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Meeting the New FDA Standard for Accuracy of Self-Monitoring Blood Glucose Test Systems Intended for Home Use by Lay Users

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Abstract

The OneTouch Verio Reflect blood glucose monitor (BGM) has market clearance in several countries based in part on fulfilling the lay user and system accuracy criteria described in ISO15197:2015. However, the Food and Drug Administration (FDA) does not recognize the accuracy criteria in ISO15197 as a basis for gaining regulatory clearance for these devices. The current study evaluates the BGM using the accuracy guidelines issued by the agency for self-monitoring blood glucose test systems for over-the-counter use. Glucose results were accurate vs comparator over a wide glucose range and met lay user and glucose accuracy criteria at extreme glucose values as described in the FDA guidance.

Clinicaltrials.gov NCT03851549

Keywords

accuracy, blood glucose, blood glucose meter, blood glucose strips, self-monitoring of blood glucose

Introduction

In 2018, the OneTouch Verio Reflect (LifeScan Global Corp., Malvern, PA, United States) blood glucose monitor (BGM) was cleared in several countries based in part on achieving the criteria described in the International Standards Organization document ISO15197:2015(E): "In vitro diagnostic test systems—Requirements for blood glucose monitoring systems for self-testing in managing diabetes mellitus".[1] In the United States, however, the Food and Drug Administration (FDA) does not recognize ISO15197 as the standard for BGM accuracy, and in 2016, the agency issued guidelines for self-monitoring blood glucose (SMBG) test systems for over-the-counter use.[2]

Both ISO15197 and the FDA guideline require a lay user evaluation in which the intended user, ie, a person with diabetes, performs the finger stick blood glucose test themselves using only the instructions for use provided with the BGM system. ISO15197 requires at least 100 subjects with diabetes, whereas FDA guidance requires at least 350 subjects and specifies that "at least 10% of the study participants should be naïve to SMBG and may include non-diabetic subjects." In ISO15197, a two-tiered approach is taken to lay user accuracy requirements. If BG is ≥100 mg/dL, then results must be within ±15% of the reference standard. If BG is <100 mg/dL, then results must be within ±15 mg/dL of the reference comparator. In total, 95% of all results must fall within these criteria. However, in the FDA guidelines, 95% of all BG results must be within ±15%, and 99% within ±20%, of the reference comparator regardless of where in the glucose range the results fall.

Another key difference in the FDA guideline from ISO15197 is a system accuracy evaluation is not required. System accuracy is when a trained operator obtains the blood sample from a volunteer subject. Instead, the FDA guidelines require a separate test not found in ISO15197, namely an evaluation of SMBG performance at "extreme glucose values." At least 50 capillary whole blood samples <80 mg/dL and 50 samples >250 mg/dL should be used. These samples should be collected by a trained operator and may be manipulated by spiking or allowed to glycolyze in order to obtain the appropriate glucose concentration. These data are analyzed separately from the lay user evaluation data but use the same review criteria.

The current study evaluated the accuracy of a new glucose meter system according to the new FDA guidelines cited above. The guidance also contains information about

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precision, interferences, linearity, flex, and conditions testing. These tests were conducted but are not the subject of this manuscript.

Materials and Methods

Study Materials

Sponsor provided 8 glucose meters and 12 strip vials from three lots of Verio test strips randomly sourced and sequestered from supply chain batches: Lot A: #4492008; Lot B: #4498118; and Lot C: #4498132. All lots had expirations dated September 30, 2019. Sponsor also provided Yellow Springs Instruments (YSI) 2300 STAT PLUS Analyzers (Yellow Springs, OH, United States) as required.

Study System

The OneTouch Verio Reflect meters provide glucose results over the range of 20 to 600 mg/dL within a hematocrit range of 20% to 60% and an operating temperature range of 10°C to 40°C without the need for user calibration coding. The system uses test strips which utilize a flavin adenine dinucleotide-dependent glucose dehydrogenase enzyme to provide plasma-equivalent glucose results with minimal interference.[3,4] The strip requires 0.4 µL of fresh capillary blood, has a five-second test time, and corrects for hematocrit, temperature, and common electroactive interferences.[5]

The meter has a ColorSure® Dynamic Range Indicator that points to low, high, or one of the five in-range segments that lets patients know where their result lies according to their customizable glucose range (Figure 1(a)).[6] The meter has a Blood Sugar Mentor™ which provides personalized guidance (Figure 1(b)), insight (Figure 1(c)), and encouragement (Figure 1(d)) based on individual results.[6] When used in conjunction with the OneTouch Reveal® mobile app, readings from the meter will automatically sync with the app via *Bluetooth* low energy connectivity.

Lay User Testing

Subjects were aged ≥15 years with a current diagnosis of type 1 diabetes (T1D) or type 2 diabetes (T2D) and screening hematocrit values within 20% and 60%, the hematocrit range proposed in the FDA guidance. Protocols were approved by the responsible ethical review committees and all participants gave written informed consent prior to study procedures. Testing was performed from March to April 2019 by subjects without experience with the system tested. Subjects were briefed on the study requirements and provided with a copy of the system Owners Booklet but no training on the system was provided. Study staff collected blood from the same finger puncture for hematocrit and reference plasma glucose testing. Lay user evaluations were conducted in the United Kingdom at the Royal Infirmary of Edinburgh, Birmingham Heartlands Hospital, and Highlands Diabetes Institute, Inverness; and at the Institute for Diabetes Technology (IfDT), Ulm, Germany.

Extreme Glucose Test

Study staff carried out finger sticks on subjects from March to April 2019 and measured the initial glucose value on a screening glucose meter. The subject's capillary blood was collected in a 600 µL heparinized collection tube and the sample adjusted by means of either glycolysis or spiking with glucose to achieve the desired glucose level as required by the test design. For glycolyzed samples, the tube was placed in a water bath set to 36°C.

Data Analysis and Acceptance Criteria

To assess bias, meter test results were compared to the reference method (YSI 2300) and assessed against the accuracy standards in the FDA guidance. Comparator testing was in duplicate, ie, two assays were performed with the plasma sample on separate YSI instruments. YSI 2300 performance was verified daily using manufacturer's glucose linearity standard traceable to National Institute Science and Technology standards and always met the operational specifications stated in the YSI 2300 manual.

Results

Lay User Testing

A total of 354 evaluable subjects (193 males and 161 females) participated in the study. Median age was 59.9 years, with a range of 15.8 to 82.6 years. A total of 38.4% of subjects had T1D; 57.6% had T2D; and 4.0% did not have diabetes. A total of 69% of all subjects were taking insulin either by bolus, insulin pump, or with oral medications. The mean time since diabetes diagnosis for the 340 subjects with diabetes was 16.8 years with a range of 0.8 to 62.7 years. Subjects conducting SMBG ($n=318$) had a mean frequency of 2.8 tests per day. A total of 11 subjects had unaltered samples with BG <80 mg/dL and 62 subjects with unaltered samples >250 mg/dL, fulfilling the FDA requirement of at least 10 unaltered samples in each range.

Lay user accuracy criteria were met with 99.2% of results within ±15% and 100% of results within ±20% of the reference standard (Table 1). A bias plot (Figure 2) and a regression plot (Figure 3) including the line of identify ($y=x$) and regression fit line show the relationship between results from the meter vs results from the reference standard. Regression statistics included a slope of 1.02 (1.01-1.04, 95% confidence limits), a y-intercept of −2.7 (−5.4 to 0.1 mg/dL, 95% confidence limits), a standard error of 10.6 mg/dL, and an R^2 correlation coefficient of 0.98 ($P<.001$).

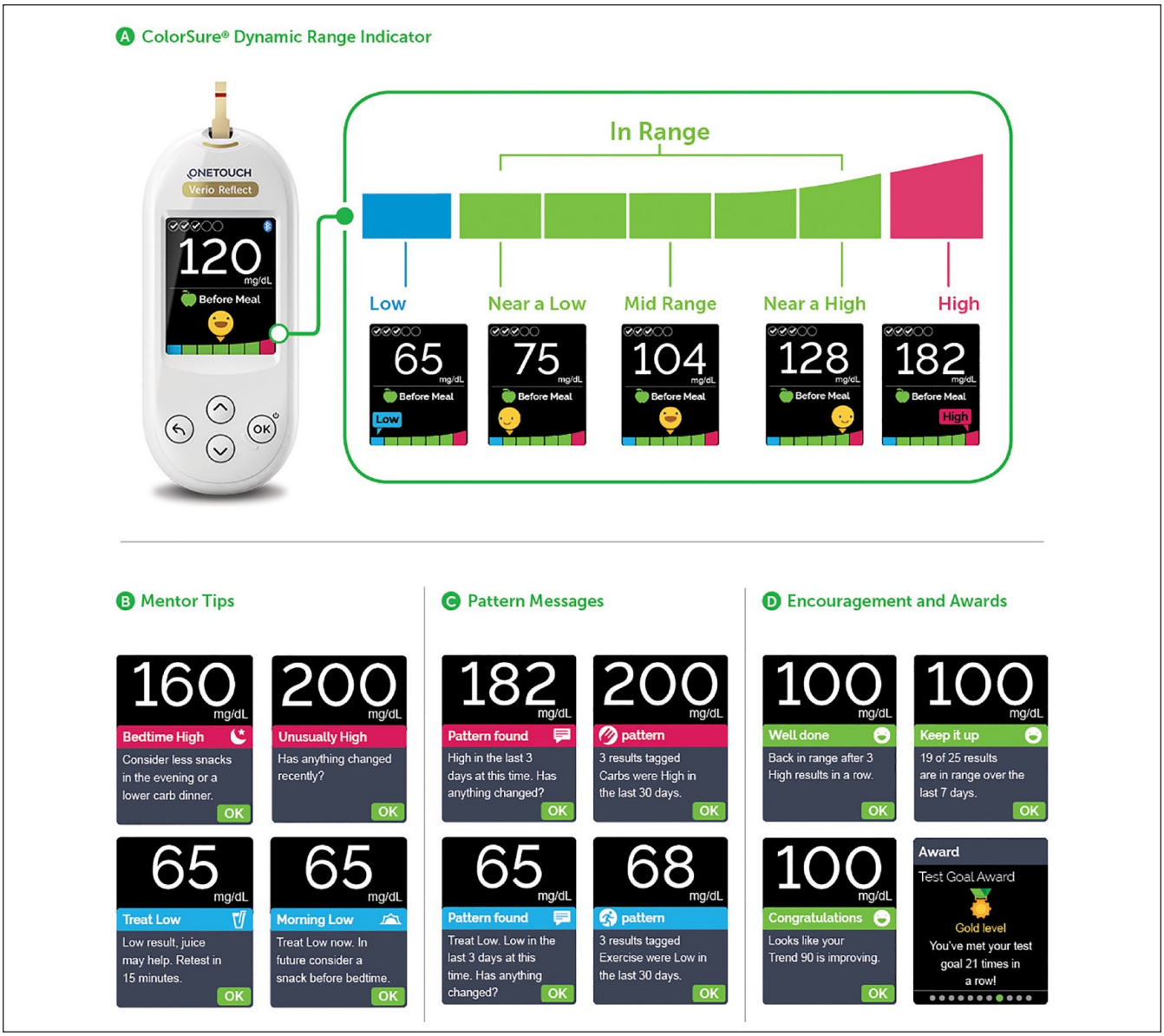

Figure 1. OneTouch Verio Reflect blood glucose monitoring systems. (a) ColorSure Dynamic Range Indicator. A changing emoji pointing to the green color bar indicates that the current blood glucose result is in range or is nearing high or nearing low. A message points to the blue bar if the result is low and points to the red bar if the result is high. (b) Mentor tips. (c) Pattern messages. (d) Encouragement and awards.

Table 1. Clinical Accuracy of OneTouch Verio Reflect Blood Glucose Monitoring System.

		Bias comparison to reference instrument			
	n	Within ±5%	Within ±10%	Within ±15%	Within ±20%
Lay user self-test[a]	354	222/354 62.7%	333/354 94.1%	351/354 99.2%	354/354 100%
Extreme glucose test[b]	300	200/300 66.7%	290/300 96.7%	298/300 99.3%	300/300 100%

[a]Data shown are from patient conducted finger stick samples compared to reference standard (YSI 2300) sample from the same finger stick across the entire glucose range.
[b]Data shown are from 50 blood glucose samples <50 mg/dL and 50 blood glucose samples >250 mg/dL compared to reference standard (YSI 2300) each tested on three strip lots.

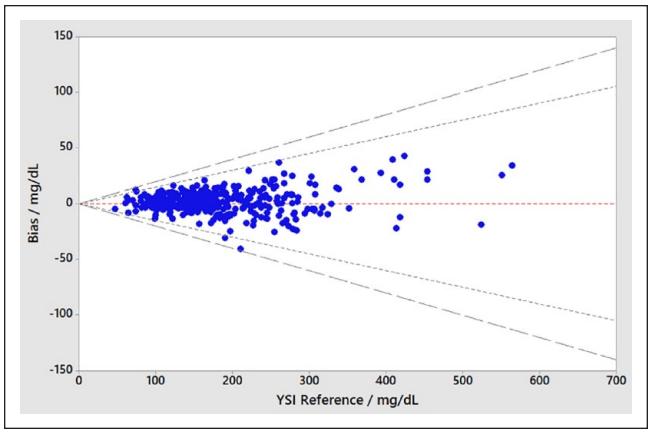

Figure 2. Bias plot for the subject self-test dataset. Dots represent blood glucose results. In total, 351 of 354 results fell within ±15% accuracy limit lines (inner dashed line) for three lots. The ±20% accuracy limit line (outer dashed line) is also shown. All 354 results fell within these limit lines. YSI, Yellow Springs Instruments.

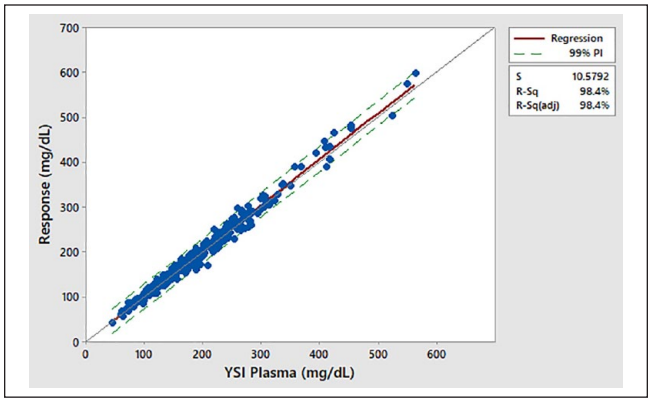

Figure 3. Regression plot for the subject self-test dataset. Dots represent blood glucose results. In total, 351 of 354 results fell within ±15% accuracy limit lines for three lots. Line of identity ($y = x$) and regression fitted line plot response (in red) are shown. YSI, Yellow Springs Instruments.

Extreme Glucose Test

The final dataset included 100 evaluable subjects of which 50 had final glucose concentrations between 20 and 80 mg/dL and 50 had final glucose concentrations between 250 and 600 mg/dL, fulfilling the FDA requirement for number of samples <80 and >250 mg/dL. Accuracy criteria across all three test lots were met with 99.3% of results within ±15% and 100% of results within ±20% of the reference standard (Table 1). Similar results were seen in each individual test lot (data not shown). A bias plot (Figure 4) shows the relationship between results from the meter vs results from the reference standard.

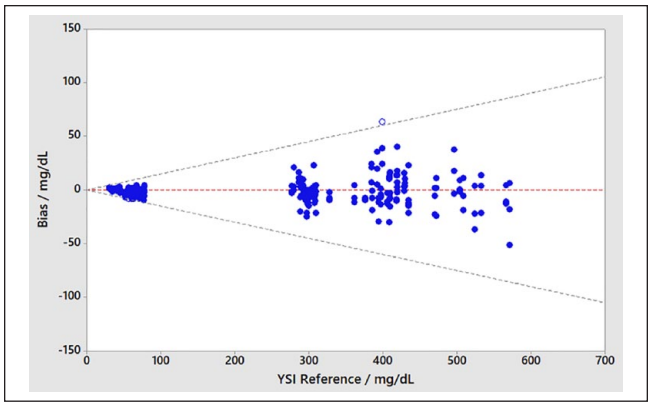

Figure 4. Bias plot for the extreme glucose dataset. Blue dots represent blood glucose results within ±15% accuracy limit lines for three lots. Open circles represent blood glucose results outside these limits. Blue dots, $n = 298$; open circles, $n = 2$. YSI, Yellow Springs Instruments.

Safety and Tolerability

There were no adverse effects observed other than the anticipated effects of the lancing procedure such as bleeding and transient mild pain at the site of lancing.

Discussion

In a previous clinical evaluation, the OneTouch Verio Reflect BGM met ISO15197 accuracy criteria.[6] The accuracy criteria specified in the ISO15197 guideline are used for regulatory clearance in most countries in the European Union and Canada. In the United States, however, the FDA does not recognize ISO15197 as the standard for BGM accuracy, and in 2016, the agency issued guidelines for SMBG test systems for over-the-counter use. Because this guideline specifies using a 15% bias across the entire glucose range as opposed to a 15 mg/dL bias at glucose <100 mg/dL, bias results must meet a tighter criteria in the FDA guidance at low glucose levels than in ISO15197. In addition, 99% of the bias results must fall within 20% of the reference standard, a requirement not found in ISO15197. Finally, at least 10% of the subjects must be naïve to SMBG, further challenging the BGM to deliver accurate results during lay user self-testing. Despite these more stringent requirements, the device tested met the new FDA guidelines for self-testing accuracy.

The FDA guidelines require an accuracy test at "extreme glucose values" not found in ISO15197. In a sense, this test replaces the system accuracy evaluation found in ISO15197 for glucose values at the upper and lower limits of the claimed measuring range. The BGM tested also met this new accuracy test.

Despite advances in technology and medications, only about 50% of people with diabetes are at their target blood glucose levels and there has been little improvement in this

level since 2003.[7] Many people living with diabetes do not achieve their blood glucose targets due to a lack of understanding of their results and the inability to know what action to take.[8] The BGM tested has features that automatically generate color-coded messages of personalized guidance that display diabetes management information when results are trending low and high, when the meter identifies a pattern of results falling outside the high and low range limits and provides encouragement with motivational messages. Although we have no clinical data from patients in this study, in a previous study, patients using this meter felt strongly that these features would be of potential benefit to them.[6]

In summary, a BGM previously tested under conditions described in ISO15197 passed different accuracy criteria described in the FDA guidelines for SMBG systems.

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: LK, LS, DK, and HC are full-time employees of LifeScan Global Corporation.

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