Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use

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Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of In Vitro Diagnostic Device Evaluation and Radiological Health
Division of Chemistry and Toxicology Devices

Preface

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Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use:

Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. Introduction

This draft guidance document describes studies and criteria that FDA recommends be used when submitting premarket notifications (510(k)s) for self-monitoring blood glucose test systems (SMBGs) which are for over-the-counter (OTC) use by lay-persons. When finalized, FDA intends for this document to guide manufacturers in conducting appropriate performance studies and preparing premarket notifications for these device types.

This guidance is not meant to address blood glucose monitoring test systems which are intended for prescription point-of-care use (e.g., hospitals, physician offices, long term care facilities, etc.). FDA is issuing another draft guidance entitled "Blood Glucose Monitoring Test Systems for Prescription Point-of-Care Use" to address those device types.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Background

Portable blood glucose monitoring systems (also called glucose meters) that measure blood glucose concentrations are used by millions of people with diabetes every day. These devices are used by patients in a variety of settings including in their homes, at work, and in schools.

Historically, the FDA has not recommended different types of information in premarket submissions (510(k)s) for blood glucose monitoring systems used by medical professionals as compared to OTC devices intended for use by lay users. However, it has become increasingly clear that these different use settings create distinct intended use populations with unique characteristics and device design requirements. For example, medical professionals are generally more proficient at performing testing and at running appropriate controls, and they typically have a better understanding of test limitations as compared to lay-persons. Further, the term "lay-person" encompasses a group of individuals with wide ranges in age, dexterity, vision, training received on performing testing, and other factors that can be critical in the patient's ability to accurately use the device and interpret test results.

SMBG devices and the associated test strips used by lay-persons are also more likely to undergo more varied storage and handling conditions compared to devices used in professional settings. As such, these devices should be designed to be more robust and reliable to accommodate actual use conditions.

In order to distinguish between prescription use blood glucose meters, which are intended for use in point-of-care professional healthcare settings, and those intended for OTC self-monitoring by lay-persons, the Agency is issuing two separate draft guidances for (i) prescription use blood glucose meters, for use in point-of-care professional healthcare settings, and (ii) SMBG devices intended for OTC self-monitoring by lay-persons. The FDA believes that in making this distinction, SMBG devices can be better designed to meet the needs of their intended use populations, thereby ensuring greater safety and efficacy.

In recent years, concerns have been raised citing infection control issues related to glucose meters and the lancet device. According to the Centers for Medicare and Medicaid Services (CMS) and the Centers for Disease Control and Prevention (CDC), blood glucose monitoring devices (meters and lancing devices) can transmit bloodborne pathogens if these devices are contaminated with blood specimens and are shared between users without effective cleaning, disinfecting and appropriate infection control measures. Though SMBG devices are intended for home use, they should also be designed to withstand appropriate cleaning and disinfection procedures over the life of these devices. These disinfection procedures should be properly validated (see Section IV below) for this type of device and appropriate instructions provided for the user. Validation methods should take into account the way in which the device is used, e.g., by lay users at home (or in other non-professional settings).

III. Scope

This draft guidance document is limited to SMBGs, which are regulated under 21 CFR 862.1345, Glucose Test System. The product code NBW applies to SMBGs.

This document is **not** meant to address the following types of devices:

- Blood glucose monitoring test systems intended for use in prescription point-of-care settings (e.g., hospitals, physician offices, long term care facilities, etc.)
- Devices used to screen and diagnose diabetes (such as clinical chemistry analyzers or semi-quantitative strips).
- Implanted or continuous glucose sensors.
- Non-invasive glucose measurement devices, (i.e., devices that do not require removal of a blood sample from a fingerstick or other anatomical site).
- Devices for measurement of blood glucose in neonates.

The device types addressed in this document typically use capillary whole blood from fingersticks or alternative anatomical sites. This device is not intended for use in healthcare or assisted-use settings such as hospitals, physician's offices, or long-term care facilities because it has not been determined to be safe and effective for use in these settings, including for routine assisted testing or as part of glycemic control procedures. Use of this device on multiple patients may lead to transmission of Human Immunodeficiency Virus (HIV), Hepatitis C Virus (HCV), Hepatitis B Virus (HBV), or other bloodborne pathogens.

We recommend that you contact the Division of Chemistry and Toxicology Devices in the Office of In Vitro Diagnostics and Radiological Health if you have questions regarding alternate intended uses of your device.

IV. Reducing the Risk of Bloodborne Pathogen Transmission in Diabetes Care

Because SMBG devices use blood specimens for glucose measurement, their design and instructions for use are very important factors in reducing the risk of bloodborne pathogen transmission during use. According to the Centers for Medicare and Medicaid Services (CMS) and the Centers for Disease Control and Prevention (CDC), blood glucose monitoring devices, as well as blood lancet devices, can transmit bloodborne pathogens such as viral hepatitis if these devices are contaminated with blood specimens and are shared between users without effective cleaning and disinfection. You should address the following considerations for device design and labeling:

- All SMBG devices should be intended for single patient use. The intended use should clearly state that the SMBG device is intended for use by lay users and should only be used for a single user.
- Meters should be designed such that all external materials can be cleaned (removal of organic soil) and disinfected (microbicidal process).
- All external surfaces of the meter, including seams and test strip port, should be designed for both ease of use and ease of cleaning and disinfection.

- You should develop an effective disinfection method that can be easily employed by lay users at home. You should provide the validated cleaning and disinfecting procedures for your SMBG device in your submission as well as in the labeling. Cleaning and disinfection are different processes and need separate validation procedures and specifications. See Sections IV.A and B. below for details on the recommended cleaning and disinfecting validation studies.
- You should validate the use of any disinfectant you recommend for use with your device, as described in more detail below. We recommend you consult the Environmental Protection Agency's (EPA) list of disinfectants that are registered for use against infectious bacteria and viruses[1] when choosing disinfectants to validate for use with your device.
- You should clearly warn users that lancing devices are for single-patient use only and should NEVER be shared.
- Labeling concerning safe device use can reduce the risk of user error; therefore, instructions for cleaning and disinfection should be clear and detailed. Labeling for all test system components should incorporate the same proprietary device name (ABC blood glucose test system, ABC blood glucose meter, ABC blood glucose test strips, etc.). See Section IX, Labeling below for detailed labeling recommendations.

Validation of cleaning and disinfection procedures involves both validation that the cleaning and disinfection products are effective against the primary viruses of concern (HIV, Hepatitis B, Hepatitis C) and validation that the cleaning and disinfection procedures do not deteriorate the device or alter device performance. FDA recommendations for such validation are outlined in the following sub-sections.

A. Validated cleaning and disinfection procedures

You should select cleaning and disinfection products that do not result in physical deterioration of the device overall, or any device component, such as the housing, touch pad, or buttons. You should make note of these physical indicators during your validation study and provide this information in your 510(k). The disinfectant product you choose should be effective against HIV, Hepatitis C, and Hepatitis B viruses. Outbreak episodes associated with glucose monitors have been primarily due to transmission of Hepatitis B viruses. Please note that 70% ethanol solutions are not effective against viral bloodborne pathogens, and the use of 10% bleach solutions may lead to physical degradation of your device.

To demonstrate that your disinfection protocol is effective against Hepatitis B virus you should perform disinfection efficacy studies to demonstrate that your procedure is effective with the external meter materials. Studies have demonstrated that viruses can remain infective for different time periods, depending on the surface. Viral survival may increase or decrease with the number of microbes present on a surface. Increasing

[1] . Selected EPA-registered Disinfectantshttp://www.epa.gov/oppad001/chemregindex.htm

amounts of microbes can protect viruses from disinfection, but damaging effects may also result from microbial proteases and fungal enzymes. Factors that influence survival on surfaces include fomite properties, initial viral titer, virus strain, temperature, humidity and suspending media. The simplest disinfection method would be the use of towelettes pre-saturated with a selected disinfectant. Disinfection with a towelette will reduce the risk of liquid getting into the meter device, therefore minimizing the chance of affecting the glucose meter reading. However, you should choose a disinfectant that is effective (against Hepatitis B Virus) and compatible with your specific device. In addition, you should choose a disinfection method that uses products that would be readily available to the home user.

We recommend you refer to the following standards:

- ASTM standard E1053-97(Reapproved 2002), Standard Test Method for Efficacy of Virucidal Agents Intended for Inanimate Environmental Surfaces

- ASTM standard E23620-09, Standard Practice for Evaluation of Pre-saturated or Impregnated Towelettes for Hard Surface Disinfection.

B. Demonstration that the device is robust to cleaning and disinfection procedures

You should demonstrate through bench studies that your SMBG device is robust to cleaning and disinfection procedures after multiple cleaning and disinfection cycles. You should describe in your submission the study design and results demonstrating that the analytical performance of the blood glucose monitoring system is not impacted by the cleaning and disinfection procedures.

You should address the following in designing your study:

- You should choose worst case scenarios with regard to cleaning and disinfection frequency and end user environment to determine the number of cleaning and disinfection cycles that should be tested. For example, the number of times you clean and disinfect the meter should be representative of the cleaning and disinfection that the meter will be exposed to in its use life (typically 3-5 years).
- We recommend using the same disinfectant product for both cleaning and disinfection. The effects of multiple products on the efficacy of the disinfectant products are not well understood.
- You should demonstrate that the test strip port and all other openings are able to withstand your recommended cleaning and disinfection procedures. The test strip port and material seams are highly susceptible to blood contamination, therefore it is important to be able to clean and disinfect these portions of your meter to reduce the risk of bloodborne pathogen transmission.
- When you evaluate your device after the cleaning and disinfection phase you should ensure that the procedure does not cloud the face/display of the meter and does not corrode or erode the plastic housing or buttons. You should note all

these physical indicators throughout your study and include these results in your submission. You should evaluate the performance of the meter to ensure that repeated cleaning and disinfection does not affect performance (accuracy). You should also demonstrate that lifetime cleaning and disinfection of any re-useable lancing devices packaged or recommended for use with your meter does not affect its performance or exterior materials.

- You should include infection control in your risk analysis studies and incorporate your validated cleaning and disinfecting procedures into your risk assessment.

You should incorporate your labeling instructions for cleaning and disinfection in your user study (see Section VI-C, below**)** to determine the effectiveness and clarity of the instructions in your labeling for lay users.

V. Device Description

You should provide a general description of the SMBG device in your 510(k). Typically, much of this information is also included in the User Manual; however, some of the information is not appropriate for the intended user (e.g., highly technical explanations) and should be included in the 510(k) only. You should provide the following in the 510(k):

General device description:

- Physical components of the system (including diagrams where appropriate).
- Manufacturer's performance specifications.
- Description and explanation of the test principle, including chemical reactions.
- Description of the format of results, including units of measure and whether results are reported in whole blood or plasma equivalents[2].
- Description of the composition and levels of control material.
- User maintenance needs (e.g., batteries).
- Features of the device, such as data transmission capabilities or features designed to enhance robustness, including ease of use.
- Features designed to minimize the risk of bloodborne pathogen transmission among patients.

Description of features controlled by the software:

- Displays and user messages: This includes how the system determines and displays the glucose concentration; messages or displays that appear while a user is taking a measurement; and features such as how a user can retrieve past results from storage in

[2] Note that for SMBG devices intended for use in the U.S., plasma equivalent results should generally be reported.

the device.

- Error messages: This includes any error messages that the SMBG displays. Examples include displays or messages that the user sees when a strip is inserted incorrectly or removed prematurely; too small a sample is applied to the test strip; or damaged, incorrect or deteriorated strips are used. You should also describe the error tolerance for user actions, such as these, that are inconsistent with device operation.

- User prompts: You should describe prompts that the device provides to the user, expected user responses, and timing issues (e.g., how quickly does the user need to respond, what happens if they respond after the allowed time). Examples of a user prompt are messages to the user to insert the test strip into the meter, add blood sample to the test strip, calibrate the meter, or store a result in memory.

- Alarms and other feedback: You should describe how the system responds to errors in user action, user inaction, or system status, e.g., low batteries or high ambient temperature. This includes methods by which the system detects and alerts the user when glucose levels are outside of the linear range of the system. Further, you should explain any self-diagnostic routines that the system performs.

It is important that you identify the expected responses by the user to messages. This includes whether and how the user should input information or press certain buttons to correctly set up the meter or to respond to a message.

VI. Performance Evaluation and Criteria for SMBG Devices

Sections A-F below indicate the types of device performance information that you should include in a 510(k) submission for a SMBG device.

In this section, the term "reference method" refers to 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., internationally recognized, reference material and/or method. The traceability chain should include as few stages as possible to reduce bias. FDA's current thinking on the issues that should be addressed and the recommended study designs and device performance evaluations are discussed below in Sections A-F.

A. Precision Evaluation Study

You should evaluate both repeatability and intermediate precision for your SMBG. The following sections outline FDA's current thinking on appropriate study design and analyses to evaluate repeatability and intermediate precision for SMBG devices.

Measurement Repeatability Evaluation:
In order to assess imprecision of the device across the claimed measuring range, you should evaluate samples containing the following five glucose concentration intervals provided in the table below:

Table 1. Glucose Concentrations for Repeatability Evaluation

Interval	Glucose Concentration Range (mg/dL)
1	30-50
2	51-110
3	111-150
4	151-250
5	251-400

You should determine repeatability using venous blood samples. Altered venous blood samples such as those that are spiked, diluted, or allowed to glycolyze in order to obtain the appropriate glucose concentrations are acceptable to facilitate coverage of the entire glucose concentration range using the concentration intervals outlined in Table 1. However, you should clearly identify all altered samples (spiked, diluted, or glycolyzed) in all submitted data. A minimum of 500 test strips from at least 10 vials and 3 manufacturing lots should be used in the study. For each sample concentration, a minimum of 10 meters should be used for these studies, with at least 10 measurements taken by each meter (i.e., 100 measurements per concentration). These tests strips should be taken from the same vial and/or package for each meter.

We recommend you present the results as the mean value of the 10 measurements per meter with the corresponding standard deviation (SD) and percent coefficient of variation (CV). For each glucose concentration range in Table 1, you should also provide the mean value, standard deviation (with 95% confidence intervals) and percent CV for data combined over all meters. You should describe the statistical procedures used in the analysis. You should also include a summary of any identified outliers that were excluded from statistical analysis, the method of outlier identification and the results of these outlier investigations.

Intermediate Precision Evaluation:
Intermediate precision measurement studies are designed to measure imprecision under normal conditions of use by the intended user (i.e., measurement by individuals over multiple days, with the same meter, and reagent system lot). These studies should be performed with prepared materials, such as control materials for use with the SMBG device.

The total number of meters and individual users in these studies is at the discretion of the sponsor, however a minimum of 10 devices should be used for each concentration. Precision should be evaluated over a minimum of 10 days, taking at least 1 measurement

per day of a sample from each glucose concentration interval listed in Table 1, for a minimum of 10 measurements per meter for each concentration (and 100 measurements per concentration). You should use a minimum of 500 test strips from a minimum of 10 vials or packages and 3 manufacturing lots. These tests strips should be taken from the same vial and/or package for each meter. The study should demonstrate acceptable precision for all lots, users and meters.

You should present data including the mean value of the measurements per meter with the corresponding standard deviation (SD) and percent coefficient of variation (CV). For each glucose concentration in Table 1 you should also present the mean value, standard deviation (with 95% confidence intervals) and percent CV for data combined over all meters. You should describe the statistical procedures you use. You should provide results based on all data. If any outliers were excluded from any of your statistical analyses, you should fully describe the method of outlier identification and the results of these outlier investigations.

B. Linearity Evaluation Study

You should evaluate the linearity of your device across the entire claimed measuring range. We recommend that studies include an evaluation of at least 11 evenly spaced concentrations tested and analyzed according to "Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach", CLSI document EP6-A. Linearity studies should be performed using venous blood samples. Altered venous blood samples such as those that are spiked, diluted, or glycolyzed are acceptable to facilitate coverage of the entire glucose concentration range. You should clearly identify all altered samples (spiked, diluted, or glycolyzed) within the submitted data.

You should submit a detailed description of the study design, target concentrations, a list of all data collected in this study, summary of the results and conclusions drawn from the study, and a description of the statistical analysis used.

C. Method Comparison/User Evaluation

1. ***General Study Design:***

We recommend that you design a single evaluation to assess both system accuracy in the hands of the intended users, as well as other aspects to support lay use, such as labeling assessment and usability. This type of design will more accurately reflect the device performance in the hands of the intended user, therefore providing a better estimate for total accuracy of the SMBG device.

FDA recognizes that most study evaluations performed for pre-market submissions occur in idealized conditions, thereby potentially overestimating the total accuracy of the SMBG device, even when performed in the hands of the intended user. It is important to design your study to most accurately evaluate how the device will perform in the hands of

the intended use population. Therefore, the study should be conducted under conditions that reflect the expected use of the device by the intended use population. These conditions should be consistent with the validated environmental conditions of the device (e.g., temperature, humidity, altitude etc.). You should fully describe the conditions of your study in your pre-market submission.

You should include at least 350 different subjects in your method comparison study. Fresh capillary samples should be obtained with sufficient volume to be measured on both the candidate device and the reference method. If you are planning to include claims that your device can be used at alternative sites (e.g., forearm, palm, etc.), you should obtain and evaluate 350 samples from each site.

For each claimed anatomical site the samples should adequately span the claimed measuring range of the SMBG device. Though it may be difficult to obtain samples at the extreme ends of the measuring range, the study should contain at least 10 unaltered samples with blood glucose concentrations < 80 mg/dL, and at least 10 unaltered samples between 250 mg/dL glucose and the upper limit of the claimed measuring range of the device. If these ranges are not covered after collecting samples from 350 subjects (for each sample site), additional subjects should be enrolled until adequate sample concentrations are collected. Data from all subjects in the study should be submitted, and no subjects should be excluded from the data analysis.

The subjects you enroll in the method comparison/user study should accurately reflect the intended use population of the device. The study group should be comprised of both naïve and non-naïve SMBG users. At least 10% of the study participants should be naïve to SMBG devices. You should describe the inclusion and exclusion criteria for enrolling the study participants, as well as the demographic characteristics of the subjects that participated in the study.

Prior to testing, study subjects should be given the device labeling (instructions for use, user manual etc…) that will be provided to the user with the device once on the market. For purposes of the study these instructions for use should be written in English only; translations into other languages should not be provided to these study participants. Prior to the study, you should perform a readability assessment (in terms of grade level) of the user manual, test strip insert, and control solution insert. For an over-the-counter product the reading level should be at an 8^{th} grade level or less. We recommend using the Flesch-Kincaid, SMOG, or equivalent computer program to assess the readability grade level of the labeling. You should describe the assessment and results in your submission.

The study subjects should obtain their own capillary sample and perform a blood glucose test using only the device labeling as instructions. No other training or prompting should be provided to the user, and they should not receive assistance from a study technician or healthcare provider to obtain the test result. Study subjects should be sequestered in such a way so they can not observe or be influenced by the testing technique of other study

participants or technicians. Once the study participant has obtained their own result using the SMBG device, the technician should then obtain an additional capillary sample for testing on the reference method. Since the intended user population of SMBG devices is the lay-person, it is not necessary for the technician to obtain capillary results on the SMBG device for comparison to the reference value.

You should include a minimum of 3 test strip lots and a minimum of 10 test strip vials or packages in the study. All test strips used in the study should have undergone typical shipping and handling conditions from the site of manufacture to a U.S. user prior to being used in the study. You should describe these shipping and handling conditions in your premarket submission.

Hematocrit values should be determined and recorded for each of the study participants. You should present individual hematocrit values in the 510(k) along with the meter results.

Blood glucose test results are used by people with diabetes to make critical decisions about their treatment; therefore, it is important that the results are accurate so that nutritional and drug dosing errors are better avoided. In order to demonstrate that your SMBG device is sufficiently accurate to be used safely by diabetic patients for this purpose, you should demonstrate that 95% of all SMBG results in this study are within +/- 15% of the reference measurement across the entire claimed measuring range of the device and that 99% of all SMBG results are within +/- 20% of the reference measurement across the entire claimed measuring range of the device. You should include all results in the submission. If there are any SMBG test results that are >20% relative to the reference, you should provide a justification for why the errors occurred and describe why the potential for that error does not render the device unsafe and ineffective, even when extrapolated to the intended use setting (e.g., when billions of tests are performed). We will review the justification to determine whether the data suggests that patients may be put at risk, or whether the sponsor's justification and proposed mitigation would be adequate.

FDA understands that some SMBG devices may not be able to measure reliably within 15% of the reference method at very low concentrations. If this is the case, you may need to raise the lower end of the claimed measuring range to the concentration where your device is sufficiently accurate according to the above described criteria. We expect that to meet the clinical needs of the user population, SMBG devices should minimally be able to measure blood glucose accurately down to 50 mg/dL and up to 400 mg/dL. The SMBG device should identify and provide an error code in situations where the measured glucose falls outside of the device's stated measuring range. For example, meter XYZ has a measuring range that can detect glucose concentrations down to 50 mg/dL; therefore, blood samples with glucose concentrations below 50 mg/dL should provide an appropriate error code (e.g., "LOW - Less than 50").

Method comparison and user performance studies for SMBG systems include multiple users and multiple blood glucose monitoring devices. Individual lancing devices should be used for each subject. The protocol for these studies should include measures in place to mitigate the risk of potentially transmitting disease between healthcare providers, subjects and users (for example use of disposable gloves or other physical barriers). The study protocol should also include details on how often and when gloves of the trained health professionals should be changed between users. Refer to Section IV above (Reducing the Risk of Bloodborne Pathogen Transmission in Diabetes Care) for additional information regarding the validation of cleaning and disinfecting of SMBG devices. You should describe these aspects of the protocol in your 510(k).

You should also describe the following in your 510(k):

- Study setting (i.e. description of the type of study location and operators used for the study and a justification of how the selected study conditions simulate intended use conditions).
- Type of study participants and the inclusion and exclusion criteria used to select the participants.
- Patient demographics (age range, education level, native language, work experience, disease state) and whether they are naïve SMBG device users or not.
- Details of procedures performed by lay users and study technicians.
- Instructions provided to users in the study. (Note: All instructions must be provided to users in English only.)
- Type of sample collected (anatomical collection site(s)).
- Number of test strip lots, number of test strip vials, and number of meters used in the study.
- Description of the shipping and handling conditions of the test strips prior to use in the study.
- A user questionnaire should be provided for the study participants to fill out after completing the study. A copy of the questionnaire and the results should be provided in the submission.

2. *Data Analyses:*

You should present all data in the submission, including cases in which the meter displays an error code, a 'High' or 'Low' message, or no result. All outliers that do not conform to the minimum accuracy criteria should also be included. All such outlier results should be investigated and explained when possible. To assist in this investigation, you should collect information regarding patient medications, hematocrit measurements, disease states during your study. You should include the following in your description of the results:

Regression analysis:

You should present the difference between individual study subject results and the reference value (or mean of the reference value, if multiple replicates are measured on the reference method) by plotting the candidate SMBG device as the dependent variable and the reference value as the independent variable. The plot should include the regression line and line of identity, as well as the 95% and 99% confidence intervals. Your summary of results should include the slope and y-intercept, calculated using suitable regression analysis procedures, and the estimate of the deviation such as the standard error (*Syx*). You should describe all statistical methods used and clearly identify and describe any outliers in the analysis.

Tabular data presentation:
In addition to providing the results of regression analysis, you should also present results in the following tabular format for each sample matrix. In this table, X= the number of samples within the specified difference from the reference method, and Y= total number of samples.

Table 2. Summary of data within specified mg/dL of the reference method:
For glucose concentrations across the entire range:

Within +/- 5 mg/dL	Within +/- 7 mg/dL	Within +/- 10 mg/dL	Within +/- 15 mg/dL
X/Y (%)	X/Y (%)	X/Y (%)	X/Y (%)

Accuracy at Extreme Glucose Values
Because the user study may not provide a sufficient evaluation of the device performance in the extreme upper and lower ends of the measuring range, you should perform additional studies using blood samples altered to less than 80 mg/dL and greater than 250 mg/dL. These samples should mimic unaltered patient samples as closely as possible. These additional studies should be performed separately from the above mentioned method comparison/user performance evaluation (Section VI.C) and may be performed in a laboratory setting (e.g., at the manufacturer's facility).

Capillary whole blood samples should be used for these studies. You should include a minimum of 50 prepared samples containing glucose concentrations below 80 mg/dL and 50 samples greater than 250 mg/dL. These samples should evenly cover the lower and upper limits of the claimed measuring range. Samples may be altered by spiking or allowing the samples to glycolyze in order to obtain the appropriate glucose concentrations. Samples should be measured on both the SMBG device and the reference method. You should analyze the data using the same methods described above for the user evaluation studies. FDA will also apply the same review criteria.

Error Codes for Samples Outside the Measuring Range:
You should demonstrate in your premarket submission that your device provided the appropriate error codes when glucose concentrations were out of the device's stated measuring range.

D. Interference Evaluation

You should evaluate the effect of potentially interfering endogenous and exogenous substances and conditions on device performance. This includes icterus, lipemia, and varying hematocrit levels, as well as the effect of common medications.

1. ***Endogenous/Exogenous Substances***

Study design:

You should perform interference testing using samples containing glucose concentrations across the range of the device. Specifically, testing should be performed in samples with glucose concentrations of 60 mg/dL, 120 mg/dL, and 250 mg/dL to evaluate clinically relevant decision points.

You should evaluate each potentially interfering substance at clinically relevant concentrations. You should test all substances at a minimum of two concentrations – the concentration that is expected or the therapeutic concentration, and the concentration that is the highest that could potentially be observed in a whole blood sample. For example, acetaminophen should be tested at the expected therapeutic concentration 20 µg/mL and also at the high, toxic concentration 200 µg/mL. Table 3 below lists our recommendations on the substances and concentrations that should be tested for interference. Table 4 below provides a sample format.

Table 3. List of Potential Interferents for SMBG Devices

Interferent	Therapeutic Level	High Toxic Concentration
Acetaminophen	20 µg/mL	200 µg/mL
Ascorbic acid	0.8 mg/dL	3 mg/dL
Bilirubin	1 mg/dL	25 mg/dL
Cholesterol	154 mg/dL	309 mg/dL
Creatinine	1 mg/dL	10 mg/dL
Dopamine	20 pg/mL	200 µg/mL
EDTA	0.1 mg/mL	2 mg/mL
Galactose	1 µg/mL	100 µg/mL
Gentisic acid	0.1 mg/mL	10 mg/mL
Glutathione	5 µmol/L	100 µmol/L
Hemoglobin	14 g/dL	20 g/dL
Heparin	0.5 IU/mL	5 IU/mL
Ibuprofen	10 µg/mL	500 µg/mL
L-Dopa	2 µg/mL	5 µg/mL
Maltose	1 mg/mL	100 mg/mL
Methyldopa	10 mg/L	10 g/L
Salicylate	100 µg/mL	500 µg/mL
Sodium	120 mEq/L	175 mEq/L
Tolbutamide	100 mg/L	1000 mg/L

Tolazamide	40 mg/L	400 mg/L
Triglycerides	100 mg/dL	500 mg/dL
Uric acid	5 mg/dL	10 mg/dL
Xylose	20 mg/dL	200 mg/dL
Sugar Alcohols*	0.03 mg/100mL	0.09 mg/100mL

*All common sugar alcohols should be tested including mannitol, sorbitol, xylitol, lactitol, isomalt, maltitol and hydrogenated starch hydrolysates (HSH). Sponsors should determine appropriate levels to test for interference with SMBG devices based upon common concentrations of these substances in the blood of diabetic patients.

You should provide a reliable estimate of the interference predicted for individual samples. To do this, we recommend the following method of measuring and calculating interference: Each sample should be tested on the reference method in replicates (minimum of 4). An average of reference measurements, for example, may give greater confidence in the true glucose concentration of the sample. You should use at least 3 test strip lots to evaluate interference. Each test sample should be tested on the new SMBG device in replicates of 30 (10 replicates per lot of test strips, for a total of 30 replicates per sample). Each replicate should be compared to the average value obtained from the reference method and a bias and % bias calculated. The % bias for each replicate should be combined to produce an average % bias for the sample (with 95% confidence intervals).

In the rare case where the substance being evaluated for interference with the new device also interferes with the reference method, a reference sample should also be created for each substance that contains the identical glucose concentration but solvent/vehicle in lieu of the potential interfering substance. The test sample can then be compared to the reference sample value as measured by the reference method. You should provide information demonstrating interference with the reference method for each substance in this category.

For SMBG devices intended for lay use, the degree of acceptable interference may vary by substance tested. For example, a small interference at extremely high acetaminophen concentrations may be able to be communicated through labeling because users are aware that they have or have not taken that drug. Other potential risks, e.g., observed interference from uric acid, may be more difficult to mitigate through labeling because the user may be unaware of their condition or incapable of determining at home whether they may be at risk. Therefore, you should report in the 510(k) the observed average percent bias for each sample/substance tested and any observed trends. If interferences are observed, then you should propose appropriate labeling to mitigate the risk of the interference in the lay user population; the labeling language appropriate for the observed interference will be discussed during the review of the submission. We do not recommend that final labeling be printed prior to receiving FDA input during the review.

If significant interference is observed at one substance concentration but not the other, you should perform additional analyses to determine the concentration at which interference begins to occur. For example, if a bias of 12% is observed at 200 μg/mL

dopamine and no significant bias is observed at dopamine concentrations of 20 pg/mL, additional testing should be performed to determine the lowest concentration between 20 pg/mL and 200 μg/mL where interference is first observed. In the 510(k), you should provide your definition of "significant" interference for that substance.

The substances listed above in Table 3 represent known or reasonable potential interferents for current glucose measurement technologies. As new drugs are developed or new interfering substances are identified, you should evaluate them for potential interference with your device. For example, if a new drug intended to treat cardiac complications in diabetic patients is approved, you should conduct a robust evaluation to determine whether the new drug interferes with your device. You should report to FDA if significant new interferences are observed with any cleared glucose monitoring device that is on the market. You should also evaluate new drugs/potential interferents when new or significantly modified technology is introduced.

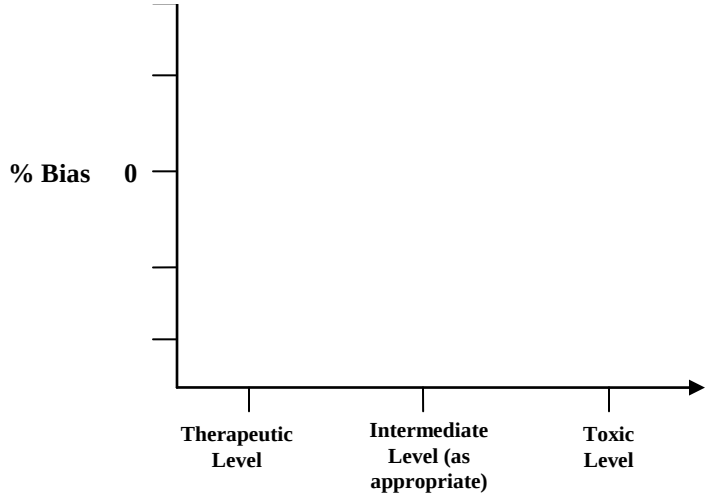
Data Analysis:
You should provide raw data sets as well as a summary table for all results in your submission. Please note that the summary tables should be presented separately for each test strip lot and glucose level tested. Table 4 below provides a sample format.

Table 4. Recommended Summary Table Format:
Lot 1/Glucose Concentration (60 mg/dL)
Potential Interferent: Acetaminophen

Mean Glucose Value (YSI)	**Interference Level**	**Mean Glucose (Meter)**	**Bias (mg/dL)**	**% Bias**	**Confidence Interval**
60 mg/dL	20 μg/mL				
	100 μg/mL				
	200 μg/mL				

We recommend you also present data graphically for each individual test strip lot. Graphs should describe the percent bias for all data points included in the study at therapeutic, toxic and any intermediate levels. The graph should include the mean glucose measurement obtained by the meter as well as the confidence intervals around the bias. A sample graph is shown below:

Figure 1. Sample Format for Interference Graph



In your 510(k) you should include a detailed description of the study design, a list of all data collected in this study, the summary tables and graphs indicated above and a description of the conclusions drawn from the study.

2. *Hematocrit*

Study Design:

You should evaluate the effect of hematocrit on the performance of your system to assess whether the device can be used safely in the intended use population across your claimed hematocrit range. The observed hematocrits may be very broad in the intended use population for this type of device; the majority of intended users may reasonably be expected to have hematocrit values between 20 and 60% hematocrit. Therefore, we recommend 20-60% hematocrit as the claimed range for this type of device. If your device is subject to significant interference from hematocrit within that range, you should include limitation statements in your labeling cautioning against use when certain physiological conditions are present or suspected (e.g., anemia, etc.). Because lay users generally have no way to adequately determine their hematocrit status, devices that cannot adequately measure glucose across the range of 30-55% hematocrit (which includes the greatest proportion of users) cannot be safely used to monitor blood glucose and may not be determined to be substantially equivalent.

Because a reasonably sized method comparison study still may not include the full range of hematocrit values expected in the intended use population, you should perform a separate study to determine how much analytical error may be contributed by this condition. You should evaluate hematocrit interference by measuring samples containing various glucose concentrations in reconstituted blood. The samples should be prepared to contain designated levels of hematocrit that span the claimed hematocrit range for the device. The blood sample may be adjusted by spiking or allowing it to glycolyze to obtain the desired glucose concentration. Specific percentages of hematocrit may be

achieved for each sample by manipulating the plasma to packed cell ratio following centrifugation. Hematocrit levels tested should span the claimed range in 5% intervals. For example, if your claimed hematocrit range is from 20-60%, you should test samples at 20, 25, 30, 35, 40, 45, 50, 55, and 60 % hematocrit. The samples should also span the claimed measuring range for blood glucose. Samples should include 5 different blood glucose concentrations evenly spread and targeted to the following ranges: 30 – 50, 51 – 110, 111 – 150, 151 – 250, and 251 – 400 mg/dL.

Each sample should be tested on the reference method in multiple replicates (a minimum of 4). An average of reference measurements, for example, may give greater confidence in the true glucose concentration of the sample.

A minimum of 3 test strip lots should be used to evaluate interference from hematocrit. Each test sample should be tested on your new SMBG device in replicates of 30 (10 replicates per lot of test strips, for a total of 30 replicates per sample). Each replicate should be compared to the average reference value for the sample and a bias and % bias calculated. The percent bias for each replicate should be used to produce an average percent bias for the sample (with 95% confidence intervals).

Because hematocrit interference is only one of the variables that will contribute to the overall analytical error of the system, it is important that it represent only a portion of the allowable error for the system. For this reason, bias observed in this study should be less than 8% on average, and no individual value should be greater than 15% of the reference method.

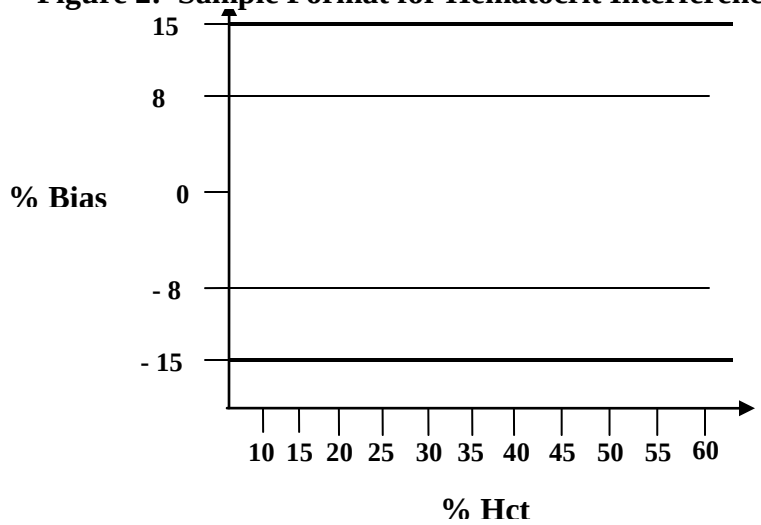
Data Analysis:
You should provide raw data sets as well as a summary of the hematocrit interference study (see recommended format below). Please note that the summary tables should be presented separately for each test strip lot and glucose level tested.

Table 5: Sample Format for Hematocrit Results:
Lot 1, Glucose Level 1 (30-50 mg/dL)

Mean Glucose Value (YSI)	**Hct (%)**	**Mean Glucose Value (Meter)**	**Bias (mg/dL)**	**% Bias**	**# of Observations > +/- 15% Bias**

You should also present the data graphically for each individual test strip lot. Graphs should include percent bias for all data points included in the study. The graph should include confidence intervals around the percent bias

Figure 2: Sample Format for Hematocrit Interference Graph



You should submit a detailed description of the study design, a list of all data collected in this study, the summary tables and graphs indicated above, and a summary of the conclusions drawn from the study.

E. Flex Studies

There are typically fewer controls in place in OTC settings to mitigate risk. In addition, the users are often untrained and may not know how to identify or address an incorrect result. It is therefore assumed that the OTC devices are designed so the risk of an erroneous result should be far less than with laboratory-based tests. You should therefore demonstrate that your SMBG device design is robust (e.g., insensitive to environmental and usage variation) and that all known sources of error are effectively controlled. In general, flex studies should be used to demonstrate robust design while risk management should be used to demonstrate identification and effective control of error sources, although the two are not mutually exclusive.

Most risk control measures should be fail-safe measures or failure alert mechanisms. Examples of fail-safe mechanisms are lock-out functions to ensure that a test system does not provide a result when test conditions are inappropriate, such when there is a component malfunction or operator error. Other examples are measures within the system to prevent operator error, such as guides or channels that prevent improper strip placement. We recommend that test system design incorporate fail-safe mechanisms whenever it is technically practicable. If fail-safe mechanisms are not technically practicable for some risks, failure alert mechanisms should be used. Failure alert mechanisms notify the operator of any test system malfunction or problem. They may include measures such as internal procedural controls or electronic controls. Devices with such mechanisms allow the operator to correct the error, or put the operator on notice that the results will be unreliable due to the error. For example, in cases where the result

exceeds the reportable range (e.g., extremely high or low glucose result) and the result is a critical value, the device should give a message such as "out of range high" or "out of range low."

Flex studies, or studies that stress the operational limits of a test system should be used to validate the insensitivity of the test system to performance variation under stress conditions. Where appropriate, flex studies should also be used to verify and/or validate the effectiveness of control measures at operational limits. Flex studies are particularly important for OTC SMBG devices as these devices are intended for use by lay users and undergo a variety of environmental and user-associated conditions that could affect system performance.

In order to identify all relevant flex studies for your SMBG device, we recommend that you conduct a systematic and comprehensive risk analysis that identifies all potential sources of error, including test system failures and operator errors, and identifies which of these errors can lead to a risk of a hazardous situation. You should then identify control measures, including fail-safe and failure alert mechanisms that will reduce risks for these sources of error. When the control measures have been implemented, you should (1) verify that each control measure has been properly implemented, and (2) verify and/or validate the effectiveness of each control measure. When appropriate, flex studies should be used to verify and/or validate the effectiveness of these control measures.

Below we have identified several flex studies that we believe are important for you to perform in order to demonstrate adequate performance of OTC SMBG systems. At the same time, we continue to encourage you to perform risk analyses to determine whether your device includes any unique or new features that should be validated through flex studies.

If your SMBG device does not perform adequately in flex studies, we recommend you either provide a justification, determined by means of thorough risk analysis, as to why adequate performance under that flex study is not required for safe effective use of the device or indicate an additional validated control mechanism implemented to assure safe and effective use of the device. FDA will review such justifications to determine whether the proposed mitigation strategies are adequate to protect patients.

In the case of the following flex studies, it is acceptable for you to provide documentation indicating that flex studies have been conducted in accordance with a recognized industry standard. We recommend you include the type of testing performed, the reference standard followed, the acceptance criteria, and whether the SMBG device passed testing requirements.

The flex studies we recommend performing in this manner are:

- Mechanical Vibration Testing
- Shock Testing

- Electromagnetic compatibility (EMC) Testing
- Electrostatic Discharge/Electromagnetic Interference Testing

Unless otherwise indicated, we recommend that you clearly identify all flex studies performed on your device in your premarket submission. A detailed description of the following attributes should be included:

- Study goal
- Study protocol and methods
- Methods used to apply samples to test strips
- Description of sample type and any anticoagulants used
- Study results
- Description of conclusions made from the study

We have also identified additional flex studies that we believe are important for manufacturers to perform in order to demonstrate adequate system performance in intended use settings. A list of these recommended flex studies as well as recommended study designs are included below.

1. Test Strip Stability Testing

You should perform a study to assess test strip performance throughout its claimed shelf life. We request that you submit only the study protocol, the acceptance criteria for the test strip stability study, and the conclusions of the study.

You should evaluate precision and accuracy of test strips at various time points throughout their stated shelf life. You should indicate the time points that are assessed in this stability protocol (e.g. 1 month, 3 months, 2 years); a combination of real-time and accelerated aging studies are acceptable. You should perform both precision and accuracy evaluations at each identified time point as described below. Through these evaluations, you should demonstrate that the CV calculated in this study is within the labeled performance of the SMBG device.

Precision Evaluation:

Precision with Control Materials

This study should be completed over 5 days and use glucose controls. At least two SMBG devices should be included in this study and at least 10 measurements should be taken per control level per meter.

Precision with Whole Blood Samples

This study should be completed over 10 days using whole blood samples spanning the SMBG device's stated measuring range. Samples may be altered by spiking with glucose or allowing the samples to glycolyze in order to evaluate the extreme end of the system's measuring range. At least two SMBG devices should be included in this study and at least 10 measurements should be taken per glucose level, per meter.

Accuracy Evaluation:
The study should be performed using patient whole blood samples that span the SMBG device's stated measuring range. It is acceptable for samples to be spiked with a known concentration of glucose, or allowed to glycolyze to achieve the desired concentration in order to evaluate the extreme ends of the system's measuring range. Glucose concentrations should be measured on the SMBG meter and compared to values obtained with the reference method.

2. Temperature and Humidity Effects on SMBG Device

We believe the following recommendation for conducting temperature and humidity effects studies most closely represents actual use conditions experienced by users of OTC SMBG devices.

We recommend the simultaneous evaluation of temperature and humidity effects on blood glucose meters and blood glucose test strips under "Open Vial" (i.e. to mimic use of test strips after an individual user has opened a test strip vial) and "Extended Open Vial" (i.e. to mimic use of test strips from vials that have been left completely open for the duration of the claimed test strip vial shelf-life) conditions. Separate testing of test strip and meter shipping and storage conditions are not necessary if, for these temperature and humidity studies, only packaged blood glucose meters and blood glucose test strips that have undergone appropriate storage conditions and the longest possible shipping duration (both as specified by the manufacturer) are used. In addition, tested temperature and humidity ranges should not only cover the claims specified in the device labeling, but test conditions should also stress the SMBG device and include ranges outside of labeling claims. We recommended that you test the effects of fluctuating temperate and humidity on blood glucose meters and blood glucose test strip performance, as well as effects of heat and humidity changes across the open vial shelf life. We recommend you use multiple meters and test strip vials in these studies.

We recommend that you present results for temperature and humidity studies as the mean values of measurements per meter. You should also include corresponding standard deviations (SD) and coefficients of variation, as well as the grand mean, pooled variance, pooled standard deviation (with 95% confidence intervals) and pooled CV. You should describe your statistical methods. For statistical analysis, ANOVA is the preferred method for calculating intermediate precision. You should also include a summary of any identified outliers that were excluded from statistical analysis, the method of outlier identification and the results of outlier investigations.

We encourage manufacturers to also consider ways in which temperature and/or humidity detectors might be incorporated into test strip containers to alert users when strips have not been handled correctly or stored according to recommended and validated conditions.

3. Altitude Effects

You should evaluate the effect of altitude on performance for your SMBG devices by comparing results from whole blood samples with the candidate device to the reference method. These studies should include a pressure change. Studies based on oxygen tension instead of pressure change are not adequate, because oxygen tension is only one component that changes with altitude. Altitude pressure changes can be accomplished by physically increasing altitude (e.g., in an airplane, on a mountain), or by simulating increasing altitudes and atmospheric conditions in a pressurized chamber. Results should support the altitude labeling claim for your device. You should provide your definition for terms, such as "sea level". The definition of sea level should not extend past 500 feet. You should test your SMBG device at a minimum of 10,000 feet above sea level.

4. Short Sample Detection

Blood glucose measurement from short samples (samples of reduced volume) can lead to inaccurate results. To avoid the risk of inaccurate results, SMBG devices should be able to detect that a short blood sample has been applied to the test strip and should not provide a result to the user. Short sample detection systems should not rely on visual verification by the user.

The volume required to classify a test sample as a short sample is dependent upon the SMBG device. In your short sample detection studies you should include blood samples with known glucose concentrations in the following three ranges: 50-65 mg/dL, 100-120 mg/dL, and 200-250 mg/dL. You should test blood samples with your candidate SMBG device at each of the glucose concentrations listed above. Blood samples with serially reduced volumes should be measured on the device until an error is either generated by the device or the test result falls outside of the device's stated performance range. Results obtained from the candidate device should be compared to the reference method. In your submission you should describe the results from both the candidate device and the reference method, as well as the sample volume tested for each of the tested glucose concentration ranges.

5. Sample Perturbation Study

Sample perturbation occurs when a user has applied an appropriate volume of blood to the test strip for glucose measurement but an event such as wicking of blood away from the test strip, flicking of the test strip or flicking of the meter occurs during the start of measurement and alters the volume of the initial sample application. Sample perturbation often leads to a short sample.

You should adequately demonstrate how your SMBG handles sample perturbation, through a sample perturbation study. In such a study, once a sample has been applied to the test strip and the SMBG device has begun to read the sample, the test strip should be perturbed. The sample perturbation study should incorporate blood samples with known glucose concentrations in the following three ranges: 50-65 mg/dL, 100-120 mg/dL, and 200-250 mg/dL. In your 510(k) submission you should describe your protocol, including

your specific method of perturbing the test sample, as well as meter results compared to the reference method.

6. Intermittent Sampling

Intermittent sampling occurs when a short sample is applied to a test strip, a glucose measurement begins, and the user adds more sample to the test strip before the glucose measurement is complete.

You should adequately demonstrate how your SMBG handles intermittent sampling by conducting a study. The intermittent sampling study should incorporate blood samples with known glucose concentrations in the following three ranges: 50-65, 100-120, and 200-250 mg/dL. You should perform intermittent sampling studies that are representative of actual events. For instance approximately one half of the sample should be applied to the test strip prior to the start of sample measurement, then the other half of the sample should be applied to the strip once the sample starts reading. You should describe how the device responds to this scenario, including whether a result is reported, whether this result is accurate (relative to the reference method) and when an error code is reported.

7. Testing with Used Test Strips

We recommend that SMBG devices be designed to automatically recognize the insertion of used test strips. Insertion of used test strips into a blood glucose meter should not provide glucose measurement results to the user. If an automatic used test strip recognition function has been incorporated into your SMBG device, you should perform a flex study to demonstrate the functionality of this recognition system. If an automatic used test strip recognition function has not been incorporate into the design of the blood glucose meter, you should submit flex study results demonstrating that the insertion of used strips for glucose testing generates an appropriate error code to the user. In your submission you should provide the study protocol, acceptance criteria and results.

F. Calibration and External Control Materials

The use of external control solutions allows consumers to periodically check the accuracy of the SMBG device and test strip. In order to further promote the use of external control solutions by the user, you should include at least two levels of control materials to the customer with each test strip vial. We recommend you follow FDA's "Guidance for Industry and FDA Staff - Assayed and Unassayed Quality Control Material" [http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm079179.htm] and submit the recommended information to support clearance of your assayed glucose quality control material.

Control solutions provided should not be labeled in a descriptive manner such as "low", "normal," or "high" since that may be misleading to the user. Users may confuse a label that says "normal" as meaning that that is a clinically normal value even when the control concentration is not within the normal range that is recommended by an individual user's

physician. Control solutions should be labeled non-descriptively (e.g., numerically - 1, 2, 3).

For a description of more points to consider regarding calibration and quality control materials, please reference the guidance document "In Vitro Diagnostic Devices: Guidance for the Preparation of 510(k) Submissions – Appendix K – Points to Consider for Review of Calibration and Quality Control Labeling for In Vitro Diagnostic Devices" (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094635.htm).

You should describe how the candidate system recognizes and distinguishes calibration or control materials from patient specimens as well as explain how the system compensates for differences between strip lots or strip types.

VII. Test Strip Lot Release Criteria

Your test strip lot release criteria should be sufficient to ensure consistent performance of your SMBG test strips. You should provide a description of the lot release criteria and a summary of the sampling scheme in your premarket notification.

We recommend that you select a sampling scheme appropriate for the operation of your device and test each outgoing test strip lot or batch using the precision and accuracy evaluations described below. Your release criteria should be designed to ensure that all released lots conform to the labeled SMBG device performance *in the hands of the intended user*. Therefore, these criteria should be more stringent than the criteria used to evaluate total error in the user studies. Estimates of the device's imprecision and average bias may be used to determine appropriate criteria. For example, if the device has an average CV of 3% and an average bias of 5%, these may be considered in determining the appropriate lot release criteria.

Precision Evaluation:

Precision using Control Materials

This study should be completed over 5 days and use glucose controls. At least two SMBG devices should be included in this study and at least 10 measurements should be taken per control level per meter.

Precision using Whole Blood Samples

This study should be completed over 10 days using whole blood samples spanning the SMBG device's stated measuring range. Spiking samples with glucose, or including samples in which glucose was allowed to glycolyze is acceptable in order to evaluate the extreme end of the system's measuring range. At least two SMBG devices should be included in this study and at least 10 measurements should be taken per glucose level, per meter.

Accuracy Evaluation:
The accuracy evaluation should be performed using patient whole blood samples that span the SMBG device's stated measuring range. It is acceptable for samples to be spiked with a known concentration of glucose, or to include samples in which the glucose was allowed to glycolyze in order to evaluate the extreme ends of the system's measuring range. Glucose concentrations should be measured on the SMBG meter and compared to the reference method.

Third Party Test Strips:
Third party test strips refer to test strips manufactured and distributed by a company other than the company that manufactures and distributes the glucose meter. Third party strip manufacturers should ensure that they are aware of any design changes to the meter, because such changes could affect compatibility of the strip with the meter. We strongly recommend that agreements between the third party strip manufacturer and the meter manufacturer are in place to ensure that the third party strip manufacturer is made aware of any design changes to the meter. In cases where this is not possible, the third-party strip manufacturers should sufficiently address, in their submission, how they will mitigate the risk of incorrect results due to meter design changes.

VIII. Software

For software descriptions of SMBG devices, their components, and accessories, we recommend that you follow **Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089543.htm**. Generally, FDA considers glucose meters to be a moderate level of concern because glucose results will be the basis for treatment, including determination of insulin dosage by the patient or health care provider. Incorrect glucose results or failure of the software to detect an error could result in improper diabetes management. (Also see Section VI, above regarding software descriptions in your 510(k)).

IX. Labeling

The labeling of a SMBG includes a user manual, package inserts for both test strips and controls, and box and container labels for the meter, test strips, and control materials. The package inserts for test strips and controls, and the user manual should be simple, concise, and easy to understand. Graphics such as line drawings, illustrations, icons, photographs, tables, and graphs are very useful tools. Manufacturers should ensure that the same terms are used consistently throughout the labeling to identify the device and its parts, avoiding synonyms or alternate phrases. Symbols should not be used in the labeling of OTC devices. We recommend that you refer to the following documents for information on important principles for developing clear and complete home use IVD labeling:

- **Guidance on Medical Device Patient Labeling; Final Guidance for Industry and FDA** (2001), http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070782.htm.
- **Labeling of Home-Use In Vitro Testing Products; Approved Guideline**, CLSI GP-14 (1996).
- Device Advice website titled **Labeling Requirements - In Vitro Diagnostic Devices** [http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/DeviceLabeling/InVitroDiagnosticDeviceLabelingRequirements/default.htm]

Technical information, required by 21 CFR 809.10(b), should be described so that lay users can understand the information or locate it if necessary. Detailed technical information (e.g., chemical details of test principle or statistical analyses of data) may be presented in a separate section followed by clarifying statements appropriate for lay users.

The premarket notification must include labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e). Final labeling must also satisfy the requirements of 21 CFR 809.10.

The following items are intended to further assist sponsors in complying with the requirements of 21 CFR 809.10 for test strip and meter labeling.

1. The device container and package insert must contain the proprietary and common names of the device. 21 CFR 809.10(a)(1) and 21 CFR 809.10(b)(1). The various test system components should have the same name (ABC blood glucose test system, ABC blood glucose meter, ABC blood glucose test strips, etc.) to aid in identification of system components.
2. You must include on the label and labeling the intended use of the product. 21 CFR 809.10(a)(2) and 21 CFR809.10(b)(2). The intended use for OTC SMBG devices should be similar to the example below:

   The XYZ Blood Glucose Monitoring System is intended for use in the quantitative measurement of glucose in capillary whole blood from the finger. It is intended for use by people with diabetes mellitus at home as an aid in monitoring the effectiveness of a diabetes control program. The XYZ Blood Glucose Monitoring System is intended to be used by a single person and should not be shared.

3. You must include warnings appropriate to the hazard presented by the product. (21 CFR 809.10(b)(5). You should include the following warning *prominently* on the outer box labeling and package insert.

   This device is not intended for use in healthcare or assisted-use settings such as hospitals, physician's offices, or long-term care facilities because it has not been

determined to be safe and effective for use in these settings, including for routine assisted testing or as part of glycemic control procedures.

Use of this device on multiple patients may lead to transmission of Human Immunodeficiency Virus (HIV), Hepatitis C Virus (HCV), Hepatitis B Virus (HBV), or other bloodborne pathogens.

4. Labeling must include the chemical, physical, physiological, or biological principles of the procedure (21 CFR 809.10(b)(4)). The discussion of these principles should include identification of the enzyme and description of the reaction. Labeling should specify whether results are determined in terms of whole blood or plasma equivalents. SMBG devices intended for use in the U.S. should report results in terms of plasma equivalents.

5. The label must include a means by which the user may be assured that reagents meet appropriate standards of identity, strength, quality and purity at the time of use. (809.10(a)(6)).

6. The labeling must provide instructions for specimen collection and preparation. (21 CFR 809.10(b)(7)). Instructions should include a statement to users on the importance of thoroughly washing and drying the skin before taking a sample, because contaminants on the skin may affect results. See also instructions for cleaning and disinfection , below.

7. The labeling must provide a step-by-step outline of recommended procedures (21 CFR 809.10(b)(8)), and operating instructions for the instrument (21 CFR 809.10(b)(6)(v)). Numbering, rather than bullets should be used for clarity when appropriate (e.g. procedural steps, etc.). You should include this information in the User Manual.

8. Labeling must include a statement of limitations of the procedure including known extrinsic factors or interfering substances affecting results (21 CFR 809.10(b)(10)). You should include testing conditions that may cause clinically significant errors (due to bias or imprecision) with your device (e.g., specific drugs, oxygen therapy, high altitude). You should indicate the most extreme conditions (e.g., the highest altitude) at which device should be used based on the results of performance testing.

9. You should clearly indicate to users what display they will expect to see when their measured glucose is lower or higher than the measuring range of the meter. For example, meter XYZ has a measuring range that goes down to 50 mg/dL. All glucose values measured below 50 mg/dL will provide the following error code: "Less than 50". Meter XYZ's labeling would include a statement explaining this error code: "When your glucose value is less than 50 mg/dL you will see the following error code 'Less than 50'".

10. Labeling must describe details of calibration and of quality control procedures (21 CFR 809.10(b)(8)(v) and 21 CFR 809.10(b)(8)(vi)). This is to help ensure optimal performance of the system. This section should include recommendations for how and when to perform quality control checks and instructions for what to do if the control

material values are not within the manufacturer's allowable range. As part of the quality control information in your labeling, we recommend sponsors advise users that they should periodically review their technique and compare a result obtained with their meter to a result obtained using a laboratory method or a well-maintained and monitored system used by their healthcare provider.

11. Labeling must include expected values (21 CFR 809.10(b)(11)). FDA recommends that the expected values in the package insert should be those for non-diabetics. FDA does not recommend including additional ranges adjusted for diabetics because such ranges are individualized and determined by the clinician. The expected values should be cited from in-house studies or up-to-date reference sources.

12. Labeling must include specific performance characteristics (21 CFR 809.10(b)(12)). Sponsors should briefly describe all studies and summarize results in the package inserts. FDA recommends that this include performance data summaries from in-house and user studies. For presentation of accuracy in particular, see the charts below for an example. Performance should be presented separately for each anatomical site and matrix.

    Accuracy information:
    So that home users have the ability to choose the SMBG device that is right for them, it is important to clearly describe the performance of the device in a way that is easy for them to understand. It is also important for this information to be located in a prominent place in product labeling so that lay users can understand the performance of an individual SMBG device both prior to purchase and also when they are learning to use the device they have purchased. Therefore, both the outer box labeling and the package insert should have easily understood depictions of the clinical study results.

    In the package insert for the test strips and the user manual for the SMBG device, accuracy information should be prominently and logically placed within the label. We recommend that this information be included in the section where the manual describes how a user will obtain a result. In the test strip insert, this section should be large and centrally placed so that users understand the performance of the system using these test strips. We recommend the following types of presentations to represent the results of your accuracy studies in the user manual and test strip inserts.

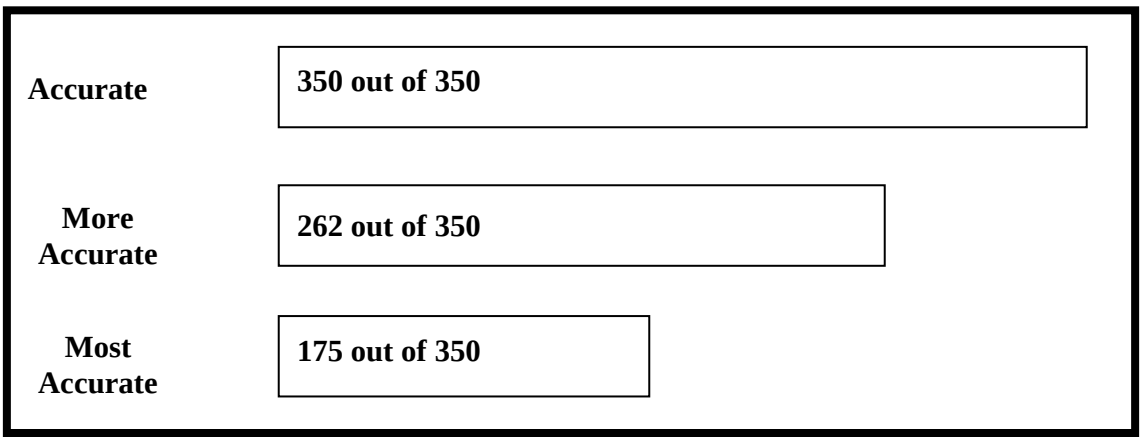
Suggested Representation of Accuracy for Lay Users - Example

Your ABC Meter result may vary slightly from your actual blood glucose value. This may be due to slight differences in technique and the natural variation in the test technology.

The chart below shows the results of a study where 350 typical users used the ABC meter to test their blood glucose level. For example, in this study, the ABC meter gave results within 15% of their true blood glucose level 340 out of 350 times.

Difference range between the true blood glucose level and the ABC meter result.	Within 5 %	Within 10 %	Within 15 %	Within 20%
The percent (and number) of meter results that match true blood glucose level within x%	57% (200/350)	94% (330/350)	97% (340/350)	100% (350/350)

Accuracy information should also be included on the SMBG device and test strip outer box labeling and test strip vials as well as in the package inserts and user manual. We recommend that this outer box label accuracy information refer readers to the package insert and graphically represent the user study data. An example of this type of presentation is shown below. Numbers represent the number of meter results that were within the level of accuracy shown, relative to the laboratory device.



Accuracy key	**Percentages listed are meter values as compared to laboratory values**
Accurate	+/-15%
More Accurate	+/-10%
Most Accurate	+/-5%

13. You must describe the principles of operation for the instrument as well as service and maintenance information (21 CFR 809.10(b)(6)). Labeling should include a list or summary of error messages, descriptions of what those error messages mean, and appropriate troubleshooting procedures for those error messages.

14. You should provide a working U.S. toll free telephone number for user assistance in the manual and package insert, and include hours of operation. If user assistance is not provided 24 hours/7 days a week/365 days a year, sponsors should provide instructions for what measures the user should take when user assistance is not available.

15. The label and labeling must include statements of warning or precautions as appropriate to the hazard presented by the product (21 CFR 809.10(a)(4), (b)(5)(ii)). We recommend that you include instructions to lay users to contact their healthcare provider, if they obtain results that are not consistent with the way they feel, and to not change their medication regimen without approval from a healthcare provider.
    You should clearly and prominently state the important warnings for this device in the front of the label, in a section containing **Important Safety Instructions.** Important warnings and safety information should be included on all test system instructions (User manual, test strip labeling, etc.):

    You should stress the risk of disease transmission when using SMBGs and reference any relevant public health notifications, standard practice guidelines, or other resources available to users. At a minimum, the following warnings should be included:

    - The meter and lancing device are for single patient use. Do not share them with anyone including other family members! Do not use on multiple patients!
    - All parts of the kit are considered biohazardous and can potentially transmit infectious diseases, even after you have performed cleaning and disinfection.

    You should include these references:

    "FDA Public Health Notification: Use of Fingerstick Devices on More than One Person Poses Risk for Transmitting Bloodborne Pathogens: Initial Communication" (2010)
    http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm224025.htm

    CDC website on *"Infection Prevention during Blood Glucose Monitoring and Insulin Administration",* http://www.cdc.gov/injectionsafety/blood-glucose-monitoring.html

    In the section(s) describing **how to obtain a blood sample**, you should re-iterate the risk of bloodborne pathogen transmission. You should stress that a lancing device is intended only for a single user and should not be shared. You should stress that users should clean hands thoroughly with soap and water after handling the meter, lancing device, or test strips.

The user manual should contain detailed instructions for how and when users should perform **cleaning and disinfection procedures** for the meter and/or lancing devices, based on the validation studies performed. Specifically the instructions should include the following:

- An explanation of why the cleaning and disinfection should be performed in language that is appropriate for the intended user audience. You should explain the difference between "cleaning" and "disinfection."
- The recommended frequency. For example, the meter should be cleaned and disinfected at a minimum of once per week. An explanation should be provided for how this number relates to the number of validated cycles over the life of the device. The use life of the device should be clearly stated.
- A list of the materials needed for cleaning and disinfection should be provided. Instructions on how these products can be purchased or prepared need to be clearly outlined.
- A detailed procedure describing what parts of the device should be cleaned and disinfected, the amount of time the cleaner or disinfectant needs to remain on the meter or lancing device (contact time), etc. You should include graphics/photographs to assist the user.
- A statement that users should clean hands thoroughly with soap and water after handling the meter, lancing device, or test strips.
- A contact telephone number for technical assistance or questions should be prominently listed in the cleaning and disinfection section along with a list of signs of external deterioration and deteriorating performance that the user should look for.

16. If studies have not been presented supporting the use of alternative site testing (AST) for a SMBG device, you should include a prominent warning in the labeling against use of the device for AST. Sampling from anatomical sites other than the fingertip, i.e., forearm, upper arm, thigh, calf, palm, may be indicated for some SMBG devices.

    Some users may prefer obtaining blood from alternative sampling sites because of less pain or greater choice in puncture sites. However, studies have shown that during times of rapidly changing glucose (i.e., after meals, medication, or exercise), the glucose level in blood from the alternative site may be significantly different from the glucose level from the finger. Additionally, glucose levels may not rise as high or fall as low as levels in the fingertip. This can result in a delay, or a failure to detect, hypoglycemia when glucose is measured in alternative sites during non-fasting times.

    When alternative sampling sites have been validated, and are indicated, you should clarify that results from these sites may lag behind finger stick during periods of glucose change, or reduced peripheral circulation (e.g., shock).

If the AST studies conducted do not include any challenges evaluating rapid increases or decreases of glucose levels, you should include the following limitations in your package insert:

- Alternative site results may be different from fingertip results when glucose levels are changing rapidly (e.g., after a meal, after taking insulin, or during or after exercise).
- Do not rely on test results at an alternative sampling site, but use samples taken from the fingertip, if any of the following applies:
  - you think your blood sugar is low.
  - you are not aware of symptoms when you become hypoglycemic.
  - the site results do not agree with the way you feel.
  - after a meal.
  - after exercise.
  - during illness.
  - during times of stress.
- Do not use results from alternative site samples to calibrate continuous glucose monitoring systems (CGMS), or for insulin dose calculations.

Appendix 1. Potential sources of error to consider for SMBG Devices

The following table lists potential sources of error associated with the design, production, and use of SMBG devices. We do not intend for this to be a complete list. You should consider all sources of error based on your knowledge of your specific device. Documents such as CLSI EP-18A and ISO 14971 also provide lists of preanalytical, analytical, and post-analytical errors to consider.

Category	**Source of error or failure**
Operator	**Failure to follow procedure correctly, for example:** • **Sample contamination** • **Incorrect specimen collection (e.g., poor lancing technique and incorrect volume)** • **Application of an insufficient amount of blood to the strip or incorrect application of blood to strip** • **Use of a sample from an alternative site at inappropriate times or from a site not validated by the manufacturer** • **Application of the specimen to the strip more than once (for example, if the user believes not enough specimen was added the first time)** • **Incorrect insertion of strip into meter** • **Inaccurate timing** • **Use of contaminated, outdated, or damaged strips or reagents, including calibrators or quality control materials** • **Failure to understand or respond to meter output.** • **Errors in meter maintenance or cleaning** • **Errors in calibration or failure to calibrate or otherwise adjust the meter or check performance with quality control materials, as directed by labeling** • **Incorrect saving or use of stored data** • **Improper storage or handling of the meter, calibrators, quality control materials or test strips, or maintenance of the meter** • **Inadvertent changes of parameters (such as units of measurement)** • **Failure to contact physician when necessary (OTC)** • **Incorrect incorporation of results into overall treatment plan (professional use)** • **Use of strips not validated for use on the monitor**
Reagent	• **Expired strips or reagents**

	• **Damaged or contaminated strip** • **Failure of strips, calibrators, or quality control materials to perform adequately** • **Incorrect manufacturing; product fails to conform with specifications** • **Incorrect dimensions of reagent strip** • **Interference with chemical reaction on strip (e.g., reducing substances)** • **Inadequate design of container for strips or other reagents; failure to prevent deterioration; failure of desiccant used to keep strips dry**

Environmental	• **DEVICE EFFECTS**
	  • **Temperature**
	  • **Humidity**
	  • **Altitude; hyperbaric conditions**
	  • **Electromagnetic radiation**
	  • **Visible light; sunlight**
	• **HUMAN FACTORS**
	  • **Lighting, glare off meter surfaces**
	  • **Distractions, visual and auditory**
	  • **Stressful conditions**
	  • **Limited manual dexterity**

Software	• **Confusing or obscure user prompts and feedback** • **Incorrect mathematical algorithm** • **Undetected or unrecognized signal errors** • **Timing failure** • **Incorrect storage of test results in memory, including matching result with correct patient or time of test** • **Other software failures**
Hardware	• **Electronic failure** • **Physical trauma or vibration** • **Damage to the device from incorrect strip dimensional tolerances (third party manufacturer)** • **Electrostatic discharge** • **Electromagnetic/radiofrequency interference** • **Battery reliability, lifetime, and replacement** • **Component(s) failure** • **Incorrectly manufactured**

System	• **Physical trauma or vibration** • **Incorrect calibration/adjustment (between lots of strips)** • **Calibration failure, interference, instability or use beyond the recommended period of stability.** • **Labeling not geared to intended user.** • **Meter or operation complexity not geared to intended user** • **Inadequate training**
Clinical	• **Interference from endogenous substances.** • **Severe conditions (e.g., dehydration, hypoxia, hyperglycemic-hyperosmolar state, hypotension or shock, ketoacidosis).** • **Interference from other sugars (e.g., maltose intravenous solutions)**

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Appendix 2. Special 510(k)s and SMBG Devices

What is a special 510(k) and how does it apply to your blood glucose meter submission?

A special 510(k) submission is an alternative to the traditional method of demonstrating substantial equivalence for certain modifications that do not alter the intended use or fundamental scientific technology of the device. For such modifications, the Agency believes that the rigorous design control procedure requirements outlined in the Quality System Regulation (QS reg) [See 21 CFR part 820] produce highly reliable results that can form, in addition to the other 510(k) content requirements, a basis for the substantial equivalence determination.

As such, under the special 510(k) option, a manufacturer who is intending to modify his/her own legally marketed device will perform and present the risk analysis and the necessary verification and validation activities to demonstrate that the design outputs of the modified device meet the design input requirements. Once the manufacturer has ensured the satisfactory completion of this process, a "Special 510(k): Device Modification" may be submitted.

Eligibility for a Special 510(k)

To determine whether a modified SMBG device is eligible to be submitted as a special 510(k), you should consult the FDA Guidance Document entitled "The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications - Final Guidance" which can be found at: www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080187.htm. Sponsors should also consult the document "How to Prepare a Special 510(k)" at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm134573.htm

As noted above, a special 510(k) is appropriate where the candidate device is a modification of a sponsor's own legally marketed device, which would serve as the predicate for the modified device. This usually means that the candidate device and predicate device are part of the same device design file. The existence of *similarities* between the predicate device A and candidate device B does not by itself necessarily mean that device B is a modification of device A.

FDA believes that to ensure the success of the Special 510(k) option, there should be a common understanding of the types of device modifications that may gain marketing clearance by this path. In this vein, it is critical that Industry and Agency staff can easily determine whether a modification is appropriate for submission as a Special 510(k). To optimize the chance that a Special 510(k) will be accepted for review, sponsors should evaluate each modification to ensure that the device modification does not: (1) affect the intended use or (2) alter the fundamental scientific technology of the device.

Based on FDA's experience with blood glucose meters, we can offer the following list of modifications that may or may not be eligible for review as a special 510(k). This list is not intended to be all-inclusive.

Modifications that are generally eligible for a special 510(k):

- Minor changes in user interface
- Addition of wired data transfer capability (e.g., adding the ability to transmit glucose results to a personal computer)
- Change in memory capabilities (e.g., adding the ability to store additional results)
- Elimination of strip coding requirements through a restriction of test strip lot release criteria
- Addition of a voice (speaking) feature if the device is not intended for visually impaired users

Modifications that are generally NOT eligible for a special 510(k):

- Significant change in the sample volume applied to the glucose test strip
- Addition of alternate sampling sites (e.g., adding the palm in addition to the fingertip)
- Addition of sample matrices (e.g., adding venous blood in addition to capillary blood)
- Change to the measuring algorithm used to calculate a glucose concentration
- Change in enzyme used in the chemical reaction (e.g. from glucose dehydrogenase to glucose oxidase)
- Use of a test strip cleared for meter A for use on separately cleared meter B
- Any modification that affects the intended use of the device
- Any change in fundamental scientific technology

We recommend that you contact OIR to discuss any specific questions you have regarding your SMBG device's eligibility to be submitted as a special 510(k).