Evaluation of Count Accuracy of a Top-Mounted Dose Indicator for a Pressurized Metered-Dose Inhaler (pMDI): A Study Involving Adult Participants Naïve to the Product

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Summary

Background: The USFDA advocates that manufacturers add Dose Counters or Indicators to pMDIs to provide means for the user to know when to replace their inhaler. Patient handling studies are a key part of the process to confirm the accuracy of such counters/indicators. However, they are challenging to undertake due to compliance issues related to accurate completion of user-diaries, and user/device-induced variability affecting dose delivery gravimetric assessment. This study demonstrates outcomes from simulated use, in which the gravimetric method for assessment of count accuracy was developed to minimize the impact of actuation weight variability, and the effect of varying the offset between the force-to-fire (FTF) of the pMDI and force-to-count (FTC) the indicator was examined.

Materials and Methods: 44 inhaler-dose indicator naïve participants were each allocated 3 pre-weighed placebo pMDIs, each equipped with a dose indicator (AeroCount® TMAI-200 model, Trudell Medical International, Canada), so that a given user had three pMDIs all having their nominal FTF at 28-N. Each inhaler was mounted with a unique dose indicator that was manufactured to one of three FTC settings (18-N, 22-N and 25-N). During 3-weeks, each participant delivered 6-actuations per inhaler twice daily (12-actuations/device/day). Canister weight was recorded after every 6-actuations to minimize the effect of user- and device-induced actuation weight variation.

Results: Each pMDI FTF/FTC setting combination was evaluated over at least 7,500 actuations. No undercounting was observed with the 18-N and 22-N FTC settings and an incidence occurrence of only 0.01% was detected with the 25-N setting. The incidence of overcounting was only 0.3% for both 18-N and 22-N settings and 0.25% with the 25-N setting.

Conclusions: The TMAI-200s evaluated in this investigation were measured to have a total combined discrepancy rate of 0.28% that is well within previously reported figures on other commercially available dose indicators and counters. The magnitude of the FTC offset within the study limits had minimal effect on performance, demonstrating a robust device design space.

Introduction

Since 2003, due to the lack of a straightforward means for patients to assess the number of actuations remaining in their inhalers [2, 3], the USFDA has advocated that manufacturers of pMDIs provide dose counters/indicators [1] to allow the user to know when to replace their inhaler. The AeroCount® TMAI-200 model dose indicator is capable of detecting every actuation of the pMDI, even though the user interface seen by the patient advances every 10 actuations through use from full to empty. The AeroCount® dose indicator developed by Trudell Medical International (London, Canada) is a compact dose indicator that locates on-top of the pMDI canister as a single unit that is integrated with the inhaler as part of the assembly process (Figure 1). The patient actuates the inhaler in the same way as would be the case without the dose indicator, applying force to depress the canister in order to fire (actuate) the inhaler. The TMAI-200 operates on the principle of achieving a force-to-count (FTC) that is defined to a tight specification in terms of the inter- and intra-device variability for a batch of indicators. The relationship between this specification and the corresponding specification for the force-to-fire (FTF) of the inhaler that is set by the manufacturer of the drug product is critical. Significant overlap in the FTC and FTF distributions could result in under-counting, with the potential result that the user may perceive there to be more drug available than is actually contained within the inhaler. This is a potential safety condition, particularly with rescue medications, and should therefore be avoided. If, however, the FTC and FTF distributions are too far apart, over-counting may be possible. This condition, although less serious than undercounting, is perceived by the regulators as undesirable because of potential drug product waste [1].

Patient handling studies are a key part of the process to confirm accuracy of dose counters/indicators. However, they are challenging due to a variety of compliance issues, for instance, accurate completion of user-diaries, either manual or electronic, and user/device-induced variability affecting dose delivery gravimetric assessment.

The primary goal of the present handling study, undertaken with adult inhaler-dose indicator/counter naïve participants, was to determine the count discrepancy rate of the TMAI-200, manufactured to three different FTC settings.

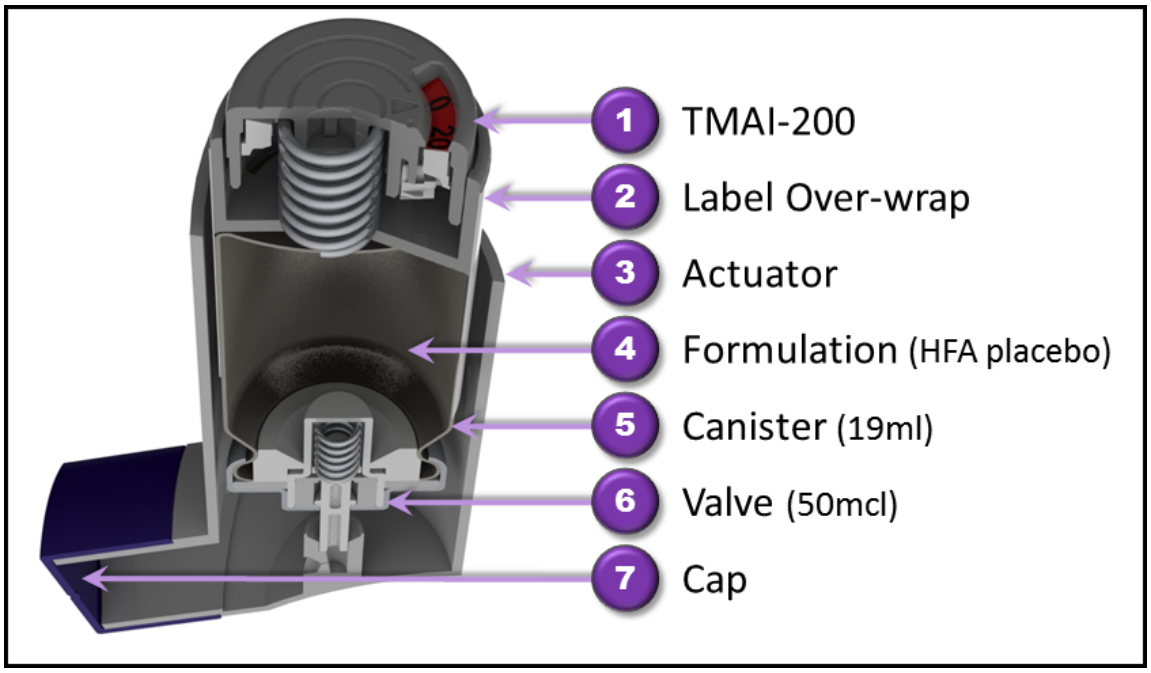

Figure 1: Schematic of TMAI-200 Dose Indicator Integrated with a Pressurized Metered Dose Inhaler

Materials and Methods

44 inhaler-dose indicator naïve participants were each allocated 3 pre-weighed placebo pMDIs all having their nominal FTF at 28-N, and each equipped with a unique dose indicator manufactured to one of three FTC settings (18-N, 22-N and 25-N). During the 3-weeks (15 days) of the investigation, each participant was instructed to perform 6-actuations per inhaler twice daily (12-actuations/device/day). Devices were weighed after each 6-actuation interval to minimize the impact of cumulative variation in inhaler actuation weight over extended intervals, such as at the beginning and end of use. At the conclusion of the study, participants returned their devices before the zero count was reached so that a study coordinator could assess the exact count of each dose indicator.

Results

Each pMDI FTF/FTC setting combination was evaluated over 7,482 user applied actuations. The gravimetric method was determined to be 99% accurate in assessing the exact number of times a given pMDI was fired; a critical element to count accuracy assessment that is deemed very challenging with error prone patient logs or diaries. No undercounting was observed with the 18-N and 22-N FTC settings and a undercount discrepancy of only 0.01% of inhaler actuations was detected with the 25-N setting (Table 1) that had the greatest potential for force overlap with the pMDI and therefore the greatest theoretical potential for undercount. Over-counting discrepancy was 0.31% with the 18-N setting, 0.28% with the 22-N setting, and 0.24% with the 25-N setting (Table 1). The total combined discrepancy rate for all TMAI-200 devices tested was 0.28%, calculated over 22,446 user applied actuations.

Table 1: Discrepancy Rate as a Percentage of Number of User Applied Actuations for Three FTC Options of the TMAI-200 Dose Indicator

	Discrepancy Rate (%)		
Device Type	Undercount	Overcount	Combined
TMAI-200 (18 N)	0.00	0.31	0.31
TMAI-200 (22 N)	0.00	0.28	0.28
TMAI-200 (25 N)	0.01	0.24	0.25
		Total	0.28

An additional method of representing the counting accuracy is shown in Figure 2. In this representation the severity of any observed count inaccuracies can be identified for each inhaler tested.

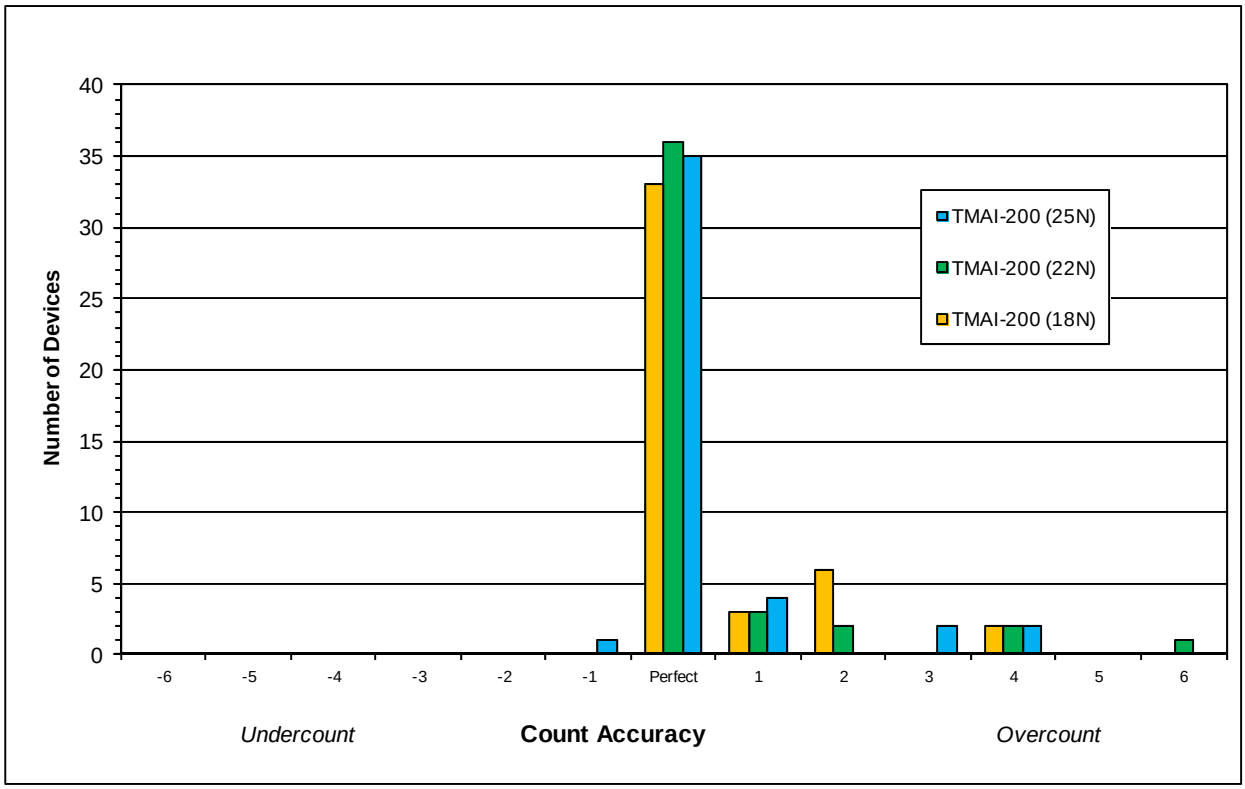

Figure 2: Counting Accuracy for Three FTC Options of the TMAI-200 Dose Indicator Based on Device Number

The 18N and 22N options produced no undercounting and the one 25N device that indicated an under-count was for one count only. For overcounting, all instances were less than 7 actuations (<5% nominal) and all but one less than 5 actuations (<2.5% nominal). The probability of overcounting was not linked significantly to any of the FTC/FTF combinations tested.

Conclusions

Published discrepancy rates for other dose counters and indicators that are on approved commercially available pMDIs range from 0.13% to 0.94% [4, 5, 6, 7]. The TMAI-200s evaluated in this investigation were measured to have a discrepancy rate of 0.28%, which is at the lower end of the range for such previously reported competitor studies. This study also demonstrates the importance of assessing count accuracy using a well designed gravimetric method which should eliminate the known unreliability when using patient logs or diaries.

References:

1. Food and Drug Administration. Guidance for Industry: Integration of Dose-Counting Mechanisms into MDI Drug Products. March 2003. On-line at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071731.pdf visited June 20th, 2014.

2. Holt S, Holt A, Weatherall M, Masoli M, Beasley R: Metered dose inhalers: A need for dose counters. Respirology 2005;10:105-106.

3. Rickenbach MA, Julious SA: Assessing fullness of asthma patients' aerosol inhalers. Br J General Pract 1994;44:317–318.

4. Weinstein C, Staudinger H, Scott I, Amar N, LaForce C: Dose counter performance of mometasone furoate / formoterol inhalers in subjects with asthma or COPD. Respir Med. 2011:105(7):979-988.

5. Wasserman R, Sheth K, Lincourt W, Locantore N, Rosenweig J, Crim C: Real world assessment of a metered dose inhaler with integrated dose counter. Allergy Asthma Proc. 2006; 27(6):486-492.

6. Sheth K, Wasserman R, Lincourt W, Locantore N, Carranza-Rosenweig J, Crim C: Fluticasone propionate/salmeterol hydrofluoroalkane via metered dose inhaler with integrated dose counter: performance and patient satisfaction. Int J Clinical Practice. 2006;60(10):1218-1224.

7. Given A, Taveras H, Iverson H, Lepore M: Prospective, open label assessment of albuterol sulfate hydrofluoroalkane metered dose inhaler with new integrated dose counter, Allergy Asthma Proc. 2013;34(1):42-51.