

FDA Executive Summary

Prepared for the
March 30, 2018 meeting of the
Clinical Chemistry and Clinical Toxicology Devices Panel
Measuring Blood Glucose Using Capillary Blood with Blood Glucose Meters
in all Hospital Patients

Introduction

This document is the FDA Executive Summary for the meeting of the Clinical Chemistry and Clinical Toxicology Devices Advisory Panel meeting on the use of capillary blood samples with blood glucose meters in patients throughout the hospital. This meeting is to discuss the general use of blood glucose meters with capillary samples from patients throughout the hospital and is not related to a particular pre-market submission.

Portable blood glucose meters that measure blood glucose values are used by millions of people every day as an aid in diabetes self-management. These types of devices are also used by healthcare professionals in a variety of clinical settings including acute and chronic care facilities, general hospital wards and intensive care units, physicians' offices, emergency departments, assisted living facilities, and nursing homes.

This document will provide background on the history of blood glucose monitoring systems and their use in the hospital, present new performance data from capillary samples obtained from hospitalized patients receiving intensive medical intervention/therapy including those in intensive care units, and discuss the history and importance of CLIA waiver for these devices. FDA is seeking the panel's opinion on the benefits and risks of measuring capillary blood using blood glucose meters in patients receiving intensive medical intervention/therapy, and the considerations for CLIA waiver for this use.

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I. History of Blood Glucose Meter Use

Portable blood glucose monitoring systems (BGMS) are devices that measure glucose in small blood specimens, typically capillary blood collected from a fingertip. Though these devices have been available for approximately 50 years, home monitoring of blood glucose by patients with diabetes became common in the 1990s and is the standard of care for diabetes glucose monitoring today. Throughout the 1990s technological advances made these devices easier to use, and they became smaller, faster, more reliable, and required a smaller blood sample. These improvements in BGMS technology were also recognized by the healthcare community and these devices, which were developed by manufacturers as intended for home use by ambulatory people with diabetes, began to be increasingly adopted for blood glucose measurement for any patient in many healthcare settings. BGMS devices were adopted for use in physicians' offices, emergency departments, acute and chronic care facilities, general hospital wards, intensive care units, assisted living facilities, and nursing homes in patients with and without diabetes.

II. Capillary Specimens in Hospital Use BGMS

FDA reviews analytical and clinical data in the evaluation of BGMS performance prior to marketing clearance. Data demonstrating a BGMS's imprecision profile, vulnerability to known potential interfering compounds (e.g., acetaminophen, uric acid, etc.), and accuracy across the measuring range are generated to validate acceptable performance. Additional factors affecting the performance of blood glucose meters include administered drugs, common physiological conditions (such as diabetic ketoacidosis), and user interface issues. For example, the administration of therapies containing maltose, which are commonly prescribed to patients in the hospital, have resulted in falsely elevated glucose results with previously used glucose measurement technologies.¹

Accuracy of the BGMS device is typically assessed through clinical studies that compare testing of blood on the BGMS to a matched sample (either the same sample or a sample collected in parallel at the same time) measured on the comparator method. Comparator methods are usually a laboratory-based glucose measurement method that has been well-validated for precision and accuracy, and that is traceable to a higher order (e.g., an internationally recognized reference material and/or method). All specimen types the BGMS manufacture claims for the device (e.g., capillary, venous, neonatal heel stick, and/or arterial blood) are evaluated in these studies.

There has been much public discussion over the last decade regarding the use of BGMS in hospital settings, including a discussion of accuracy requirements for different uses. Patient populations across the hospital vary, and the reasons for blood glucose testing vary across patients as well. In most hospitalized patients, BGMS results are not used to make immediate decisions about insulin dosing or other treatments. In other patients who may have Type 1 diabetes and require insulin boluses or infusions, or in patients that are part of glycemic control protocols, BGMS results may be used to immediately direct the administration of intravenous or subcutaneous insulin and intravenous glucose.

Glycemic control protocols became more common in the early 2000's when clinical data out of Greet Van den Berghe's group in Leuven, Belgium demonstrated that reducing hyperglycemia in intensive care patients led to better clinical outcomes.^{2,3} Her group demonstrated lower mortality in intensive care patients when glucose levels were managed to a strict range of 80-110 mg/dL using infused insulin by expert nursing staff. This practice of managing blood glucose in intensive care patients was known as "tight glycemic control." However, though the practice of glycemic control became more commonly implemented globally, other larger studies were unable to replicate the striking results observed in Leuven. Notably, the NICE-SUGAR

¹FDA public health notification: potentially fatal errors with GDH-P glucose monitoring technology, 2009. Available from: http://labmed.ucsf.edu/labmanual/db/resource/FDA_glucometer_warning_Aug_2009.pdf
Accessed 5th of March 2018.

² Van den Berghe, G. et al. Intensive Insulin Therapy in Critically ill Patients. *N Engl J Med.* 2001; 345:1359-1367

³ Van den Berghe, G. et al. Intensive Insulin Therapy in the Medical ICU. *N Engl J Med.* 2006; 354:449-461

(Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) study was discontinued after an increase in mortality due to hypoglycemia was observed in the tight glycaemic control arm.^{4,5} There have been several postulated reasons for the different outcomes including varying levels of insulin dosing expertise in the study staff, different target ranges for blood glucose, different nutritional strategies, different types of insulin administration, different specimen types (e.g., venous/arterial vs. capillary), and different instruments used to measure blood glucose. While the nurses in Leuven used blood gas analyzers to measure glucose in venous or arterial blood, institutions in the NICE-SUGAR varied in blood glucose measurement methodology and many sites used capillary blood measured by BGMS. Following these results many institutions continued to implement glycaemic control protocols in intensive care units, but no longer targeted tight control (e.g., 80-110 mg/dL) due to fears of increased hypoglycemia. Many glycaemic control protocols in use today are more conservative and aim to keep patients at approximately 150 or 180 mg/dL.

The study results described above prompted increased discussion of the accuracy requirements for hospital use BGMS. In 2010, FDA held a public meeting entitled *Clinical Accuracy Requirements for Point of Care Blood Glucose Meters*.⁶ The purpose of the public meeting was to discuss the clinical accuracy requirements of blood glucose meters and other topics related to their use in point of care settings. The workshop included a session entitled “Tight Glycaemic Control in Clinical Settings” which included presentations and discussion from physicians, laboratories, government, industry representatives, and patient advocates. Following discussions at this public meeting, FDA published a draft guidance document, *Blood Glucose Monitoring Test Systems for Prescription Point-of-Care Use*, that proposed the types of studies manufacturers of BGMS intended for use in healthcare settings should perform to assess BGMS performance, and included proposed performance goals for accuracy (see table 12 in VI. Summary). Based on hundreds of comments received on this draft guidance document, FDA published a final guidance in October 2016 which included revised accuracy performance goals for these devices (see table 12 in VI. Summary).⁷ In this guidance, FDA addresses BGMS claims for various patient populations and states that the patient population studied to assess accuracy should reflect the intended use population of the BGMS. The guidance recommends that if the BGMS intended use population is broad but includes patient sub-populations that might be particularly vulnerable to potential interferences and/or health risks resulting from meter inaccuracy, manufacturers should identify and include patients from these specific vulnerable

⁴ The NICE-SUGAR Study Investigators. Intensive versus Conventional Glucose Control in Critically Ill Patients. *N Engl J Med*. 2009; 360:1283-1297

⁵ Van den Berghe, G. et. al. Intensive Insulin Therapy in Critically Ill Patients: NICE-SUGAR or Leuven Blood Glucose Target. *J Clin Endocrinol Metab*. 2009; 94(9): 3163-3170

⁶ Federal register notice available from: <https://www.gpo.gov/fdsys/pkg/FR-2010-01-15/pdf/2010-742.pdf>. Accessed March 5th 2018.

⁷ Available from: <https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm380325.pdf>. Accessed March 5th 2018.

sub-populations in the study. Vulnerable sub-populations could be defined as patients in specific hospital wards, units, or departments— medical, neonatal, pediatric or surgical intensive care units. Vulnerable subpopulations could, for example, also be defined as categories of patients with general types of medical conditions—cardiac, surgical, pulmonary, or oncology patients.

While FDA was developing guidance, the clinical, regulatory, and manufacturing communities were developing standards for hospital use BGMS. In January 2013, the Clinical Laboratory Standards Institute (CLSI) published POCT12-A3—*Point-of-Care Blood Glucose Testing in Acute and Chronic Care Facilities; Approved Guideline—Third Edition*.⁸ This document provides “information for use by acute and chronic care facilities with laboratory support for structuring a point-of-care (POC) blood glucose testing service intended to ensure quality test results, as well as high-quality patient care.” This guideline contains information to assist hospitals in verifying and validating BGMS for use in hospital settings and recommends performance goals for BGMS accuracy throughout the hospital setting (see table 12 below). This document also recommends that in assessing BGMS performance, hospitals consider special subpopulations, including patients in glycemic control programs in intensive care units.

⁸ Available from: <https://clsi.org/standards/products/point-of-care-testing/documents/poct12/>. Accessed March 5th 2018

III. CLIA Regulation of Laboratory Testing

The Clinical Laboratory Improvement Amendments (CLIA) were passed in 1988 and established quality standards for all laboratory testing to ensure the accuracy, reliability and timeliness of patient test results regardless of where the test is performed. The Centers for Medicare and Medicaid Services (CMS) administers CLIA and has delegated the authority to FDA to assign all in vitro diagnostic tests to one of three CLIA complexity categories: high complexity, moderate complexity, and waived.

A. CLIA Complexity

High complexity tests require a high level of operator expertise and training and may require troubleshooting and/or several manual operator steps (e.g., most mass spectrometry based assays would be high complexity). In addition, any test which is not CLIA categorized, or is modified by the laboratory (e.g., a cleared or approved test that is modified), is by default a high complexity test. In some states the training requirements for operators of high complexity tests are relatively high (e.g., medical technology degrees).

Moderate complexity tests may include several steps, are usually automated, and require a moderate level of expertise from the laboratory personnel to run and maintain them. For example, most blood gas analyzer assays are categorized as moderate complexity.

According to the statute, waived tests are “simple laboratory examinations and procedures that have an insignificant risk of an erroneous result.”⁹ In other words, waived tests are simple, accurate tests with a low likelihood of incorrect results by an untrained user. Certain types of tests are waived automatically (e.g., urine pregnancy tests, visually read urine dipsticks). In addition, all tests that are cleared or approved for home use, such as over-the-counter (OTC) devices, are categorized as waived.

Tests that are not OTC or automatically waived may become waived by demonstrating via clinical and/or analytical studies that the device is simple and accurate enough to be categorized as waived.¹⁰ For context, FDA generally recommends that the lower 95% two-sided confidence bound of the percentage of the samples within an appropriate “allowable total error” zone over the entire measuring interval should exceed 92% (which is equivalent to 95% with acceptable total error in a sample size of 360 test results). Depending on the clinical use scenario of the tests, in some cases tighter performance characteristics may be needed to reasonably assure that the candidate test is “accurate”; in other cases, lower performance characteristics may be acceptable with sufficient benefit-risk justification. Tests that are simple and have demonstrated an insignificant risk of an erroneous result can be deemed waived by FDA.

⁹ 42 U.S. Code § 263a

¹⁰ Available from:

<https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070890.pdf>. Accessed March 5th 2018.

B. CLIA Requirements for Laboratories

Laboratories performing only waived tests are subject to minimal regulation. Laboratories performing moderate or high complexity tests must comply with specific laboratory standards governing certification, personnel, proficiency testing, patient test management, quality assurance, and quality control.

Laboratories who run FDA cleared or approved tests in their laboratory must “verify” test performance in their laboratory prior to offering the test. For example, a lab that is introducing a new FDA cleared Vitamin D immunoassay would perform a set of small verification studies to confirm that the results they are getting align with the expected test performance described in the test labeling.

If a laboratory performs testing using a test they have developed themselves (a laboratory developed test, or LDT) or if the laboratory has modified an FDA cleared or approved test (including modifications to the intended patient population), as stated above the test defaults to high complexity. Only laboratories with certification for high complexity testing may develop LDTs or modify FDA cleared/approved tests. In this case, the laboratory must go beyond test “verification” and perform larger analytical or clinical studies to demonstrate full test “validation” prior to offering the test for clinical use. The lab must also meet other applicable federal and state requirements for high complexity testing, such as personnel training requirements.

C. CLIA Regulation of BGMS

As stated above, glucose meters were originally designed as OTC devices intended for use at home by people with diabetes. Once these OTC meters migrated into the clinical setting, manufacturers began to add design features to make them integrate better into healthcare settings (e.g., quality control management software, user log ins, docking stations, etc.), but they continued to seek FDA clearance for these devices as intended for home use. By obtaining OTC clearance, the BGMS devices were automatically waived. However, manufacturers generally performed accuracy studies more suited to an OTC population rather than a sicker hospitalized population. Accuracy studies were performed in a relatively healthy, ambulatory population even though the devices were used in a wide variety of patient populations. These devices were also labeled with limitations against using the devices in certain populations, including patients receiving intensive medical intervention/therapy.

In late 2013, CMS released guidance to its surveyors and partners who are authorized to inspect laboratories, clarifying that hospitals using BGMS devices off label, including in intensive care settings, must meet high complexity requirements for these tests because the devices were no longer waived when used in these populations that were listed as limitations in the device labeling. They clarified that CLIA citations may be supported for laboratories who were inappropriately performing these tests as waived tests. This announcement caused considerable

angst in the hospital community because these devices were routinely being used in all parts of the hospital as waived tests, including for patients receiving intensive medical intervention/therapy. As stated above, high complexity testing requires that the laboratory have a certain type of CLIA certification, meet specific personnel and training requirements, and when using device off label, perform full validation activities prior to offering the test. For example, in some states, only laboratory professionals are permitted to perform high complexity testing, and this would not be feasible in intensive care units where nursing staff typically perform bedside testing. Many healthcare facilities were unable to meet the high complexity requirements and had to find less convenient alternatives to BGMS for glucose testing in certain hospital wards.

To address this challenge hospitals were facing, FDA encouraged manufacturers of hospital use BGMS to seek FDA clearance and CLIA waiver for use in all hospital patient populations, including for patients receiving intensive medical intervention/therapy. In 2014, Nova Biomedical became the first company to have a BGMS with FDA clearance and CLIA waiver for glucose measurement in “venous whole blood, arterial whole blood, neonatal heel stick and neonatal arterial whole blood samples throughout all hospital and all professional healthcare settings.” This clearance was supported by a large clinical study that compared venous and arterial glucose measurements using their BGMS to laboratory blood glucose measurements in 1698 patients at five different hospitals. However, Nova Biomedical’s study did not include capillary blood specimens, and the limitations surrounding use of capillary blood for testing in patients receiving intensive medical intervention/therapy remain in all hospital use BGMS.

FDA recognizes the importance of having CLIA waived BGMS in point-of-care professional healthcare settings. Additionally, FDA understands that being able to make capillary blood measurements in all hospitalized patients using FDA cleared and CLIA waived BGMS would be more convenient and feasible for hospital staff. FDA’s guidance on BGMS devices explains that though these are prescription use devices, the studies in the guidance are designed to support concurrent clearance and waiver of the BGMS, provided the data demonstrate acceptable performance. As stated above, the guidance suggests performance goals for accuracy as part of the study descriptions (see table 12 in VI. Summary).

IV. Accuracy of BGMS in Capillary Blood Samples from Intensive Care Populations

FDA has recently become aware of three relatively large datasets for two different BGMS devices in the intensive care setting comparing BGMS capillary test results to matched comparator method glucose measurements. FDA is unaware of similarly large sets of data for capillary blood in this patient population using modern BGMS technology. These data will help the clinical community better understand the accuracy that can be expected from these devices in this setting to improve patient care in the U.S. We have obtained permission from the sponsors of these studies to share this data in the context of an Advisory Panel Meeting. Our goal is to raise transparency surrounding how BGMS devices are performing when used by nurses on patients receiving intensive medical intervention/therapy. We seek to obtain advice from our Advisory Panel on this topic, and to hear public comment on this use of BGMS devices.

A. Clinical Studies

Though the three clinical studies are similar in design, there are some differences in how they were performed. The studies were performed using two different BGMS devices that are currently on the market for other intended uses. We will refer to the two meters as ‘Meter A’ and ‘Meter B.’ The following is a general description of the three studies presented below.

Study 1 (Meter A)

Capillary whole blood fingerstick specimens (N=567) were obtained from consenting patients within three different critical care units including the cardiovascular intensive care unit (CVICU), medical intensive care unit (MICU), and the operating room (OR). All BGMS testing was performed by standard CLIA waived operators (non-laboratory personnel) within each of these three critical care settings (typically nursing staff).

Capillary whole blood glucose results on the BGMS were compared to matched (collected in parallel) arterial or venous plasma results obtained on a central laboratory hexokinase method glucose test system.

Study 2 (Meter A)

Over 14,000 paired critical care capillary glucose specimens were retrospectively identified and met the following criteria:

- Within critical care departments, a capillary fingerstick specimen, and a venous/arterial glucose result were measured at the bedside by a CLIA Waived operator using the BGMS.
- Subsequently a plasma glucose test was performed on the same subject on the central laboratory hexokinase method within 15 minutes.

Capillary whole blood glucose results on the BGMS were compared to the matched arterial or venous laboratory plasma results.

Study 3 (Meter B)

Capillary whole blood fingerstick specimens (N=345) were obtained from consenting patients within the critical care units. All BGMS testing was performed by standard CLIA waived operators (non-laboratory personnel) within each critical care setting (typically nursing staff).

Capillary whole blood glucose results on the BGMS were compared to matched (collected in parallel) arterial or venous plasma results obtained on a central laboratory glucose test system.

B. Data

For context Tables 1 and 2 contain the data for the venous and arterial specimens for the Nova Biomedical hospital use meter that was cleared in 2014¹¹.

Table 1. Accuracy for Nova Biomedical’s cleared meter intended for venous and arterial testing for specimens with glucose <75 mg/dL.

Specimen Type	Within ± 5 mg/dL	Within ± 10 mg/dL	Within ± 12 mg/dL	Within ± 15 mg/dL	Exceeds ± 15 mg/dL
Arterial	163/201 (81.1%)	189/201 (94.0%)	195/201 (97.0%)	197/201 (98.0%)	4/201 (2.0%)
Venous	68/79 (86.1%)	77/79 (97.5%)	78/79 (98.7%)	79/79 (100%)	0/79 (0.0%)

Table 2. Accuracy for Nova Biomedical’s cleared meter intended for venous and arterial testing for specimens with Glucose ≥75 mg/dL

Specimen Type	Within ± 5 %	Within ± 10 %	Within ± 12 %	Within ± 15 %	Within ± 20 %	Exceeds ± 20 %
Arterial	844/1267 (66.6%)	1175/1267 (92.7%)	1220/1267 (96.3%)	1244/1267 (98.2%)	1258/1267 (99.3%)	9/1267 (0.7%)
Venous	171/268 (63.8%)	246/268 (91.8%)	260/268 (97.0%)	267/268 (99.6%)	268/268 (100%)	0/268 (0.0%)

Though not the purpose of these current studies, the arterial and venous data in the new clinical studies looks similar to the data for the cleared meter. For example, arterial and venous data collected in Study 1 using Meter A (168 arterial and 32 venous specimens from the CVICU and the MICU) are presented in Table 3.

¹¹ See https://www.accessdata.fda.gov/cdrh_docs/reviews/K132121.pdf for additional information on K132121.

Table 3. Accuracy of arterial and venous specimens using meter A.

Study 1	Within ± 5 %	Within ± 10 %	Within ± 12 %	Within ± 15 %	Within ± 20 %	Exceeds ± 20 %
Arterial and Venous	135/200 (67.5%)	186/200 (93.0%)	191/200 (95.5%)	196/200 (98.0%)	200/200 (100%)	0/200 (0.0%)

Study 1 Capillary Blood Glucose Data (Meter A)

Because the study sites have implemented glycemic control protocols in the intensive medicine population, there were no glucose results <75 mg/dL in Study 1. The results for glucose results ≥75 mg/dL are summarized in Table 4.

Table 4. Accuracy for Study 1 (Meter A) for specimens with glucose ≥75 mg/dL.

Specimen Type	Within ± 5 %	Within ± 10 %	Within ± 12 %	Within ± 15 %	Within ± 20 %	Exceeds ± 20 %
Capillary	277/567 (48.9%)	450/567 (79.4%)	484/567 (85.4%)	516/567 (91.0%)	549/567 (96.8%)	18/567 (3.2%)

Study 2 Capillary Blood Glucose Data (Meter A)

The results for glucose results <75 md/dL and ≥75 mg/dL are summarized in Table 5 and Table 6, respectively.

Table 5. Accuracy for Study 2 (Meter A) for specimens with glucose <75 mg/dL.

Specimen Type	Within ± 5 mg/dL	Within ± 10 mg/dL	Within ± 12 mg/dL	Within ± 15 mg/dL	Exceeds ± 15 mg/dL
Capillary	907/1894 (47.9%)	1470/1894 (77.6%)	1614/1894 (85.2%)	1737/1894 (91.7%)	157/1894 (8.3%)

Table 6. Accuracy for Study 2 (Meter A) for specimens with glucose ≥75 mg/dL.

Specimen Type	Within ± 5 %	Within ± 10 %	Within ± 12 %	Within ± 15 %	Within ± 20 %	Exceeds ± 20 %
Capillary	7473/14884 (50.2%)	11087/14884 (74.5%)	12799/14884 (86.0%)	13712/14884 (92.1%)	14350/14884 (96.4%)	534/14884 (3.6%)

Study 3 Capillary Blood Glucose Data (Meter B)

The results for glucose results <75 md/dL and ≥75 mg/dL are summarized in Table 7 and Table 8, respectively.

Table 7. Accuracy for Study 3 (Meter B) for specimens with glucose <75 mg/dL.

Specimen Type	Within ± 5 mg/dL	Within ± 10 mg/dL	Within ± 12 mg/dL	Within ± 15 mg/dL	Exceeds ± 15 mg/dL
Capillary	7/12 (58.3%)	11/12 (91.7%)	11/12 (91.7%)	12/12 (100%)	0/12 (0%)

Table 8. Accuracy for Study 3 (Meter B) for specimens with glucose ≥75 mg/dL.

Specimen Type	Within ± 5 %	Within ± 10 %	Within ± 12 %	Within ± 15 %	Within ± 20 %	Exceeds ± 20 %
Capillary	169/333 (50.8%)	272/333 (81.7%)	288/333 (86.5%)	308/333 (92.5%)	324/333 (97.3%)	9/333 (2.7%)

Meter B has also been tested in a healthy diabetic population. For comparison, the results from that ambulatory population using Meter B are presented below in Tables 9 and 10 for glucose results <75 md/dL and ≥75 mg/dL respectively.

Table 9. Accuracy in ambulatory diabetic patients for Meter B for specimens with glucose <75 mg/dL.

Specimen Type	Within ± 5 mg/dL	Within ± 10 mg/dL	Within ± 12 mg/dL	Within ± 15 mg/dL	Exceeds ± 15 mg/dL
Healthy Population	13/18 (72.2%)	18/18 (100.0 %)	18/18 (100.0%)	18/18 (100.0 %)	0/18 (0.0%)

Table 10. Accuracy in ambulatory diabetic patients for Meter B for specimens with glucose ≥75 mg/dL.

Specimen Type	Within ± 5 %	Within ± 10 %	Within ± 12 %	Within ± 15 %	Within ± 20 %	Exceeds ± 20 %
Healthy Population	104 / 145 (71.7 %)	137 / 145 (94.5 %)	140 / 145 (96.6%)	145 / 145 (100.0 %)	145 / 145 (100.0 %)	0 / 145 (0.0%)

V. Summary of Post-Market Safety for Blood Glucose Meters

Analysis of Medical Device Reports (MDRs) submitted to FDA for adverse events associated with blood glucose test systems (product codes “NBW” and “CGA”) is presented below. MDRs are submitted by device manufacturers, user facilities (e.g., hospitals), healthcare providers, and consumers. The MDR volume for glucose meters are among the highest volume of MDRs submitted to the agency for any device type. This may be due to the large population of people with diabetes in the US, the significant risks people with diabetes face every day, and the widespread use of these devices in patient management and care. The large volume of adverse event reports associated with these devices is also consistent with the criticality of the information they provide and the extent to which people depend on these devices on a routine basis.

From the current methods of reporting, it is unfortunately not possible to distinguish the MDRs that are from devices used at home from those used on hospitalized patients. However, Table 11 below summarizes the reports for all blood glucose meters from 2011 to 2017.

Table 11. Medical device reports (MDRs) for blood glucose meters from 2011 to 2017.

Year	MDRs (total)	Malfunctions	Serious Injuries	Deaths	Other/No Value
2011	23379	20108	3149	12	110
2012	24360	21532	2738	4	86
2013	34361	31758	2384	12	207
2014	38563	36179	2170	3	211
2015	61673	59146	2275	8	244
2016	75039	72584	2261	2	192
2017	34873	32780	2082	6	5

Because most glucose meters are used by people at home (OTC meters), a significant majority of the market for these devices represents home use; hospital use is a small proportion of sales. The number of reports each year described in this table are largely reports for meters used at home. Recently, following the publication of our final BGMS guidance, FDA has created new device product codes to allow for future separate MDR reporting for hospital and home use meters. However, the summary above may be of limited use for discussion of this current topic.

VI. Summary

Based on the replication of results in three distinct studies, FDA concludes it is probable that the performance observed in these three independent studies is representative of the performance of BGMS in capillary blood specimens in patients receiving intensive medical intervention/therapy. However, it does not appear that this information is widely understood.

There has been much public discussion about glucose meter performance in the hospital setting, including discussion of the use of glucose meters for capillary testing in patients receiving intensive medical intervention/therapy. For example, this topic has been discussed widely in clinical conferences regarding tight glycemic control in hospitalized patients. In the development of POCT12-A3, the expert working group considered this issue in developing the performance goals for glucose meters in hospital settings. As part of the development of FDA's *Blood Glucose Monitoring Test Systems for Prescription Point-of-Care Use* final guidance, there were hundreds of comments regarding appropriate performance goals for glucose meters in these settings, and many discussions about the role capillary testing plays in all parts of the hospital.

The data observed in these large studies would not meet even the most permissive of the currently used, or even proposed, criteria for glucose meter performance. Factors influencing the difference in accuracy between capillary and venous/arterial blood are unknown but may include error related to capillary blood collection or difficulty in obtaining an adequate capillary blood sample for testing in this patient population. Table 12 below contains a summary of the accuracy criteria from several guidelines or standards written to address glucose meter performance. The fact that the expert community generated these standards/performance goals appears to demonstrate a poor understanding (likely due to the paucity of robust data) in the clinical community of the accuracy and reliability of capillary blood glucose results in certain hospital settings, including in patients receiving intensive medical intervention/therapy.

Table 12. Proposed or Final Meter Accuracy criteria by guideline or standard.

	Criteria Used/Proposed
POCT12	<ol style="list-style-type: none"> 1. 95% of the results must have differences from the laboratory analyzer less than 12 mg/dl below 100 mg/dl and less than 12.5% above 100 mg/dl, and 2. The sum of the number of individual results with errors that exceed 15 mg/dl below 75 mg/dl and exceed 20% at glucose concentrations at or above 75 mg/dl should not exceed 2% of all results
FDA draft BGMS Guidance	<ol style="list-style-type: none"> 1. 99% of all values are within +/- 10% of the reference for glucose concentrations ≥ 70 mg/dL, and within +/- 7 mg/dL at glucose concentrations < 70 mg/dL, and 2. no individual result should exceed +/- 20% of the reference for samples ≥ 70 mg/dL or +/- 15 mg/dL < 70 mg/dL
FDA Final BGMS Guidance	<ol style="list-style-type: none"> 1. 95% of all values are within +/- 12% of the comparator method for glucose concentrations ≥ 75 mg/dL, and within +/- 12 mg/dL at glucose concentrations < 75 mg/dL, and 2. 98% of values should be within +/- 15% of the comparator method for glucose concentrations ≥ 75 mg/dL, and within +/- 15 mg/dL at glucose concentrations < 75 mg/dL
Range of Suggested Criteria in Comments to FDA's Draft BGMS guidance	<p>The tightest criteria proposed in stakeholder comments to FDA's draft guidance:</p> <ol style="list-style-type: none"> 1. 95% of all values are within +/- 10% of the comparator method for glucose concentrations ≥ 70 mg/dL, and within +/- 7 mg/dL at glucose concentrations < 70 mg/dL, and 2. 99% of values should be within +/- 15% of the comparator method for glucose concentrations ≥ 75 mg/dL, and within +/- 15 mg/dL at glucose concentrations < 75 mg/dL
	<p>The most permissive criteria proposed in stakeholder comments to FDA's draft guidance:</p> <ol style="list-style-type: none"> 1. 95% of all values are within +/- 12.5% of the comparator method for glucose concentrations ≥ 100 mg/dL, and within +/- 12 mg/dL at glucose concentrations < 100 mg/dL, and 2. 98% of values should be within +/- 20% of the comparator method for glucose concentrations ≥ 75 mg/dL, and within +/- 15 mg/dL at glucose concentrations < 75 mg/dL
ISO 15197:2013 (for OTC blood glucose meters)	<ol style="list-style-type: none"> 1. at least 95% of measurement results shall fall within ± 15 mg/dl of the reference value at glucose concentrations < 100 mg/dl and within $\pm 15\%$ at BG concentrations ≥ 100 mg/dl, and 2. at least 99% of measurement results shall fall within the Consensus Error Grid zones A and B

As described above, FDA's guidance for BGMS devices explains that though these are prescription use devices, the studies in the guidance are designed to support concurrent clearance and waiver of the BGMS, provided the data demonstrate acceptable performance. However, since it appears the accuracy of BGMS devices, when capillary blood is used in intensive care settings, is different than any published standards for meter accuracy in this setting, it is unclear whether there are particular clinical considerations at play, or this use would meet the accuracy standard for CLIA waiver. FDA would like to hear the Panel's discussion on this topic.

FDA recognizes the important role glucose meters play in hospital blood glucose testing, and the extensive integration of CLIA waived glucose meter testing in all departments in hospitals across the country. We are holding this advisory panel meeting to:

1. Increase transparency on the accuracy of BGMS when capillary blood is tested in CLIA waived settings on patients receiving intensive medical intervention/therapy,
2. Obtain advice from our Advisory Panel on this topic, and
3. Hear public comment on this use.

VII. Panel Questions

1. Given the data presented, please discuss any factors that should be considered in assessing the benefits and risks of glucose meters intended for measuring blood glucose in capillary blood in patients receiving intensive medical intervention/therapy.
 - a. Please discuss the benefits of such testing.
 - b. Please discuss whether there are unique risks when capillary blood is tested in patients receiving intensive medical intervention/therapy.
 - c. If there are unique risks, please discuss potential mitigations for each risk.
 - d. Please discuss the benefit to risk balance for this intended use.

2. Given the data presented, what are the relevant factors FDA should weigh in considering whether capillary blood glucose meter testing in intensively treated population would meet the criteria for CLIA waiver (i.e., “simple” and with “an insignificant risk of an erroneous result”)?