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

---

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only. Document issued on: November 30, 2018.

You should submit comments and suggestions regarding this draft document within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document, contact Leslie Landree at leslie.landree@fda.hhs.gov, or at 301-796-6147.

FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DEVICES & RADIOLOGICAL HEALTH

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Preface

Public Comment

You may submit electronic comments and suggestions at any time for Agency consideration to http://www.regulations.gov . Submit written comments to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852. Identify all comments with the docket number FDA-2013-D-1446. Comments may not be acted upon by the Agency until the document is next revised or updated.

Additional Copies

Additional copies are available from the Internet. You may also send an e-mail request to CDRH-Guidance@fda.hhs.gov to receive a copy of the guidance. Please use the document number 1756 to identify the guidance you are requesting.

Contains Nonbinding Recommendations
Draft - Not for Implementation

Table of Contents

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Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction

This draft guidance document describes studies and information 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) home use by lay-users.[1] When finalized, this guidance document is intended to guide manufacturers in conducting appropriate performance studies and preparing 510(k) submissions 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 in professional healthcare settings (e.g., hospitals, physician offices, long term care facilities). FDA addresses those device types in another guidance entitled, "Blood Glucose Monitoring Test Systems for Prescription Point-of-Care Use" (BGMS guidance - https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm380325.pdf). FDA is also issuing another revised draft of the BGMS guidance (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDoc

[1] While the majority of SMBG devices are intended for home use, this also applies to SMBG devices intended for home use that are obtained with a prescription from a healthcare professional.

uments/UCM626743.pdf) to reflect similar clarifications to the ones proposed in this draft guidance.

For the current edition of the FDA-recognized standard(s) referenced in this document, see the FDA Recognized Consensus Standards Database Web site.[2]

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 meters that measure blood glucose values are used by millions of people with diabetes every day as an aid in diabetes self-management. 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 (BGMSs) intended to be used by healthcare professionals as compared to SMBGs intended for home use by lay-users. However, it has become increasingly clear that these different use settings comprise distinct intended use populations with unique characteristics and different device design specifications, which manufacturers should take into account when designing their devices. Patients in professional healthcare settings can be acutely ill and medically fragile and are more likely than lay-users to present with physiological and pathological factors that could interfere with glucose measurements. Further, the term "lay-user" encompasses a group of individuals with wide ranges in age, dexterity, vision, training received on performing testing, and other factors that can be critical to the patient's ability to accurately use the device and interpret test results. Finally, SMBGs and the associated test strips used by lay-users are also more likely to experience varied storage and handling conditions compared to devices used in professional settings. As such, SMBGs 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 home use for self-monitoring by lay-users, the Agency is issuing two separate guidances for (i) BGMSs intended for use in point-of-care professional healthcare settings, and (ii) SMBGs intended for home use for self-monitoring by lay-users. The FDA believes that by making this distinction, SMBGs can be better designed to meet the needs of their intended use populations, thereby providing greater safety and efficacy.

[2] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm.

In recent years, concerns have been raised related to infection control issues involving blood glucose meters and lancing devices. According to the Centers for Medicare and Medicaid Services (CMS) and the Centers for Disease Control and Prevention (CDC), blood glucose 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.[3] Though SMBGs are intended for home use by lay-users, they should also be designed to withstand effective 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, i.e., by lay-users at home (or in other non-professional settings).

III. Scope

This 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 in professional healthcare settings (e.g., hospitals, physician offices, long term care facilities, etc.).
- Devices used to screen and diagnose diabetes (such as clinical chemistry analyzers).
- Continuous glucose sensors, implanted or external (e.g., continuous glucose monitoring systems (CGMs) or sensors within catheters).
- Non-invasive glucose measurement devices, (i.e., devices that do not require removal of a blood sample from a fingertip or other anatomical site).
- Devices for measurement of blood glucose in neonates.

The device types addressed in this guidance document typically use capillary whole blood from fingertip or alternative anatomical sites. These device types are not intended for use in healthcare or assisted-use settings such as hospitals, physician offices, or long-term care facilities because they have not been evaluated for use in these professional healthcare settings, including for routine assisted testing or as part of glycemic control procedures. Use of these devices on multiple patients may lead to transmission of Human Immunodeficiency Virus (HIV), Hepatitis C Virus (HCV), Hepatitis B Virus (HBV), or other bloodborne pathogens.

[3] See information at http://www.cdc.gov/injectionsafety/blood-glucose-monitoring.html.

While FDA recommends that the information described in this guidance be included in premarket submissions for SMBGs, submissions containing alternative information may be sufficient if able to demonstrate substantial equivalence to a legally marketed predicate device.

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 SMBG.

IV. Reducing the Risk of Bloodborne Pathogen Transmission

Since SMBGs 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 meters, as well as lancing 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 disinfecting, and appropriate infection control measures. To minimize the risk of bloodborne pathogen transmission with single patient use SMBGs, you should address the following in your device's design and labeling:

- All SMBGs should be intended for single patient use. The intended use should clearly state that the SMBG is intended for home use by lay-users and should only be used on 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 the 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 in your 510(k) 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 efficacy of any disinfectant you recommend for use with your device, as described below. We recommend you consult the Environmental Protection Agency's (EPA) list of disinfectants that are registered for use against infectious bacteria and viruses[4] when choosing disinfectants to validate for use with your device.

[4] Selected EPA-registered Disinfectants http://www.epa.gov/oppad001/chemregindex.htm

- 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. The various test system components should be named in such a way that they are recognized as belonging to the same system or family of products, and to distinguish them from similar devices intended for multiple-patient use (e.g., ABC blood glucose test system, ABC blood glucose meter, ABC blood glucose test strips, etc.). See Section X, (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 (i.e., HIV, Hepatitis B, Hepatitis C) and validation that the cleaning and disinfection procedures do not deteriorate the device or alter device performance. FDA's 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, including the housing, touch pad, or buttons. You should make note of any physical indicators of deterioration during your validation study and provide this information in your 510(k) submission. The disinfectant product you choose should be effective against HIV, Hepatitis C, and Hepatitis B viruses. Of these viruses, Hepatitis B is the most difficult to kill and prior outbreak episodes associated with blood glucose meters have been due to transmission of Hepatitis B viruses. Therefore, disinfection efficacy studies should be performed to demonstrate effectiveness of the chosen disinfectant against Hepatitis B virus. 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.

You should demonstrate that your disinfection procedure is effective against Hepatitis B virus by performing disinfection efficacy studies to show that your procedure is effective with the external meter materials (e.g., case, display, buttons, etc.). 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 amounts of microbes can protect viruses from disinfection and 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, thereby minimizing the chance of your disinfection procedure affecting meter function. However, you should choose a disinfectant that is effective against Hepatitis B virus and is compatible with your specific device. If you intend to claim that your disinfection procedure is effective against other pathogens, you should consider submitting a pre-submission request to discuss this with the

Agency prior to conducting your testing. For information about the pre-submission process, see FDA's guidance entitled "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff," (http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf). 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 ASTM E1053-11, Standard Test Method for Efficacy of Virucidal Agents Intended for Inanimate Environmental Surfaces.
- ASTM standard ASTM E2362 -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 is robust to cleaning and disinfection procedures after multiple cleaning and disinfection cycles. You should include in your 510(k) submission the study design and results demonstrating that the analytical performance of the SMBG is not impacted by the cleaning and disinfection procedures.

You should address the following in designing your study:

- Worst case scenarios with regards to cleaning and disinfection frequency and end user environment should be used 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 during its use life (typically 3-5 years) and may be greater than the number of cleaning and disinfection cycles recommended in the user instructions. A cleaning step should precede the disinfection step for each cleaning and disinfection cycle.
- The disinfection contact time used in the robustness study should be identical to the contact time used in the disinfection efficacy testing and described in the cleaning and disinfection instructions in the labeling.
- 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 that are susceptible to blood contamination and could either directly or indirectly be contacted by the user are able to withstand your recommended cleaning and disinfection procedures. You should ensure that you test parts of the meter that are particularly susceptible to blood contamination, such as the test strip port and any material

seams. It is important to be able to clean and disinfect all parts of your meter to reduce the risk of bloodborne pathogen transmission.

- When evaluating your device after the cleaning and disinfection phase, you should ensure that the procedure does not cloud or deface the display of the meter and does not corrode or erode the plastic housing or buttons. All these physical indicators of deterioration should be noted throughout your study and included in your 510(k) submission. You should evaluate the accuracy of the meter using blood samples compared to results obtained by a comparator method (please refer to Section VI below for the definition of comparator method) to ensure that accuracy is not affected by repeated cleaning and disinfection. The study should also evaluate the functionality of your meter features (as appropriate), for example, touch screen function, USB port function, speaking functions, etc., to ensure they are not affected by repeated cleaning and disinfection.
- You should include infection control in your risk analysis and incorporate your validated cleaning and disinfecting procedures into your risk assessment.

A description of the protocols and acceptance criteria for all studies should be included in your 510(k) submission.

V. Device Description

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

General device description:

- Description of 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 measurement and whether results are reported in whole blood or plasma equivalents.[5]
- Description of the composition and levels of control material that can be used with your system.
- User maintenance needs (e.g., batteries).

[5] Note that SMBGs intended for use in the U.S. should report results in mg/dL and in plasma equivalents.

- Features of the device, such as data transmission capabilities or features designed to enhance robustness and ease of use.
- Features designed to minimize the risk of bloodborne pathogen transmission.

Description of features controlled by the software, which should describe the following:

- Displays and user messages: This includes how the SMBG 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 the device.
- User prompts: You should describe prompts that the SMBG 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 user prompts include 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, etc.
- Error messages and alerts: This includes any error messages or alerts that the SMBG displays. You should describe how the system responds to errors in user action, user inaction, or system status. Suggested examples of error messages or alerts include: when a strip is inserted incorrectly or removed prematurely; too small a sample is applied to the test strip; damaged, incorrect or deteriorated strips are used; or when there is a low battery or excessively high ambient temperature. This should also include the methods by which the SMBG detects and alerts the user when glucose levels are outside of the linear range of the system. You should describe at what point each message is triggered and describe any self-diagnostic routines that the system performs.

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

VI. Performance Evaluation for SMBGs

Subsections A-F below indicate the types of device performance information that you should include in a 510(k) submission for a SMBG. Although many manufacturers design their SMBG validation studies based on the International Standards Organizations document 15197: "In vitro diagnostic test systems—Requirements for blood glucose monitoring systems for self-testing in managing diabetes mellitus," FDA believes that the criteria set forth in the ISO 15197 standard are not sufficient to adequately protect lay-users using SMBGs; therefore, FDA recommends performing studies to support 510(k) clearance of a SMBG according to the recommendations below.

In this guidance, the term "comparator 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., an 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 Subsections A-F.

A. Precision Evaluation Study

You should evaluate both within-run precision and intermediate precision for your SMBG and include these evaluations in your 510(k) submission. The following outlines FDA's current thinking on appropriate study design and analyses to evaluate within-run precision and intermediate precision for SMBGs.

Within-Run Precision Evaluation:
In this guidance, within-run precision studies are bench studies designed to evaluate imprecision under conditions of repeated measurement of the same sample with different meters and multiple test strip lots. In order to assess imprecision of the SMBG across the claimed measuring range, you should evaluate samples containing glucose concentrations within each of the five intervals provided in Table 1 below:

Table 1. Glucose Concentrations for Precision 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 within-run precision using venous whole blood samples. Altered venous whole blood samples such as those that are spiked, diluted, or allowed to glycolyze in order to obtain the appropriate glucose concentrations are acceptable in order to facilitate coverage of the entire claimed glucose measuring range. 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 this study. For each sample concentration, a minimum of 10 meters should be used, with at least 10 measurements taken by each meter (i.e., at least 100 measurements per concentration). Test 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 all measurements per meter for each glucose concentration range with the corresponding standard deviation (SD) and percent coefficient of variation (CV). In addition, 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.

Provided results should be based on all data; if any outlier samples were excluded from any of your statistical analyses, you should fully describe the method of outlier identification, identify the excluded samples, and provide the results of your root cause investigations into the outlier samples.

Intermediate Precision Evaluation:
Intermediate precision measurement studies are bench studies designed to evaluate imprecision under simulated normal use conditions; for example, measurement over multiple days using multiple reagent system lots. These studies may be performed with prepared control solutions rather than whole blood samples.

The total number of meters and operators in these studies is at the discretion of the sponsor; however, a minimum of 10 meters should be used for each glucose concentration. Intermediate precision should be evaluated over a minimum of 10 days, taking at least 1 measurement per meter per day of a sample from each glucose concentration interval listed in Table 1. This should produce a minimum of 10 measurements per meter for each glucose concentration and 100 total measurements per glucose concentration. You should use a minimum of 500 test strips from a minimum of 10 vials or packages that cover a minimum of 3 manufacturing lots. These test strips should be taken from the same vial and/or package for each meter.

For each glucose concentration in Table 1, you should present data for each test strip lot, as well as for pooled lots, including the mean value of the measurements for each meter with the corresponding standard deviation (SD) and percent coefficient of variation (CV). 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 and provide results based on all data. If any outlier samples were excluded from any of your statistical analyses, you should fully describe the method of outlier identification, identify the excluded samples, and provide the results of your root cause investigations into the outliers.

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 whole blood samples. Altered venous whole blood samples, such as those that are spiked, diluted, or glycolyzed, are acceptable in order to facilitate coverage of the entire claimed measuring range. You should clearly identify the number of altered samples (spiked, diluted, or glycolyzed) within the 510(k) submission.

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 an assessment of labeling and usability. This type of design will more accurately reflect the device performance in the hands of the intended user, thereby providing a better estimate for total accuracy of your SMBG.

FDA recognizes that most study evaluations performed for 510(k) submissions occur in idealized conditions, thereby potentially overestimating the total accuracy of the SMBG, 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 (e.g., temperature, humidity, altitude, etc.), but does not need to include the entire range of environmental conditions (environmental conditions are validated separately in Flex Studies discussed in Section VI.E below). You should fully describe the conditions of your study in your 510(k) submission.

You should include at least 350 different subjects in your user evaluation. In order to robustly assess the accuracy of your device, it is important that the glucose value on the comparator method be as reliable as possible. Therefore, more than one comparator measurement may be taken and averaged for each sample in order to allow a better estimate of the true glucose value of that sample. However, no measurements should be excluded from the 510(k) submission and a justification should be provided for any data that is excluded from the analysis. If you are planning to include claims that your device can be used at alternative anatomical sites (e.g., forearm, palm, etc.), you should test samples using your device from 350 subjects for each alternative anatomical site for which you are seeking clearance and evaluate the results relative to samples measured with the comparator method.

For each claimed anatomical site, the samples should adequately span the claimed measuring range of the SMBG. 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. It may be necessary to enroll more than 350 patients for each anatomical site (fingertip, forearm, palm,

etc.) in order to obtain the necessary unaltered samples. Data from all subjects in the study should be submitted in your 510(k) (even if more than 350 samples are collected), 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 SMBG. 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 SMBGs and may include non-diabetic subjects. 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 draft device labeling (instructions for use, user manual, etc.) that is representative of the labeling that will be provided to the user with the marketed device. If major revisions are made to the labeling after the user evaluation has concluded, an additional user study may be indicated if there is no other method available to validate that the changes made do not affect user performance. For purposes of the study, the instructions for use should be written in English only; translations into other languages should not be provided to 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 a product intended for home use by lay-users, the reading level should be at an 8th 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 510(k) submission.

The study subjects should obtain their own fingertip capillary (or alternate anatomical site(s)) sample and perform a blood glucose test using only the draft 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 that they cannot 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, the technician should then obtain an additional capillary sample for testing using the comparator method. Since the intended user population of SMBGs is the lay-user, it is not necessary for the technician to obtain capillary results on the SMBG for comparison to the comparator value.

Your study should include a minimum of 10 test strip vials or packages that cover a minimum of 3 test strip lots. 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 510(k) submission.

Hematocrit values should be determined and recorded for each of the study participants. You should present individual hematocrit values in the 510(k) submission 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. Your studies should demonstrate that your SMBG is sufficient for this purpose by showing that 95% of all SMBG results in this study are within +/- 15% of the comparator results across the entire claimed measuring range of the device and that 99% of all SMBG results are within +/- 20% of the comparator results across the entire claimed measuring range of the device. You should include all results in the 510(k) submission. Though we expect that with the technologies available, SMBG devices will be able to meet these criteria, there may be instances where meters may be determined to be substantially equivalent even when performance does not meet these criteria because, for example, other features of the meter or its setting of use provide benefits that compensate for different performance. For all SMBG test results that are >20% relative to the comparator method, you should provide a clinical justification for why the errors occurred and describe why the potential for that error does not affect user safety when extrapolated to the intended use setting (e.g., when billions of tests are performed). We will review any submitted justification to determine whether the data suggest that patients may be put at risk, or whether the justification and any proposed mitigation are adequate.

FDA understands that some SMBGs may not be able to measure reliably within 15% of the comparator method at very low glucose concentrations. If this is the case, you should raise the lower end of the claimed measuring range to the concentration where your device is sufficiently accurate, according to the above described criteria. To meet the clinical needs of the user population, SMBGs should minimally be able to measure blood glucose accurately between 50 mg/dL and 400 mg/dL, or a clinical justification should be provided for alternate measuring ranges. A SMBG should identify and provide an error code in situations where the measured glucose value 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 mg/dL").

Method comparison and user performance studies for a SMBG should include multiple blood glucose meters being used amongst the 350 lay-user study participants. Individual lancing devices should be used for each subject and meters should be cleaned and disinfected using validated instructions during the course of this study. You should provide procedures to mitigate the risk of potentially transmitting disease between healthcare providers and subjects during the study (for example, use of disposable gloves or other physical barriers), including details on how often and when gloves worn by the trained health professionals should be changed between subjects. 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 SMBGs. You should describe these aspects of the study in your 510(k) submission.

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

- Study setting, including the size, type, and location of each site and a justification of how the selected study conditions simulate intended use conditions. Study sites should be representative of where SMBGs are used in the U.S. and you should include an explanation of why you believe each site is representative of where SMBGs are used.
- Criteria used to select study subjects, including inclusion and exclusion criteria. Include patient demographics (age range, education level, native language, laboratory or healthcare work experience, disease state) and whether they are a naïve SMBG user or not.
- Details of procedures performed by lay-users and study technicians.
- Instructions provided to users in the study. (Note: All instructions should 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 blank questionnaire and the analysis of the results should also be provided.

Accuracy at Extreme Glucose Values

Because the user study described above using real patient samples may not provide a robust evaluation of SMBG performance in the extreme upper and lower ends of the claimed measuring range, you should perform additional studies using blood samples altered to achieve glucose concentrations of less than 80 mg/dL and greater than 250 mg/dL. These samples should mimic unaltered patient samples as closely as possible. This additional extreme glucose value study should be performed separately from the user study (see Section VI.C) described above and may be performed in a laboratory setting.

Capillary whole blood samples should be used for these studies - a professional may need to collect the capillary blood to ensure the sample size is sufficient. 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 and the comparator method. You should analyze these data separately from the user evaluation data but

using the same methods described below for the user evaluation studies. FDA will apply the same review criteria to both studies.

2. *Data Analyses:*

Data exclusion and outliers:

You should present all data in the 510(k) submission, including cases in which the meter displays an error code, a 'High' or 'Low' message, or no result. All outliers (e.g., data points that do not conform to the minimum accuracy criteria) should also be included. You should investigate all outlier results and describe the results of these investigations, providing explanations for the occurrence of outliers when possible. To help inform your investigations into outlier results, you should collect information regarding patient medications, hematocrit measurements, and disease states during your study.

Analysis of results:

You should present the difference between individual study subject results and results of the comparator method (or mean of the comparator measurement, if multiple replicates are measured on the comparator method) by plotting the data on an X-Y graph. The plot should include the regression line and line of identity. Your summary of results should include the slope and y-intercept, along with 95% confidence intervals, calculated using a suitable analysis procedure (e.g., Linear Regression, Deming Regression), and the estimate of the deviation (standard error). Difference plot of Y-X vs X may also be presented. You should describe all statistical methods used and clearly identify and describe any outliers in the analysis.

Tabular data presentation:

You should present the results of your analysis in the following tabular format for each sample matrix. In Table 2 below, X= the number of samples within the specified difference from the comparator method, and Y= total number of samples.

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

Within +/- 5%	Within +/- 10%	Within +/- 15%	Within +/- 20%
X/Y (%)	X/Y (%)	X/Y (%)	X/Y (%)

D. Interference Evaluation

You should evaluate the effect of potentially interfering endogenous and exogenous substances and conditions, such as icterus, lipemia, and varying hematocrit levels, as well as the effect of common medications on your SMBG's performance. Conditions that are known to interfere with glucose monitoring test systems, such as ketoacidosis, should be included in the labeling as limitations. If you would like the labeling to not include these limitations or if you would like to remove these conditions from the labeling, you should

provide interference testing demonstrating that these conditions do not interfere with your device.

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 target glucose values of approximately 50 - 70 mg/dL, 110-130 mg/dL, and 225-270 mg/dL to evaluate clinically relevant decision points.

You should evaluate each potentially interfering substance at clinically relevant concentrations, and should test all substances at the highest concentration that could potentially be observed in a whole blood sample; if significant interference is observed, you should perform dilutions of the interferent to determine the concentration at which interference begins to occur. For example, if interference is observed with 20 mg/dL acetaminophen, additional testing should be performed with samples containing lower concentrations of acetaminophen, such as 15 mg/dL, 10 mg/dL and 5 mg/dL, to determine the lowest concentration of acetaminophen where interference is first observed. If the results from the additional testing determine that interference is not observed in the sample containing 5 mg/dL acetaminophen and interference is observed in the sample containing 10 mg/dL acetaminophen, then 5 mg/dL is the highest concentration of acetaminophen where no interference is observed.

The substances listed below in Table 3 represent known or potential interferents for current blood glucose measurement technologies and comprise the minimal list of substances that should be tested for interference.

Table 3. List of Known or Potential Interferents for SMBGs:

Interferent	Recommended Test Concentration
Acetaminophen	20 mg/dL
Ascorbic acid	6 mg/dL
Conjugated Bilirubin	50 mg/dL
Unconjugated Bilirubin	40 mg/dL
Cholesterol	500 mg/dL
Creatinine	15 mg/dL
Dopamine	0.09 mg/dL
EDTA*	0.1 mg/dL
Galactose	60 mg/dL
Gentisic acid	1.8 mg/dL
Reduced Glutathione	4.6 mg/dL
Hemoglobin	1000 g/dL
Heparin*	300 IU/dL

Interferent	Recommended Test Concentration
Ibuprofen	50 mg/dL
L-Dopa	0.75 mg/dL
Maltose	480 mg/dL
Mannitol	1800 mg/dL
Methyldopa	2 mg/dL
Salicylic acid	60 mg/dL
Sodium	180 mmol/L
Tolbutamide	72 mg/dL
Tolazamide	9 mg/dL
Triglycerides	1500 mg/dL
Uric acid	23.5 mg/dL
Xylose	600 mg/dL
Sugar Alcohols**	0.09 mg/dL

*The inclusion of EDTA and Heparin in this table refers to their use as therapeutic substances and not as anticoagulants for sample preparation.

**All common sugar alcohols, including but not necessarily limited to, sorbitol, xylitol, lactitol, isomalt, maltitol should be independently tested.

In addition to the list of potential interferents provided in Table 3, you should conduct an interference risk analysis and carry out bench studies to evaluate interference from additional drugs commonly used in your intended use population. These bench studies of additional drugs should be conducted in the same manner described in this Section.

You should provide a reliable estimate of the interference predicted for each potential interferent. To do this, we recommend the following method of measuring and calculating interference. First, blood samples should be generated at each target glucose concentration described above. Each glucose sample should be tested in replicates with the comparator method (we suggest at least 4 replicates in order to reduce standard error) to establish the glucose concentration in the sample. The glucose samples should then be split into a test sample to which a specific amount of potential interferent is added and a control sample containing solvent/vehicle in lieu of the potential interfering substance. Both control samples and test samples should be measured in replicates on the SMBG. At least three test strip lots should be used for this evaluation. Each of the control and test samples should be tested on your SMBG in replicates of 30 across the three lots (10 replicates per lot of test strips for a total of 30 replicates per sample). The mean of replicates should be calculated for each control and test sample. The relative bias (mg/dL) and percent bias should be calculated using the results of the control sample relative to test sample for each concentration of potential interferent. These results should be submitted with 95% confidence intervals as part of your 510(k) submission.

For SMBGs, the degree of acceptable interference may vary by substance tested and the intended patient population of your device. Therefore, you should report in your 510(k)

submission the interference testing data as well as the expected imprecision of the system at that glucose concentration. If interferences are observed, you should propose appropriate labeling to address any observed interferences; the labeling language appropriate for the observed interference will be discussed during the review of the 510(k) submission.

As new drugs are developed that could potentially interfere with your device, or new interfering substances are identified for other SMBGs, you should evaluate these new drugs or substances 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 careful evaluation to determine whether the new drug interferes with your device. You should report to FDA if significant new interferences are observed with your device or with any cleared glucose monitoring devices that are on the market. New drugs/potential interferents should also be evaluated when new or significantly modified technology is introduced.

Data Analysis:

You should provide raw data sets as well as a summary table for all interference results. Please note that the summary tables should be presented separately for each test strip lot and for all lots pooled for each glucose level tested. Table 4 below provides a sample format of a summary table.

Table 4. Recommended Summary Table Format:
Test Strip Lot #(s)

Interferent	**Mean Glucose Value (Comparator)**	**Interferent Concentration (mg/dL)**	**Control Sample Mean**	**Test Sample Mean**	**Bias (mg/dL)**	**% Bias**	**Confidence Interval around % Bias**
Acetaminophen	60 mg/dL	20 mg/dL					
	120 mg/dL	20 mg/dL					
	250 mg/dL	20 mg/dL					

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

2. *Hematocrit*

Study Design:

Because a reasonably sized user evaluation study 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 is contributed by varying hematocrit levels. This should constitute a bench study designed to evaluate the effect of hematocrit on the performance of your SMBG to assess whether the potential for errors affects patient safety in the intended use population across your claimed hematocrit range. The observed

hematocrit levels 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 levels between 20% and 60%. Therefore, we recommend 20-60% as the claimed hematocrit 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, SMBGs should be able to adequately measure glucose across the range of 30-55% hematocrit (which includes the greatest proportion of users). If your SMBG cannot detect glucose across this range, it is possible that your device may present new technological characteristics from the predicate that raise different questions of safety and effectiveness and may not be determined to be substantially equivalent.

You should evaluate hematocrit interference by measuring blood samples containing various glucose concentrations. The samples should be prepared to contain designated levels of hematocrit that span the claimed hematocrit range for the device. Blood samples may be altered by spiking or allowing them to glycolyze to obtain desired glucose concentrations. 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, as such, 5% intervals allow for a more accurate assessment of bias from hematocrit interference than using broader intervals. Additionally, a sample having a nominal hematocrit of 42% should be tested. For example, if your claimed hematocrit range is from 20-60%, you should test samples at 20, 25, 30, 35, 42, 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 comparator method in multiple replicates (we recommend a minimum of 4 replicates). A mean of the comparator measurements ($Mean_{Comp}$) should give greater confidence in the true glucose concentration of the sample. You should test a minimum of 3 test strip lots to evaluate interference from hematocrit. Each sample should be tested on your new SMBG in replicates of 30 (10 replicates per lot of test strips, for a total of 30 replicates per sample).

Data Analysis:
An analysis should be performed for each of the 5 blood glucose concentrations tested and each test strip lot. The bias should first be determined with respect to the comparator method and then with respect to the nominal hematocrit samples, so that the hematocrit effect can be isolated.

(1) Estimation of Bias to Comparator Method

For each sample, you should calculate the average of 30 replicates of your new SMBG ($Mean_{SMBG}$). Using the $Mean_{SMBG}$ and the estimate of the true glucose concentration in

the sample, $Mean_{Comp}$, you should estimate a bias and percent bias as ($Mean_{SMBG}$-$Mean_{Comp}$) and ($Mean_{SMBG}$-$Mean_{Comp}$)/$Mean_{Comp,}$ correspondingly, for each sample. The results should be presented as in the table below and in graphical format appropriate for each specific glucose concentration range.

For glucose concentrations less than 75 mg/dL, the analysis should be presented as a graph where the X-axis represents hematocrit values and the Y-axis represents the absolute bias values. For glucose concentrations greater than or equal to 75 mg/dL, the analysis should be presented as a graph where the X-axis represents hematocrit values and the Y-axis represents percent bias values.

Table 5. Example table of bias calculated versus the comparator method for the hematocrit evaluation on a SMBG with 120 mg/dL glucose:

Hematocrit (%)	Average of Comparator measurements ($Mean_{Comp}$)	Number of measurements for SMBG	Average of SMBG measurements ($Mean_{SMBG}$)	%Bias ($Mean_{SMBG}$-$Mean_{Comp}$)/ $Mean_{Comp}$
10	118.0	30	127.6	8.1%
15	118.4	30	127.6	7.8%
20	122.4	30	130.4	6.5%
25	120.7	30	127.1	5.3%
30	123.7	30	129.5	4.7%
35	121.5	30	127.1	4.6%
42	119.7	30	124.6	**4.1%**
50	121.3	30	125.4	3.4%
55	120.8	30	122.7	1.6%
60	120.1	30	119.5	-0.5%
65	118.1	30	116.0	-1.8%
70	117.5	30	115.6	-1.6%

(2) Estimation of Bias due to Hematocrit

In order to isolate the effect of hematocrit on device performance, the bias relative to a sample having a nominal hematocrit (42%) should be determined. This nominal hematocrit is representative of the average hematocrit value of the intended use population; therefore, bias due to hematocrit is considered 0% (or 0 mg/dL) for the sample with hematocrit value equal to the average hematocrit value (42%). The estimate bias due to hematocrit for each sample should be calculated by subtracting the bias at the average (42%) from the bias of each sample.

Table 6. Example table of bias due to hematocrit calculated for the nominal hematocrit value of 42% on a SMBG with 120 mg/dL glucose:

Hematocrit (%)	Average of Comparator measurements ($Mean_{Comp}$)	Number of measurements for SMBG	Average of SMBG measurements ($Mean_{SMBG}$)	%Bias ($Mean_{SMBG}$-$Mean_{Comp}$)/ $Mean_{Comp}$	%Bias due to hematocrit
10	118.0	30	127.6	8.1%	4.0%
15	118.4	30	127.6	7.8%	3.7%
20	122.4	30	130.4	6.5%	2.4%
25	120.7	30	127.1	5.3%	1.2%
30	123.7	30	129.5	4.7%	0.6%
35	121.5	30	127.1	4.6%	0.5%
42	119.7	30	124.6	4.1%	**0.0%**
50	121.3	30	125.4	3.4%	-0.7%
55	120.8	30	122.7	1.6%	-2.5%
60	120.1	30	119.5	-0.5%	-4.6%
65	118.1	30	116.0	-1.8%	-5.9%
70	117.5	30	115.6	-1.6%	-5.7%

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

E. *Flex Studies*

Compared to professional healthcare settings, there are typically fewer controls in place in home use settings to mitigate the risk of erroneous results. In addition, users are often untrained and may not know how to identify or address an erroneous result. It is therefore assumed that devices intended for home use by lay-users are designed so that the risk of an erroneous result is far less than with laboratory-based tests. You should therefore demonstrate that your SMBG design is robust (i.e., insensitive to environmental and usage variation) and that all known sources of error have been assessed through a detailed risk assessment and 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 mechanisms or failure alert mechanisms. Examples of fail-safe mechanisms are lock-out functions to ensure that a SMBG does not provide a result when test conditions are inappropriate, such as when there is a component malfunction or operator error. Other examples are measures within the SMBG to prevent operator error, such as guides or channels that prevent improper strip placement. We

recommend that the SMBG 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 SMBG malfunction or problem. These 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 (i.e., extremely high or low glucose result) and the result is a critical value, the device should give a message such as "high" or "low."

Flex studies, or studies that stress the operational boundaries of a SMBG, 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 SMBGs 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 identify which of these errors can lead to a risk of a hazardous situation. You should then identify control measures, including fail-safe mechanisms 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 you should perform and include in the 510(k) submission of your SMBG. At the same time, we encourage you to continue to perform risk analyses to determine whether your device includes any unique or new features that should be validated through additional flex studies.

If your SMBG 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 in that flex study is not required for safe and effective use of the device, or indicate an additional implemented validated control mechanism. FDA will review any justifications to determine whether the proposed risk mitigations are adequate to protect patients.

In the case of the following flex studies, verification should include performance testing; however, it is acceptable for you to provide documentation indicating that flex studies have been conducted in accordance with an FDA-recognized industry standard in your 510(k) submission. We recommend you include the type of testing performed, the reference

standard followed, the acceptance criteria, and whether the SMBG 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 510(k) submission. A detailed description of the following attributes should be included in your 510(k) submission:

- Study goal
- Study protocols
- Methods used to apply samples to test strips
- Sample type and any anticoagulants used
- Study results
- Conclusions made from the study

We have also identified additional flex studies (described below) that we recommend be performed 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 in Subsections 1-8. These flex studies should be performed using fresh venous or capillary whole blood samples, not control solutions.

1. ***Test Strip Stability Testing***

You should perform studies that assess test strip performance throughout the test strip stability claims, including closed and open vial claims. Two studies should be performed to support test strip stability: 1) closed vial stability (shelf life) should be performed to assess the recommended shelf life and conditions when the vial is stored closed throughout the claimed expiration dating, at different combinations of temperature and humidity spanning the recommended storage conditions; and 2) open vial stability should be performed to mimic conditions under which an individual would actually use the strips where the vial is opened and closed throughout its claimed open vial life and stored at different combinations of temperature and humidity spanning the recommended storage conditions. We suggest that you submit only the study protocols for these test strip stability assessments, the acceptance criteria, and the conclusions of any studies which have been completed.

These studies (shelf life and open vial stability) should be designed to span both the claimed temperature range and humidity range at various time points throughout the duration of the respective claim. The time points that are assessed (e.g., 1 month, 3 months, 2 years) should be specified in the protocol. Combinations of real-time and accelerated stability studies are acceptable. However, if accelerated studies are provided, real-time studies should be ongoing and the protocols and acceptance criteria should be provided for both study types.

You should perform adequate precision and accuracy evaluations at each identified time point. The following are provided only as examples of such studies. Through these evaluations, you should demonstrate that the precision and accuracy calculated in these studies are within the labeled performance of the SMBG.

Precision Evaluation:

Precision with Control Materials

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

Precision with Whole Blood Samples

This study should use whole blood samples spanning the claimed measuring range of the SMBG. Samples may be altered by spiking with glucose or allowing the samples to glycolyze in order to evaluate the extreme ends of the system's claimed measuring range. At least two meters should be included in this study and at least 10 measurements should be taken per glucose level, per meter.

Accuracy Evaluation:

This study should be performed using whole blood samples that span the claimed measuring range of the SMBG. 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 spanning the claimed measuring range (e.g., 30-50, 100-150, 200-300, 350-500 mg/dL) should be measured with the SMBG and compared to values obtained with the comparator method.

2. ***System Operating Conditions Testing***

You should perform a study to assess the performance of your SMBG when used under various operating temperature and humidity conditions. These studies should be designed to represent actual use conditions experienced by SMBG users. Tested temperature and humidity ranges should not only cover the operating ranges that adequately reflect the intended use environment, and that are specified in the device labeling, but should also stress the SMBG by including ranges outside of the claimed operating range. Testing should incorporate the four extreme temperature and humidity combinations (high temperature/low humidity, low temperature/high humidity, high temperature/high humidity, low temperature/low humidity) or other testing combinations if a suitable rationale can be

provided. Measurements made on whole blood samples with your candidate device under various operating temperature and humidity conditions should be compared to values obtained using the candidate device at a nominal condition (such as 23°C, 40% relative humidity).

Separate testing of test strip and meter shipping and storage conditions is not necessary if the temperature and humidity studies outlined here use 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).

You should also include in your 510(k) submission a summary of any identified outliers that were excluded from statistical analysis, the method of outlier identification, and the results of outlier investigations.

We also encourage manufacturers to 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*

Relative to sea level, high altitude comprises a complex set of environmental differences and can induce multiple physiological changes, any or all of which might interfere with your SMBG's performance. For example, high altitude often involves extremes of temperature and humidity and can result in changes to hematocrit and blood pressure. The intended use environment of SMBGs in the United States includes high altitude conditions and, therefore, manufacturers should conduct studies on the effects of altitude on their SMBG device, or provide a justification for why altitude does not have an effect on the performance of their SMBG.

An altitude effects study should compare results from whole blood samples with your candidate device at the different high altitude conditions relative to values obtained using the candidate device at a nominal condition (such as sea level). These studies should also 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 above 500 feet. You should test your SMBG at a minimum of 10,000 feet above sea level.

4. *Error Codes for Samples Outside the Measuring Range*

You should perform adequate analyses to demonstrate that your meter provides the appropriate error codes when measured glucose concentrations are outside of the SMBG's claimed measuring range, and include these results in your 510(k) submission.

5. ***Short Sample Detection***

Blood glucose measurement from short samples (samples of reduced blood volume) can lead to inaccurate results. To avoid the risk of inaccurate results, SMBGs 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 at each of the glucose concentrations listed above. Results obtained from the candidate device should be compared to results using the candidate device at a nominal condition (such as the claimed minimum sample volume). Blood samples with serially reduced volumes should be measured on the device until an error is either generated by the SMBG or the test result falls outside of the device's claimed performance characteristics. In your 510(k) submission, you should describe the results from the candidate device under both test and nominal conditions, as well as include the sample volumes tested for each glucose concentration range.

6. ***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 the measurement and alters the volume of the initial sample application. You should adequately demonstrate how your SMBG handles sample perturbation through a sample perturbation study.

In a sample perturbation study, a sample should be applied to the test strip and after the SMBG device has begun to read the sample, but before the measurement is complete, 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 candidate device results compared to results using the candidate device under a nominal condition (such as strips with no perturbation).

7. ***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 an intermittent sampling 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 after a set period of time, such as once the sample starts reading. For systems that allow a second sample of blood to be added to the test strip without producing an error message, different time delays throughout the claimed period of second application should be tested once the sample starts reading, but before the measurement is complete. You should describe how the device responds to this scenario in your 510(k) submission, including whether a result is reported, whether this result is accurate (relative to the nominal condition, such as with the minimum claimed sample volume), and when an error code is reported.

8. *Testing with Used Test Strips*

You should perform a study to demonstrate how your SMBG device performs when a used test strip is inserted. We recommend that SMBG devices be designed to automatically recognize the insertion of used test strips. Insertion of used test strips into a SMBG should not provide glucose measurement results to the user. If an automatic used test strip recognition function has been incorporated into your SMBG, you should perform a flex study to demonstrate the functionality of this recognition system. In your 510(k) submission, you should provide the study protocol, acceptance criteria and results of your used test strip study.

F. Meter Calibration and Quality Control Materials

The use of external control solutions allows users to periodically check that the SMBG and test strips are working together properly and that the device is performing correctly. The use of external control solutions by the user should be promoted. At least two levels of control material should be specified in the labeling as available to the user. We recommend you review FDA's guidance entitled "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 value is a clinically normal value even when the control concentration is not within the normal range that is recommended by that individual user's physician. Therefore, control solutions should be labeled non-descriptively (e.g., numerically: 1, 2, 3).

For a description of more points to consider regarding quality control materials, please reference FDA's guidance entitled "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/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM094139.pdf).

Your 510(k) submission should describe how the candidate device recognizes and distinguishes control materials from patient specimens, either automatically or manually by the user, as well as explain how the system compensates for differences between test strip lots (i.e. how the meter is calibrated or coded for each test strip lot).

VII. Test Strip Lot Release Criteria

Your test strip lot release criteria should be set 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 510(k) submission. In addition, you should explain how the system compensates for differences between strip lots or strip types.

We recommend that you select a sampling scheme appropriate for the operation of your SMBG device to test each outgoing test strip lot or batch. Your test strip lot release criteria should be designed to ensure that all released lots conform to the labeled SMBG performance *in the hands of the intended user*. Therefore, these criteria typically should be tighter than the criteria used to evaluate total error in the performance studies, in order to achieve targeted performance in the intended user population.

VIII. 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 test strip manufacturers should ensure that they are aware of any design changes to the meter because such changes could affect compatibility of the test strip with the meter. Because test strips and meters work as integral systems, third party test strip manufacturers should sufficiently address in their 510(k) submissions how they will mitigate the risk of incorrect results due to meter design changes. One way to effectively ensure that the third party test strip manufacturer is made aware of any design changes to the meter is by having in place an agreement between the third party test strip manufacturer and the meter manufacturer.

IX. Software

For software descriptions of SMBGs, their components, and accessories, we recommend that you review FDA's guidance entitled "Guidance for the Content of Premarket Submissions for

Software Contained in Medical Devices,"
(http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089593.pdf). Generally, FDA considers blood glucose meters to be moderate level of concern devices 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 V, above, regarding software descriptions in your 510(k) submission.

X. Labeling

The labeling of a SMBG includes the user manual, the quick start guide (optional), the package inserts for both test strips and controls, and the 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. We recommend that you refer to the following documents for information on important principles for developing clear and complete home use IVD labeling:

- FDA's guidance entitled **"**Guidance on Medical Device Patient Labeling; Final Guidance for Industry and FDA,**"** (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070782.htm).
- CLSI GP-14: *Labeling of Home-Use In Vitro Testing Products; Approved Guideline*.
- FDA's Device Advice website entitled In Vitro Diagnostic Labeling Requirements (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 the information, 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 510(k) submission 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. You should refer to that regulation for the complete list of labeling requirements for *in vitro* diagnostic devices.

1. All device labeling 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 be named in such a way that they are recognized as belonging to the same system or family of products (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 the intended use of the product in your label and labeling documents (21 CFR 809.10(a)(2) and 21 CFR809.10(b)(2)). The intended use for SMBGs for home use by lay-users 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. The label and labeling must include warnings appropriate to the hazard presented by the product (21 CFR 809.10(a)(4) and 21 CFR 809.10(b)(5)(ii)).

   You should include the following warning *prominently* on the outer box label and package insert.

   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. The labeling must include the chemical, physical, physiological, or biological principles of the procedure, as per 21 CFR 809.10(b)(4). The discussion of these principles should include identification and source of the enzyme and description of the reaction. Labeling should specify whether results are determined in terms of whole blood or plasma equivalents. SMBGs 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, as described in 809.10(a)(6) and 21 CFR 809.10(a)(10).

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 with soap and water 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.).

8. The 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 SMBG (e.g., specific drugs, oxygen therapy, high altitude). You should indicate the most extreme conditions (e.g., the highest altitude, highest and lowest temperatures, etc.) at which the device has been validated based on the results of performance testing.

9. The labeling should clearly indicate to users what display they can expect to see when their measured glucose is lower or higher than the claimed 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 an appropriate message indicating the results are below the meter range. 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. The labeling must describe details of calibration and of quality control procedures and materials (21 CFR 809.10(b)(8)(v) and 21 CFR 809.10(b)(8)(vi)). This is to help ensure optimal performance of the SMBG. 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. The labeling must include expected values (21 CFR 809.10(b)(11)). FDA recommends that the expected values 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. The 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.

13. So that lay users have the ability to choose the SMBG that is right for them, it is important to clearly describe the accuracy 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, both prior to purchase and also when they are learning to use the device they have purchased. Therefore, the outer meter box labeling, the package insert for the test strip, and the user manual should all have easy to understand depictions of the clinical study results.

    In the package insert for the test strips and the user manual for the SMBG, accuracy information should be placed prominently within the labeling. We recommend that this information be included in the section where the labeling describes how a user will obtain a result. In the test strip package 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 convey the results of your accuracy studies in the device user manual and test strip package inserts.

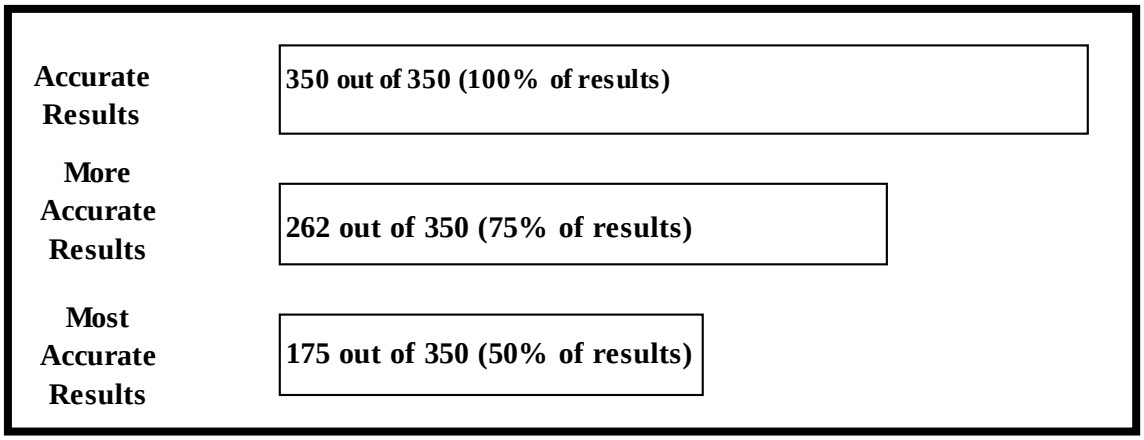
Suggested Representation of Accuracy for Home Use by Lay-Users - Example

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 outer meter box labeling, as well as in the test strip 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 result as compared to laboratory result**
Accurate Results	Meter result is +/-15% of laboratory result
More Accurate Results	Meter result is +/-10% of laboratory result
Most Accurate Results	Meter result is +/-5% of laboratory result

14. The labeling 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.

15. You should provide in the labeling a working U.S. toll free telephone number for user assistance, and include hours of operation and U.S. time zone, if applicable. 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.

16. 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) and 21 CFR 809.10(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 towards the beginning of the labeling, 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.).

The labeling 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 reiterate the risk of bloodborne pathogen transmission. Instructions should emphasize that a lancing device is intended only for a single user and should not be shared. You should stress that users should clean their 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, 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. You should explain the difference between "cleaning" and "disinfection."
- The recommended frequency at which a user should clean and disinfect the device. 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 (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.

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

    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 in blood from the fingertip. Additionally, glucose levels in ASTs 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 fingertip samples during periods of glucose change, or reduced peripheral circulation (e.g., shock).

    You should include the following limitations relating to AST testing in your package inserts:

    - Alternative site sample results may be different from fingertip sample 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 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. Sources of error to consider for SMBGs

Table 7 below lists sources of error associated with the design, production, and use of SMBGs. 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.

Table 7 – Examples of Sources of Error

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 improper maintenance of the meter** • **Inadvertent changes of parameters (such as units of measurement)** • **Failure to contact physician when necessary** • **Use of strips not validated for use on the meter**
Reagent	• **Expired strips or reagents**

	• **Damaged or contaminated strips** • **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 oxygen therapy 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 exogenous substances (e.g., maltose intravenous solutions)**

1343

1344

Appendix 2. Special 510(k)s and SMBGs

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 to a manufacturer's own previously cleared device, 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 conduct 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 is eligible to be submitted as a special 510(k), you should consult the FDA guidance entitled "The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications - Final Guidance," (www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080187.htm). Sponsors should also consult the information on FDA's website entitled "How to Prepare a Special 510(k)," (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.

We recommend that you contact the Office of In Vitro Diagnostic Devices and Radiological Health (OIR) to discuss any specific questions you have regarding your SMBG's eligibility to be submitted as a special 510(k).