

SUMMARY OF RESULTS: COMPARATIVE ACCURACY STUDY OF THREE TOPICAL DISPENSERS FOR PHARMACEUTICAL COMPOUNDS

[NOTE: This document is a summary excerpted from the above-named study, which was sponsored by Reflex Medical-UnoDose. The complete report with full details of the test procedure and all results is available upon request at www.uno-dose.com.]

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I. PURPOSE OF EXPERIMENT

To analyze the accuracy and consistency of dispensing devices commonly used for topical application of pharmaceutical and veterinary creams from three manufacturers, and to assess the effect of cream thickness on dose accuracy.

II. EQUIPMENT AND MATERIALS

Dispenser Models Tested:

The dispensers evaluated in this study were the UnoDose™ by Reflex Medical Molding, the Topi-Click® 35 by DoseLogix and the TICKER® by BIOSRX. All three of the dispensers evaluated in this study used a piston design that is moved by a central drive screw. When the screw is rotated using the external knob, the piston, which engages the thread on the screw, advances a precise distance. The dispensed volume is determined by the cross sectional area of the internal cylinder and the distance traveled per click of the knob.



Figure 1. UnoDose™, Topi-Click® and the TICKER® Dispensers

Creams:

Thin: FAGRON, Fitalite™ Natural Cream Base (500g jar)

Medium: FAGRON, HRT Supreme Cream Base (500g jar)

Thick: FAGRON, Versatile™ Rich, Enriched Cream Base (500g jar)

III. PROCEDURE

A. Experimental Overview

This study was conducted to analyze the accuracy and consistency of the dispenser devices. Data was analyzed for 0.25 ml for Trials B-G. Additionally, Trials B, D and E were analyzed for 0.50 milliliter dose measurements. Emphasis was placed on the devices' ability to maintain consistency throughout the life of the dispenser. Analysis of data was enhanced through the graphical representation of the data distribution and the measures of center found.

Although dosing is typically quantified volumetrically in milliliters (ml) by the manufacturer, the dosing evaluation was performed by making mass measurements of the device before and after each dose was dispensed. Nominal values of specific gravity for each thickness of cream were provided by Reflex Medical Molding to calculate the fill volume of cream prior to each test. Dose measurements between the different brands of dispensers were made using medium thickness cream. Dose measurements to assess the effects of cream thickness were made only on the UnoDose™ dispenser.

IV. RESULTS

A. Nominal Dispensed Amount: 0.25 ml

UnoDose™ 30 mL, Medium Cream (Trial B)

	Unit 1	Unit 2	Unit 3	Combined Data, Units 1-3
Mean Dispensed Dose Mass (g)	0.246	0.248	0.247	0.247
Standard Deviation (g)	0.019	0.019	0.017	0.018
Standard Deviation (% of Mean)	7.6	7.7	6.8	7.4
Maximum Dose Error (% of Mean)	26.6	22.9	15.8	21.7
Minimum Dose Error (% of Mean)	-21.4	-21.0	-18.6	-20.4

Topi-Click® 30 mL, Medium Cream (Trial D)

	Unit 1	Unit 2	Unit 3	Combined Data, Units 1-3
Mean Dispensed Dose Mass (g)	0.243	0.245	0.243	0.244
Standard Deviation (g)	0.019	0.016	0.020	0.018
Standard Deviation (% of Mean)	7.6	6.4	8.4	7.5
Maximum Dose Error (% of Mean)	21.2	21.4	17.9	20.2
Minimum Dose Error (% of Mean)	-19.1	-14.6	-25.6	-19.8

TICKER® 30 mL, Medium Cream (Trial E)

	Unit 1	Unit 2	Unit 3	Combined Data, Units 1-3
Mean Dispensed Dose Mass (g)	0.244	0.246	0.248	0.246
Standard Deviation (g)	0.020	0.013	0.014	0.016
Standard Deviation (% of Mean)	8.1	5.5	5.8	6.4
Maximum Dose Error (% of Mean)	16.6	23.1	13.1	17.6
Minimum Dose Error (% of Mean)	-35.8	-23.6	-29.7	-29.7

B. Nominal Dispensed Amount: Aggregated Adjacent 0.25 ml Doses to Simulate 0.50 ml Dose**Combined Data, Units 1-3 for Each Device (Trials B, D, E)**

	UnoDose™	Topi-Click®	TICKER®
Mean Dispensed Dose Mass (g)	0.494	0.488	0.492
Standard Deviation (g)	0.019	0.019	0.023
Standard Deviation (% of Mean)	3.9	3.8	4.7
Maximum Dose Error (% of Mean)	13.0	9.9	8.9
Minimum Dose Error (% of Mean)	-15.6	-10.2	-23.6

V. DISCUSSION**A. Overall Dosage Accuracy**

Data from the RESULTS section was used to evaluate overall dosing accuracy and showed overall dose accuracy of the three dispensing devices (UnoDose™, Topi-Click®, TICKER®) to be very similar in Trials B, D and E. In these trials, a nominal 0.25 ml dose of medium cream was dispensed from 3 units of each device type beginning with a nominal fill of 30 ml. When looking at combined data across the three units for each device tested, the mean dosage dispensed ranged from 0.244 g to 0.247 g between the three types of devices. The standard deviation as a percent of mean was also very similar, ranging from 6.4% to 7.5% for the three types of devices. The average maximum dose above mean ranged from +17.6% to +21.7%. Greater variation was seen in average minimum dose below mean, which ranged from -19.8% to -20.4% (Topi-Click® and UnoDose™, respectively) to -29.7% (TICKER®).

When the adjacent data point pairs from Trials B, D and E were aggregated to show a simulated dispensing of 0.50 ml of cream, the statistical variation was reduced considerably. The standard deviation dropped to a range of 3.8% to 4.7% of mean. Both the average maximum dose above mean and average minimum dose below mean saw reductions, ranging from +9.9 to +13.0% and -10.0 to -23.6%, respectively. These improvements in consistency may be explained that absolute dose errors are normalized to 0.50 ml in this measurement vs 0.25 ml in the other measurements.

B. Dosage Size Distribution for All Doses

In APPENDIX B, this data is presented on one plot for comparison between devices. Overall, these charts show a normal distribution of dose mass about the mean for all of the units. However, the TICKER® data showed several doses that were significantly smaller than the other two devices; these are described in more detail in Section C below.

C. Dosage Consistency and Quantity Across Dispensed Volume

In APPENDIX C, the amount dispensed is plotted against dose number, with 1 being the first dose dispensed and 120 being the final dose. Both the UnoDose™ and Topi-Click® showed relatively consistent doses across the dispensed volume. The raw data (available upon request) showed that both the UnoDose™ and the Topi-Click® dispensers were capable of dispensing about 128 doses before the dispensed quantity dropped significantly.

It was found that the TICKER® dosing decreased noticeably as the dose number approached 120. The cause for this reduction was thought to be due to the device having incomplete piston travel at the bottom of the dispenser, thereby allowing residual cream to remain in the device rather than be dispensed. This is explained more in Section D [in the full report]. The falloff observed in the TICKER® in dosing could be overcome by using a slighter larger initial fill volume to compensate for the residual cream.

VI. CONCLUSION

Each of the dispenser types tested (UnoDose™, Topi-Click® and TICKER®) proved to be similar in the dosing accuracy for the creams and volumes tested in both mean, minimum and maximum dispensed amount as well as dose distribution.

However, the physical attributes of the units, such as openness of fill volume, cross section shape, number of ports, etc., may provide usability differences for one device versus another. Detailed evaluation of these considerations was beyond the scope of this experiment, but could be addressed in another study.

A NOTE FROM REFLEX MEDICAL-UNODOSE REGARDING MEAN DISPENSED DOSE, ABSOLUTE ACCURACY, AND SPECIFIC GRAVITY

The UnoDose™ Metered-Dose Topical Applicator is a volumetric dispenser. Each quarter turn, or click, of the dosing dial dispenses 0.25 milliliters through the exit holes. The metered doses are not exact, but vary in a statistical range about a mean, which will also likely have some bias.

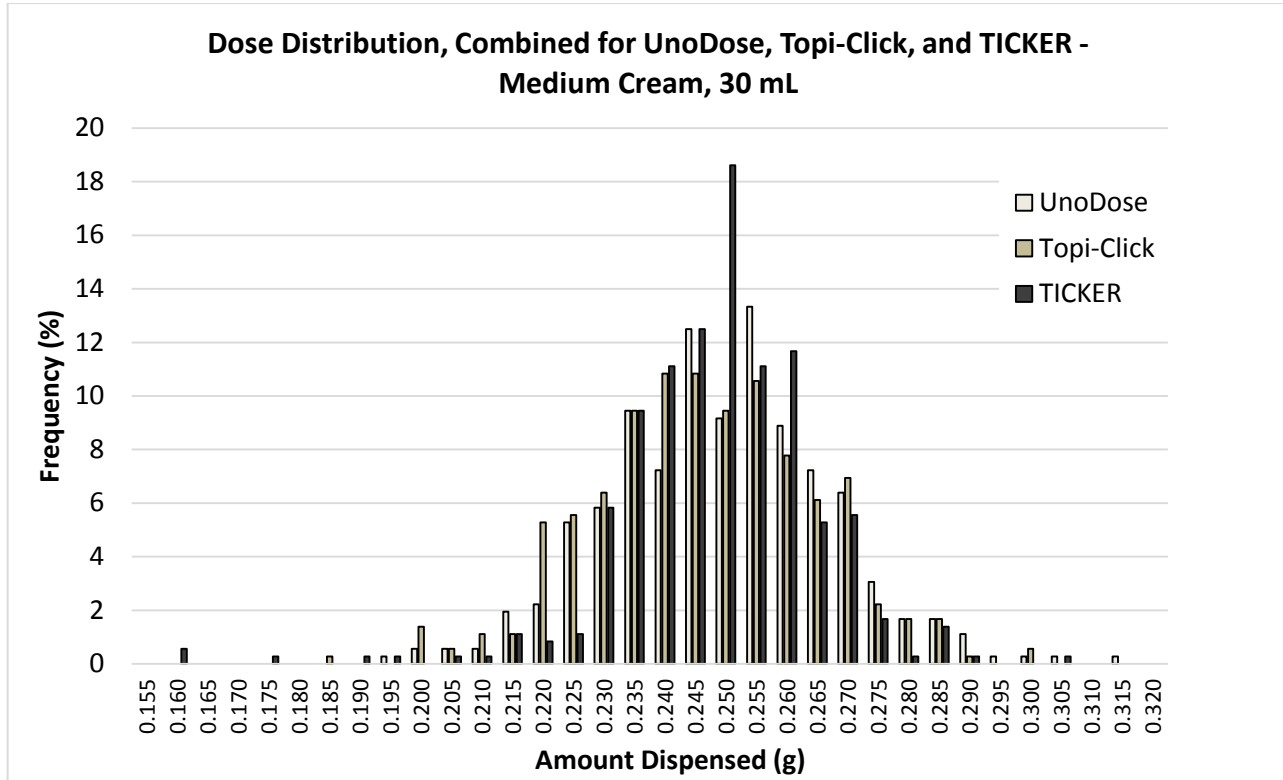
Most topical creams are less dense than water. Thus, the mean outputs reported in this study are less than 0.25 grams. Nevertheless, the results in this report are a valid analysis of precision, and the standard deviations are reasonable estimates of the devices' performance.

Based on internal testing and quality inspections, Reflex Medical believes the mean dispensed volume of the UnoDose applicators is within a 0.5% error over a full container cycle. Moreover, there appears to be no significant variation of dose output between the beginning and the end of a cycle.

When drug concentrations are stated in milligrams/gram (rather than mg/ml), the specific gravity of a formulation can significantly affect a patient's dose. This is especially true if mechanical mixing entrains air, which can further reduce the final specific gravity. Each 0.25 milliliter metered-dose will then be less than 0.25 grams, and the true patient dose is reduced unless the drug concentration is adjusted accordingly.

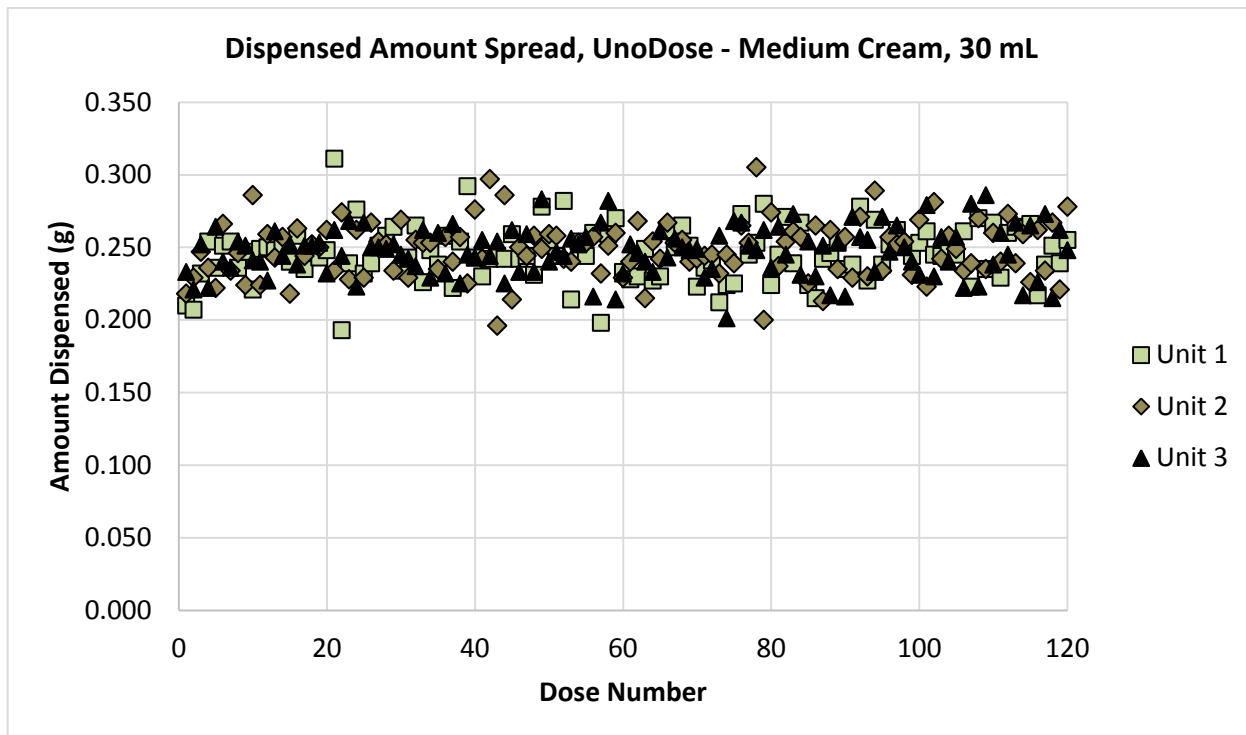
Refer to this study's complete report or contact Reflex Medical-UnoDose for more information regarding the absolute accuracy of UnoDose applicators and the effects of specific gravity on compounded cream mixtures.

APPENDIX B. DOSE SIZE DISTRIBUTION, ALL UNITS

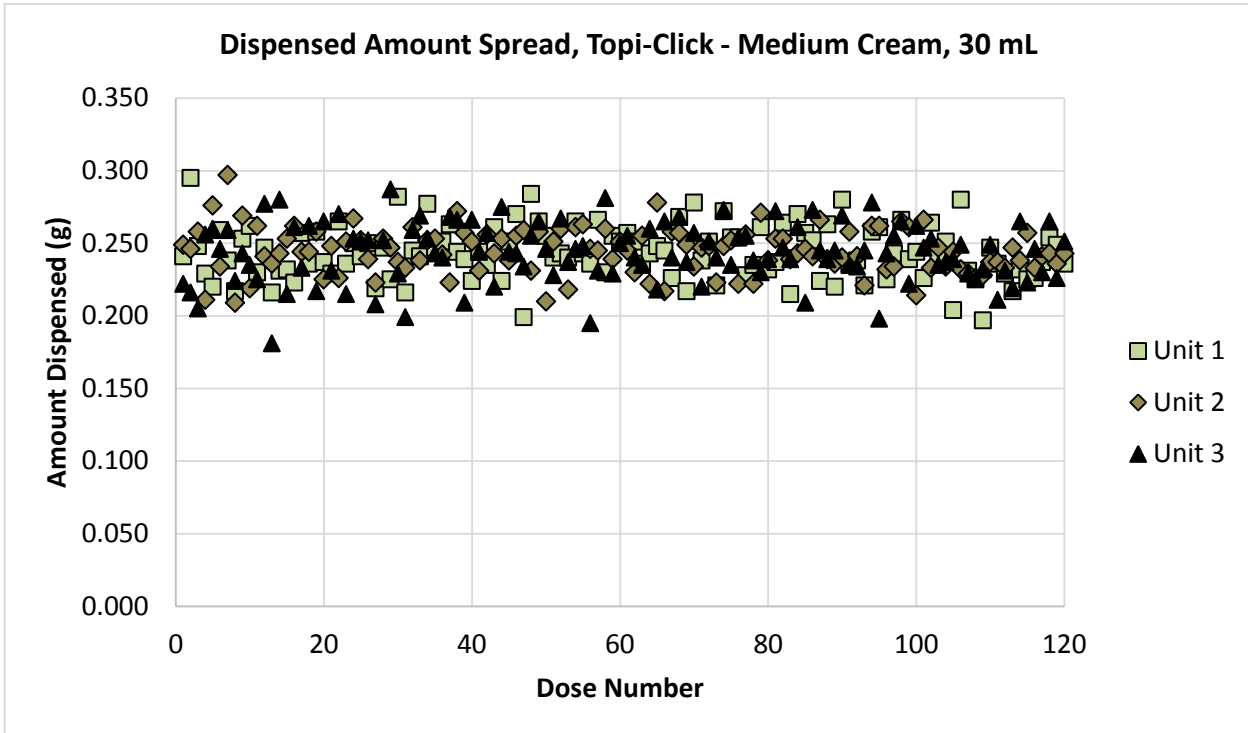


Graph 1. Dose Distribution (UnoDose™, Topi-Click®, TICKER®) - 30 mL

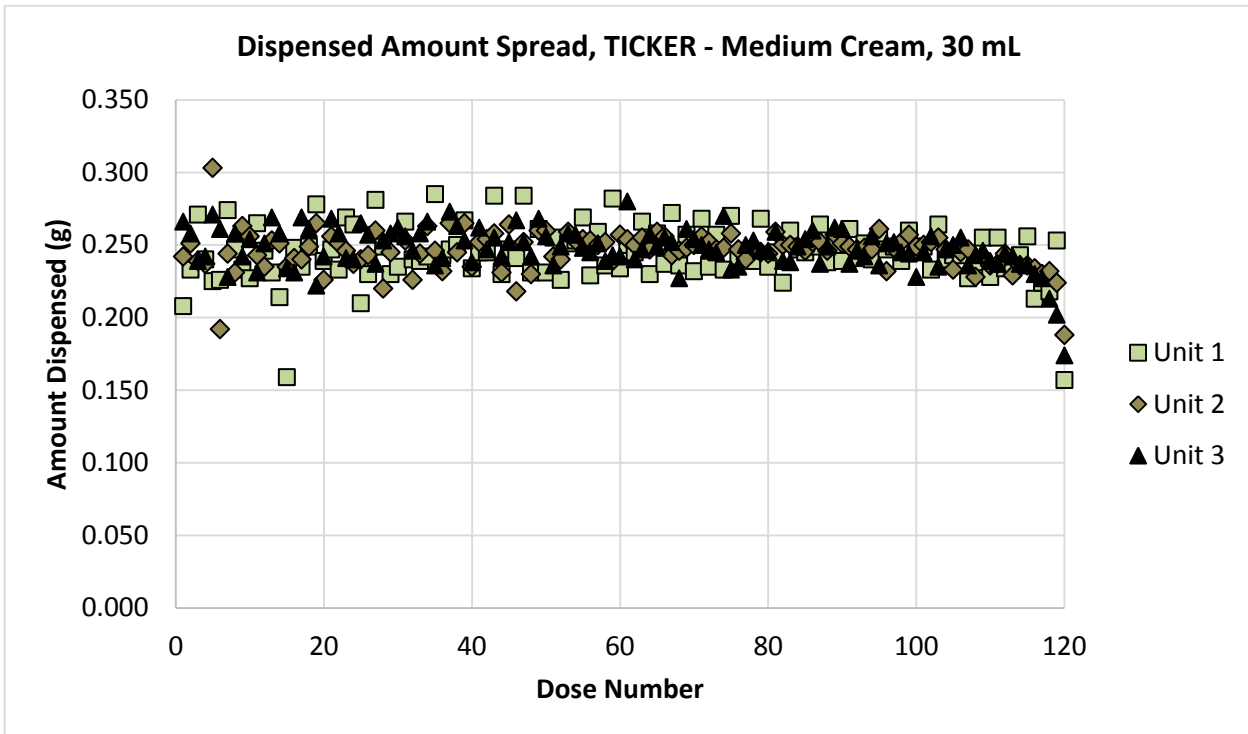
APPENDIX C. DOSE SIZE VS DOSE NUMBER



Graph 2. Dispensed Amount Spread (UnoDose™) - 30 mL



Graph 3. Dispensed Amount Spread (Topi-Click®) - 30 mL



Graph 4. Dispensed Amount Spread (TICKER®) - 30 mL