

Of the 26,317 actuations recorded by the Completer Population, there were 33 dose counter discrepancies, resulting in a dose counter discrepancy rate of 0.13 per 100 actuations (Table 3). When assessed by subject age, the dose counter discrepancy rates were higher in subjects < 65 years of age compared with those ≥ 65 years of age (0.14 vs 0.07, respectively; Table 3). Dose counter

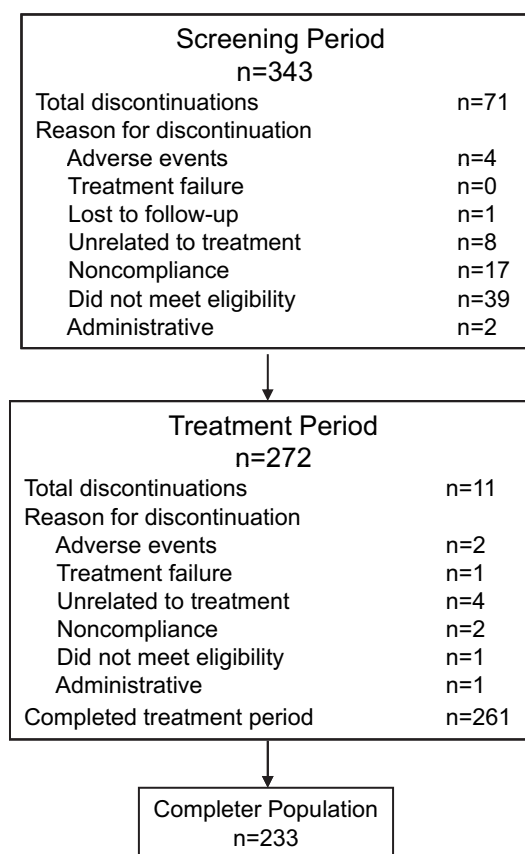


Figure 4 Subject disposition.

Table 2 Demographic and baseline characteristics for the Completer Population.^a

Characteristic	N = 233
Age, y	
Range	12–92
<65, n (%)	174 (75)
≥65, n (%)	59 (25)
Sex, n (%)	
Women	156 (67)
Race, (%)	
White	211 (91)
Disease, n (%)	
Persistent asthma	189 (81)
Chronic obstructive pulmonary disease	44 (19)

^a Subjects who took ≥90% of labeled actuations during the treatment period.

discrepancies throughout the life of the inhaler were also assessed by dividing the data into quartiles that reflected each of the 4 weekly visits during the treatment period, with the highest discrepancy rate observed in quartile 4 (0.20 per 100 actuations; Table 3). The discrepancy rate for the Treatment Period Population was 0.14 per 100 actuations, indicating that subjects who did not complete the study did not experience more dose counter discrepancies.

Without applying the DCAC to filter out random count sequence errors, 25% of the inhalers had a non-zero end-of-use agreement. After removing documented subject errors and non-compliance indicated by the DCAC, 92% of the 233 MDIs used by the Completer Population had no dose counter discrepancies, including a perfect end-of-use agreement (ie, final dose counter reading was in agreement with the total number of recorded actuations). Analysis of the Treatment Period Population produced similar results, with no dose counter discrepancies in 91% of the inhalers.

Only 13 of the 33 dose counter discrepancies in the Completer Population were due to undercounting, for a rate of 0.05 per 100 actuations (Fig. 5). All of the undercounts were attributed to a spray with no count. When analyzed by the discrepancy size, 100% were 2 counts or less, with all 13 undercounting discrepancies differing by only 1 count. Of the 20 overcounting discrepancies (rate of 0.07 per 100 actuations), 14 were attributed to a count with no spray (Fig. 5).

In vitro analysis

At the end of the treatment period, inhalers were returned for in vitro evaluation if a dose counter discrepancy was suspected (ie, indicated by the DCAC) or there was any evidence of damage.

Based on the results of this in vitro evaluation, as well as the clinical evidence provided by the investigator, the number of inhaler-related dose counter discrepancies was compared with subject-related discrepancies (Table 4).

Counterstrip discrepancies

Out of 26,317 actuations in the Completer Population, there were 353 Counterstrip discrepancies for a discrepancy rate of 1.34 per 100 actuations (Table 5). When assessed by age, the Counterstrip discrepancy rates were higher in the population of subjects ≥65 years of age compared with those <65 years of age (2.01 vs 1.11 per 100 actuations, respectively; Table 5). Most of the errors were associated with reading the Counterstrip or entering the Counterstrip reading into the e-diary.

Anomalies

Whereas subject error and non-compliance were theoretically eliminated by the DCAC to calculate true discrepancy rates, the dose counter anomalies included both true dose counter malfunctions and subject error in reading or entering a value into the e-diary (overcount or undercount), and non-compliance by failing to record an actuation (overcount) or by recording an actuation that was not performed (undercount). The overall rate of dose counter anomalies in the Completer Population was 1.19 per 100 actuations (Table 3). This indicates that the rate of subject error/non-compliance is 9 times greater than the dose counter discrepancy rate, and it demonstrates the effectiveness of the DCAC in screening out subject error and non-compliance. The anomaly rate is similar to the Counterstrip discrepancy rate of 1.34 per 100 actuations, which, as stated previously, is entirely due to subject error and non-compliance.

When assessed by age, more overall dose counter anomalies occurred in subjects ≥65 years of age compared with the younger subjects (rates of 1.78 vs 0.99 per 100 actuations, respectively; Table 3). The dose counter anomaly rate was highest in the fourth quartile of the older age group (2.06 per 100 actuations) and was much higher

Table 3 MF/F MDI dose counter discrepancy and anomaly rates overall, by age, and by quartile in the Completer Population.

Quartile	Discrepancy rate per 100 actuations			Anomaly rate per 100 actuations		
	Total N = 233	Age < 65 y n = 174	Age ≥ 65 y n = 59	Total N = 233	Age < 65 y n = 174	Age ≥ 65 y n = 59
1	0.09	0.10	0.06	1.21	0.84	2.32
2	0.06	0.06	0.06	0.94	0.74	1.51
3	0.14	0.17	0.06	0.95	0.87	1.18
4	0.20	0.23	0.11	1.62	1.47	2.06
Overall	0.13	0.14	0.07	1.19	0.99	1.78

MF/F = mometasone furoate/formoterol; MDI = metered-dose inhaler.

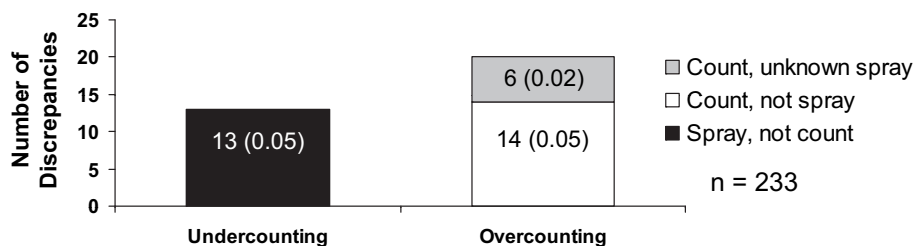


Figure 5 Number of undercounting and overcounting dose counter discrepancies (discrepancy rate per 100 actuations).

than in the corresponding quartile for the entire Completer Population (1.62 per 100 actuations; Table 3).

Compliance

Compliance with study medication, Counterstrip use, and e-diary recordings was high and few subjects discontinued because of non-compliance (Table 1). Subjects in the Completer Population recorded use of 98% of the prescribed number of actuations. The most prevalent reason for non-compliance with study medication was forgetting to take the medication. In addition to high levels of subject compliance with prescribed dosing, study medication was used as directed (ie, 1 dose consisting of 2 inhalations taken with proper MDI technique) 92% of the time it was evaluated by the study center. High average compliance was also observed in the Completer Population for the Counterstrip (99.8%) and e-diary use (98.0%). Overall, compliance was greater in the population of subjects ≥65 years compared with younger subjects (Fig. 6).

Ergonomics and safety

Regarding ergonomics (inhaler usability), nearly all subjects were able to use the MF/F MDI dose counter without assistance. Approximately 90% (210 subjects) had no failed doses. Only 4% (10 subjects) contacted the site by telephone owing to an inability to use the inhaler as directed, and none of these events required a clinic visit.

Table 4 Number of subject-related or inhaler-related discrepancies by quartile, age, and population.

	Completer age, y		Non-completer age, y		Totals
	<65	≥65	<65	≥65	
Inhaler-related discrepancies					
Q1	4	1	0	0	5
Q2	2	1	2	0	5
Q3	4	1	1	0	6
Q4	6	1	0	0	7
Totals	16	4	3	0	23
Subject-related discrepancies ^a					
Q1	1	0	1	0	2
Q2	1	0	4	0	5
Q3	3	0	1	0	4
Q4	7	1	0	0	8
Totals	12	1	6	0	19

^a Reason = undocumented actuation, subject error, count when dropped, count when canister reassembled.

In the Treatment Period Population (all 272 subjects), safety evaluations revealed no new RSIs of the finger, hand, or arm, and of the 6 subjects (2 asthma, 4 COPD) with preexisting RSI symptoms, none reported an exacerbation. Adverse event analysis determined treatment with MF/F MDI 100 µg BID was safe and well tolerated in the study. The most common adverse events were headache, oral candidiasis, upper respiratory tract infection, or oropharyngeal pain. Each of these adverse events occurred in approximately 2% of subjects. Treatment-related adverse events were reported in 4% of subjects, the most common being oral candidiasis. Only 1 severe adverse event (dysphonia) was considered treatment-related.

Discussion

The current study was designed to evaluate the accuracy, ruggedness, and ergonomic safety of the MF/F MDI dose counter, a feature that will enable patients to better track medication use and determine when to replace the inhaler. Dose counter accuracy and ruggedness were evaluated by the rate of dose counter discrepancies between subject-recorded actuations and actuations counted by the dose counter throughout inhaler life. The MF/F MDI dose counter proved to be reliable, tracking medication use with a low rate of discrepancies (0.13 per 100 actuations), and most (92%) of the MF/F MDI inhalers were without discrepancies.

Inhaler-related discrepancy rates throughout the life of the inhaler were consistent as evidenced by data across the quartiles. However, subject-induced discrepancies (ie, dropping the inhaler, reinserting the canister, undocumented actuations) were more prevalent in the later quartiles for the younger (<65 y) subjects. These data reflect the fact that the DCAC is more adept at removing random count sequence errors due to subject error than it is at filtering subject non-compliance. Therefore, the observed increase in discrepancy rate over the life of the inhaler and between

Table 5 Counterstrip discrepancy rates overall, by age, and by quartile in the Completer Population.

Quartile	Discrepancy rate per 100 actuations		
	Total N = 233	Age < 65 y, n = 174	Age ≥ 65 y, n = 59
1	1.12	0.86	1.89
2	0.81	0.53	1.63
3	1.14	0.93	1.74
4	2.22	2.05	2.72
Overall	1.34	1.11	2.01

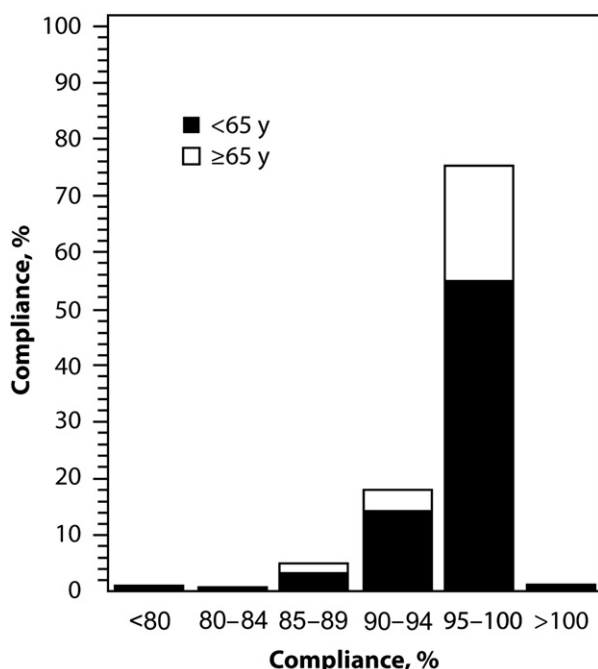


Figure 6 Percentage completed e-diary sessions vs prescribed e-diary sessions by age to illustrate overall e-diary compliance, which includes twice-daily entries of dosing data (ie, study medication use, Counterstrip use, and dose counter recordings), peak expiratory flow data, and symptom data, versus prescribed e-diary entries.

the two age groups was not considered to be a true difference in performance over the life of the inhaler.

Two other studies have evaluated the performance of MDI numeric dose counters. The first study by Sheth et al evaluated fluticasone propionate/salmeterol (FP/S) hydrofluoroalkane (HFA) MDI (Advair[®] HFA; GlaxoSmithKline, Research Triangle Park, NC) with an integrated dose counter.¹⁷ The overall discrepancy rate with the FP/S MDI was 0.94 per 100 actuations, and 58% of the subjects had no discrepancy. The second study by Wasserman et al evaluated albuterol HFA MDI (Ventolin[®] HFA; GlaxoSmithKline, Research Triangle Park, NC) with an integrated dose counter.¹⁸ The overall discrepancy rate with the albuterol MDI was 0.76 per 100 actuations, and 47% of the subjects had no discrepancy. It should be noted that in the studies by Wasserman et al¹⁸ and Sheth et al,¹⁷ subject error was not excluded from their analyses, making the discrepancy rates higher than if error was excluded as done in the current study. When the dose counter discrepancy rate from the current study (0.13 per 100 actuations) is subtracted from the dose counter anomaly rate (1.19 per 100 actuations), the resultant discrepancy rate of 1.06 per 100 actuations is closer to the rates reported by Wasserman et al and Sheth et al.^{17,18}

A third study by Shah et al investigated the functionality of a budesonide/formoterol (Symbicort[®]; AstraZeneca, Dunkerque, France) MDI with an indicator-type dose counter, rather than a direct numeric counter.¹⁹ Discrepancy rates were not reported; therefore, a direct comparison cannot be made to the dose counter discrepancy rates reported here. However, Shah et al did report the difference

between the final subject-recorded counter reading and the total subject-recorded actuations at the end-of-use as a mean difference with a 95% CI. This analysis is equivalent to the end-of-use agreement in the current study (final dose counter reading by investigator minus total number of subject-recorded actuations). We performed a post-hoc analysis to compare the Shah et al data to the Completer Population results in the current study. In our Completer Population, the average number of actuations was 112.9 (for 231 inhalers, 2 were not included because the dose counters went beyond zero). This total number of actuations is closest to one of the Shah et al study groups (group 2) in which the mean number of actuations was 116.2 (for 86 inhalers). Shah et al reported the mean difference to be -2.45 (95% CI, -3.82 to -1.08) compared with 0.09 (95% CI, -0.06 to 0.23) in this study. The mean difference in this study was closer to zero and after accounting for sample size differences, the variability between the final subject-recorded counter reading was approximately 6-fold smaller (ie, ratio of 95% CI ranges $\times \sqrt{N} = (2.74 \times \sqrt{86}) / (0.29 \times \sqrt{231})$) in this study than the Shah et al study. Unlike the MF/F numerical counter which decrements 1 unit with each actuation, the budesonide/formoterol counter does not provide a way for the patient to see whether an individual actuation has been performed. Therefore, it cannot be used by the patient to monitor individual actuations/inhalations or daily dosing like a numerical counter.

The MF/F MDI was designed to favor counting before spraying in order to result in an overcount rather than an undercount if the subject did not fully actuate the inhaler. Of the 33 dose counter discrepancies in the current study, only 13 (39%) were due to undercounting, meaning less medication was available than the dose counter indicated. The overall discrepancy rate for undercounting was low (0.05 per 100 actuations) and is lower than that reported for the FP/S MDI dose counter (0.33 per 100 actuations)¹⁷ and the albuterol MDI dose counter (0.13 per 100 actuations).¹⁸ Undercounting is a less acceptable form of dose counter error because of the potential for administration of a sub-therapeutic dose.¹⁵ In vitro analysis demonstrated that the undercounts were mostly associated with the MDI spraying in advance of counting (data not shown).

The magnitude of undercounting is also important. All of the MF/F MDI dose counter discrepancies were within 2 counts, indicating that patient overestimation or underestimation of remaining medication was no more than 1 dose, and all of the undercount discrepancies were within 1 count (ie, half a dose). In comparison, 87% and 88% of the FP/S MDI and albuterol MDI dose counters, respectively, were within 2 counts; 5% and 3%, respectively, were off by more than 5 actuations.

There were several unique features of the current study compared with previous dose counter performance studies. The first unique feature was the incorporation of the familiarization period using a placebo without a dose counter, which enabled subjects to become comfortable with the inhaler before the start of the study. Possibly as a result of this period, only 1 subject failed to enter the study because of an inability to use the inhaler as directed. In addition, there were no discontinuations attributed to an inability to use the MF/F MDI with the dose counter during the study, which supports the contention that the presence of the dose counter does not alter the basic MDI technique.

The second unique feature was the selection of subjects based on compliance with the e-diary and Counterstrip, in addition to study medication. This allowed for exclusion of subjects who were not compliant in recording their medication usage, which could affect discrepancy results.

The third unique feature of this study was the use of the DCAC, which enabled subject error and non-compliance to be segregated from dose counter discrepancies.¹⁶ Random errors were eliminated by incorporating site observations of the actual dose counter and actual Counterstrip values.

The fourth unique feature of the current study was that subjects were instructed to record dose counter values after each inhalation, not only after each full dose. This facilitated the detection of random entry errors and helped to establish the reliability of the dose counter in counting down only 1 number with every actuation. Alternatively, the dose counter theoretically could have stuck after the first actuation and counted down 2 numbers after the second actuation, effectively disguising a malfunction.

The fifth unique feature was the use of the Counterstrip in conjunction with the dose counter. Unlike the dose counter, the Counterstrip is non-mechanical. Therefore, Counterstrip discrepancies are always a result of subject error or non-compliance. The overall Counterstrip discrepancy rate is analogous to the difference between the dose counter discrepancy rate and the dose counter anomaly rate (both are measures of subject error or non-compliance). When the dose counter discrepancy rate is subtracted from the anomaly rate ($1.19 - 0.13 = 1.06$), the rate of dose counter subject error and non-compliance can be estimated. Using this estimate, a relative increase of 26% more errors were made by subjects using the Counterstrip than with the dose counter, and older subjects (≥ 65 y) made more errors with the Counterstrip compared with younger subjects. However, the older subjects were more compliant with study medication and when compliance differences were taken into consideration there were no discernible differences in dose counter performance between the older and younger subjects. The overall count sequence differences (anomaly rate) between the dose counter and Counterstrip was 0.93 per 100 actuations, which is better than between either of the individual counters and the subject-recorded actuations, suggesting that both counting methods are more accurate than the total recorded e-diary actuations.

The ergonomic safety of the inhaler was evaluated as recommended by FDA guidance on the integration of dose counters into MDI delivery devices.¹⁵ The addition of a dose counter to an MDI should not impede a patient's ability to use the delivery device, although the integration of the dose counter into the MDI delivery device requires additional force to actuate the delivery device compared with an MDI alone. RSI of the hands, wrists, and arms are common in working adults, with prevalence estimated from 5% to as high as 40% in some populations.²⁰ Therefore, it is important that the delivery device not exacerbate those conditions. In the current study, no new exacerbations of RSI in the 6 subjects with prior injuries were associated with the MF/F MDI-integrated dose counter device.

Conclusions

The MF/F MDI dose counter was demonstrated to be accurate and rugged in a population of adolescents and adults with asthma or COPD. Furthermore, the dose counter was easy to use, and no new RSIs or exacerbations of existing ergonomic injuries were associated with inhaler use.

Acknowledgments

This study was supported by Schering-Plough Corp., now Merck & Co. The authors wish to gratefully acknowledge the programming and statistical support of Matias Morrison and Hanzhe Zheng. Medical writing and editorial assistance was provided by Erin P. Scott, PhD, of Complete Publication Solutions, LLC, Horsham, PA. This assistance was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ.

Funding source

Merck & Co.

Role of study sponsor

The study sponsor was involved in the study design, data analysis and interpretation, and writing of the manuscript. The sponsor provided financial support for editorial assistance in the drafting of the manuscript. The final decision to submit the manuscript was made by all of the authors.

Conflict of interest

CW and HS are employees of Merck & Co. NJA and CL were investigators for the study. IS has served as a consultant for Schering-Plough (now Merck & Co.).

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