AdvaMedDx
Vital Insights | Transforming Care

May 7, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2013-D-1146; Draft Guidance for Industry and FDA Administration Staff on Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use"

Dear Sir or Madam:

On behalf of AdvaMedDx, a Division of the Advanced Medical Technology Association (AdvaMed), we provide these comments on the Food and Drug Administration (FDA) "Draft Guidance on Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use; Draft Guidance for Industry and Food and Drug Administration Staff."

AdvaMedDx member companies produce advanced, *in vitro* diagnostic tests that facilitate evidence-based medicine, improve quality of patient care, enable early detection of disease and reduce overall health care costs. Functioning as an association within AdvaMed, AdvaMedDx is the only multi-faceted, policy organization that deals exclusively with issues facing *in vitro* diagnostic companies in the United States and abroad. Our membership includes manufacturers engaged in the development of innovative blood glucose testing systems.

GENERAL COMMENTS

AdvaMedDx appreciates FDA's efforts to share its thinking regarding expectations for premarket notifications for these products. Industry shares commitment to designing and manufacturing glucose meters that help patients better manage their diabetes. Tremendous advances have been made since these technologies were first introduced that have improved health care and supported better patient outcomes. Manufacturers' continual improvements have encouraged appropriate testing and promoted compliance to physician recommendations, reduced the potential for use error, and contributed to overall improved quality of testing for patients. Accuracy is one of multiple factors contributing to meter performance with usability and regular testing as integral.

AdvaMedDx member companies share the goal of improving meter accuracy and supported recent updates to International Organization for Standardization (ISO) 15197: 2013, the worldwide industry standard for self-monitoring/home use blood glucose meters. In that vein, we are concerned that, while well-intentioned, this draft guidance and its counterpart proposed point-of-care (POC) guidance disregard various international standards and guidances already in place and implemented worldwide.

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This draft guidance is highly prescriptive in nature and contains many provisions in direct conflict with recommendations made in ISO 15197 and other FDA-recognized standards and guidelines. For example, the use of percent bias across the glucose measuring range contradicts ISO 15197 and the method of bias calculation described for interference and hematocrit studies contradicts the methods described in CLSI EP7-A2 (FDA recognition number 7-127). FDA should work to better harmonize with current worldwide consensus standards, which represent significant advances in device development and ensure access to safe and effective devices. FDA served as developers and reviewers for these standards. FDA should carefully consider the comments of industry and support efficient and effective use of standards for its policies.

Furthermore, the highly detailed nature of the guidance only reinforces the importance of clarifying approaches that might be acceptable to FDA explicitly in the guidance. Careful consideration is needed as the guidance includes extensive analytical testing including interference testing and flex studies as well as specific information that is generally not required for premarket notification, such as manufacturing specifications, strip lot release criteria, line-item data for parameters, detailed protocols, and reports well beyond worldwide product standards. In a number of cases, criteria notably lack clinical relevance. Any proposed changes should be scientifically grounded and must hinge on ultimate clinical importance and impact on clinical decisionmaking (likelihood to make a clinically significant different decision based on the result). Our comments are all provided in that context with focus on the way in which the device is used.

Implications of guidance should be carefully considered, including less user-friendly meters—larger meters with increased test times, increased complexity of testing and blood sample size—could likely be some of the unintended outcomes along with likely increased cost to patients and payers. Any changes must be assessed in the larger clinical context and with regard to the impact on clinical outcomes.

We support efforts to promote transparency and clear and meaningfully understood labeling to promote patient education on knowing how to correctly use home glucose meters and the critical importance of regular testing for disease control. In that vein, we support many of the new requirements aimed to enhance comprehension and proper use, including encouraging discussion with healthcare providers and reinforcing lancets are for single patient use. At the same time, care must be taken to assure that information is comprehensible and not overly technical or confusing.

In all cases, care must be taken neither to jeopardize choice and access to safe and effective meters that meet individual needs nor to discourage innovation and continued investment in new technology. In light of the scope and complexity of proposed changes and issues raised, we urge appropriate process for implementation of this guidance. Until all comments are considered and final guidance is issued, this draft guidance must not be implemented. A substantially revised guidance should be issued that integrates necessary revisions to address key issues as outlined. Until such time as a carefully revised guidance is issued, this draft over-the-counter (OTC) guidance (and similarly its

counterpart POC guidance) should not be implemented for premarket blood glucose monitoring (BGM) submissions. When such guidance is finalized, there must also be a transition period following issuance that takes into account products under review or near clearance so as not to hold up the review process. We note that prior issued changes had led to FDA product holds upwards of one year for new products, which does not well serve public health nor state-of-the-art innovation for patients and healthcare professionals. It should also be clear that the guidance outlines new expectations for submissions and does not place into question currently legally marketed assays. Furthermore, provisions implemented in FDA guidance are recommended in nature and must afford acceptance of alternative but equivalent measures by sponsors who work in good faith to meet FDA expectations. We have made best efforts to provide such constructive recommendations for inclusion in the guidance as other alternative but equivalent means for specific inclusion by FDA in the guidance.

We note that the list of new proposed requirements is extensive and in a number of cases not clinically relevant and/or speculative. For example, the guidance does not recognize that today's BGMs already incorporate many of the safety/analysis features and in effect forces failure modes where none can exist and at other times ignore differences in how certain BGMs may be designed and operated. By way of another illustration, the guidance requires the data to be analyzed against laboratory reference for all non-clinical studies, such as hematocrit study and interference studies (VI.D). These samples are manipulated to achieve the conditions of the test and in many cases are not fresh samples that the product is actually indicated for. It is therefore unrealistic to expect the manipulated samples to meet acceptance criteria more stringent than unaltered fresh samples. Therefore, the acceptance criteria should be appropriately assessed against a control condition where the test samples have been exposed to the same sample manipulation process. In other cases, study design in the guidance is not described clearly and is in fact too vague to clearly define a test condition (e.g., proposal for evaluating temperature and humidity effects), and/or whether provisions apply to all studies or only specific studies. Thus, apart from the necessary investment and extensive proposed changes, revisions to the guidance are necessary to assure understanding of the details and address technical challenges so that the manufacturer can reasonably conduct the referenced experiments.

We also encourage the holding of a workshop prior to issuance of the final guidances with industry and other stakeholders. Such a forum would provide the opportunity to discuss scientific and technical issues and optimal mechanisms to support public health and innovation in BGMs for patients. Other BGM guidances, notably ISO 15197 and CLSI POCT(12), included multiple face-to-face meetings and discussion of experts from regulatory agencies (including FDA), other governmental agencies (e.g., NIH), universities, healthcare professionals, and industry.

We hope the Agency will take the opportunity to consider all of these factors, to develop an improved guidance that will not only protect patients, but will also benefit patients by facilitating access and innovation. We urge careful consideration of our comments in

order to address critical feedback from industry. Substantial comments outlining constructive revisions along with rationale are provided in our specific comments to address concerns and improve the guidance. We believe they are necessary for meaningful implementation of this guidance and reflective of mechanisms that can be reasonably achieved by industry.

SPECIFIC COMMENTS

AdvaMedDx's specific comments on the draft guidance follow and provide more detailed recommendations.

Sincerely,

/s/

Khatereh Calleja
Vice President, Technology and Regulatory Affairs

ADVAMEDDX SPECIFIC COMMENTS

AdvaMedDx Comments on Draft Guidance for Industry and FDA Staff—
Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use

Comment Number – Edit number

Change – Proposed change to the guidance

Section –Section of the guidance

Comment/Rationale – Reason for proposed change

Line No. – Guidance line number

Comment Number	Section	Line No	Change	Comment/Rationale
1.	General	General	Recommend updating the guidance to be consistent with methodologies described in FDA-recognized standards and guidelines.	Consistent with general comments, there are many aspects of this guidance that are in direct conflict with the recommendations made in FDA-recognized standards and guidelines. For example, the use of percent bias across the glucose measuring range contradicts the ISO 15197:2003 standard (FDA recognition number 7-100) and the method of bias calculation described for the interference and hematocrit studies contradicts the methods described in CLSI EP7-A2 (FDA recognition number 7-127).
2.	General	General	Recommend evaluating bias (in mg/dL) at low glucose levels and % bias at high glucose levels throughout the studies recommended in the document.	The concept of evaluating bias (in mg/dL) at low glucose concentrations and percent bias at high glucose concentrations for blood glucose systems is standard practice for blood glucose monitoring (BGM) test systems and is described in standards and guidelines relating to blood glucose systems, such as ISO 15197 and CLSI POCT-12. Studies described in this draft guidance (e.g., the method comparison and hematocrit studies) should work to adopt this approach and promote better overall harmonization with worldwide standards.
3.	II	39	Remove “more.”	Statement relates to necessary robustness and reliability to accommodate actual meter use.

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4.	II	42-46 and related references including title	Revise as follows (delete stricken text and add text in underline): "In order to distinguish between ~~prescription~~ point-of-care blood glucose meters, which are intended for use in ~~point-of-care~~ professional healthcare settings, and those intended for ~~OTC~~ self-monitoring by laypersons, the Agency is issuing two separate draft guidances for (i) ~~prescription~~ point-of-care blood glucose meters, for use in ~~point-of-care~~ professional healthcare settings, and (ii) ~~SMBG~~ over-the-counter devices intended for ~~OTC~~ self-monitoring by laypersons."	The title of these guidances and references to "prescription use" is inappropriately termed and confusing. Many lay users obtain prescriptions for their self-monitoring blood glucose (SMBG) systems so specifying that prescription use is only professional is misleading. Point-of-care (POC) meters for professional healthcare settings and over-the-counter (OTC) for self-monitoring are better choices for accurate descriptions. It should be noted that AdvaMedDx has provided extensive comments regarding the prescription BGM guidance, which provide in-depth analysis of concerns regarding the proposed guidance and overly broad restriction on the use of OTC BGMs in all professional settings for any and all ways in which the device is used. Devices may provide adequate performance in certain professional settings. Furthermore, the draft guidance should better differentiate and require professional and home use labeling rather than override existing statutes that allow for home use products to be used in CLIA-waived environments. "Home use" does not mean that the use of the product is restricted to the home. In the case of clinical situations where greater accuracy is necessary (e.g., tight glycemic control) and a manufacturer intends its product for such intended use, FDA must require such accuracy (and appropriately, fall outside the scope of the OTC guidance). However, if a manufacturer's intended use for a BGMS is as an aid in monitoring the effectiveness of a diabetes control program in adults (a common, FDA-cleared, intended use for a BGMS that would be subject to the OTC Guidance), and the test provides sufficient performance for this use in a patient's home, such use should not be prohibited in professional environments for the identical use. This critical issue

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				is discussed in further detail in our POC comments along with likely unintended impact of the overly broad guidance. We share concerns with healthcare professionals regarding the false assumption that physical location of the patient renders it inaccurate. In fact, FDA itself notes in the OTC guidance that "medical professionals are generally more proficient at performing testing and at running appropriate controls, and they typically have a better understanding of test limitations as compared to laypersons."
5.	II	56	Replace "appropriate cleaning" with "effective cleaning."	This revision allows for clearer, improved terminology to better describe rationale for cleaning. "Appropriate" is vague and cannot be defined.
6.	II	60	Recommend that the FDA clarify what "other non-professional settings" is referring to in this statement.	Agree that emphasis should be on the way in which the device is used. However, it is unclear what "other non-professional settings" refers to in this context.
7.	III	69	Remove "etc."	Either identify the specific settings or remove the generic reference to "etc." Define the setting.
8.	III	75	Clarify "[d]evices for measurement of blood glucose in neonates."	Is this a special pro-code? Also, FDA should cross-reference any relevant FDA guidance related to measurement of blood glucose in neonates.
9.	IV	101	Revise as follows (add text in underline): "All <u>"OTC"</u> SMBG devices…"	Improved definition
10.	IV	104-105, 182-183	Revise so that cleaning and disinfection can be considered one cycle. Alternatively, if separate steps are necessary, then a mild detergent solution for cleaning should be acceptable.	FDA has recently required that cleaning and disinfection (C&D) be considered 2 separate steps. If using the same agent, we suggest that C&D may be considered one cycle. See line 182.
11.	IV	107	Revise as follows (delete stricken text): "All external surfaces of the meter, including seams and test strip port, should be designed for ~~both ease of~~ ~~use and~~ ease of cleaning and disinfection."	Ease-of-use is the subject of Section VI.C.1. The focus of this section is cleaning and disinfection.

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12.	IV	109	After “lay users at home”, add “, which includes a variety of settings, including work or school.”	The use of “at home” could be interpreted very narrowly. Furthermore, there is no recognition that other settings might have additional users (e.g., family member, school teacher).
13.	IV	114-131	Reference the 2010 letter to industry on cleaning and disinfection of BGMs.	We agree with wording, but we also recommend the FDA reference the 2010 letter to industry on cleaning and disinfection of BGMs.
14.	IV	117	Clarification regarding reference to EPA list of disinfectants.	It should be noted that the EPA website includes a number of lists (probably referring to List D) and that the List D has not been updated since 2009. The list includes specific products; it would be better to identify specific agents (included in the brand name on the list).
15.	IV	122-125	Replace the current statement with the following: “Labeling for all test system components should incorporate a common naming structure to clearly identify each individual component as being part of the overall system. In some cases, the same proprietary device name can be used for all components (ABC blood glucose system, ABC blood glucose meter, ABC blood glucose test strips, etc.). In cases in which a test strip is shared by several different meters, a common naming identifier must be used to link the individual components together (ABC DEF blood glucose system, ABC DEF blood glucose meter, ABC blood glucose test strips, etc.).”	The guidance that the labeling for test system components should incorporate the same device name is not strictly possible when multiple devices use the same test strip. As drafted, the current guidance does not describe situations in which one strip type is shared by many different meters or vice versa. It would not be manageable to provide multiple, differently branded strip types on store shelves (retail outlets will only accommodate a limited number of SKUs). The recommended wording updates the language to describe situations in which the strip is shared by multiple meters or vice versa.
16.	IV-A	General 133-165	Update guidance language to indicate that, while disinfectant used must be effective against Hepatitis B, Hepatitis C, and HIV, studies involving disinfecting effectiveness must only be carried out involving Hepatitis B.	Consistent with Lines 155-156, it should be clear if the intent is that the disinfecting effectiveness study must only be carried out with Hepatitis B.
17.	IV	134-136	Define “overall” and clarify that deterioration should be considered in light of safety/efficacy.	It would also be helpful to define “overall” and clarify that deterioration should be considered in light of

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				safety/efficacy. Also clarify that cleaning and disinfection data should be a factor considered in useful lifecycle and defined by manufacturer protocol.
18.	IV	141	Reconsider "use of 10% bleach solution may lead to physical degradation of the device."	10% bleach solutions are common and can be found in many household cleaners. This may be permitted as long as it can be shown safe/effective.
19.	IV	144-146	Revise as follows (delete stricken text and add text in underline): "To demonstrate that your disinfection protocol is effective against Hepatitis B virus you should perform disinfection efficacy studies to demonstrate that your procedure is effective with the external meter materials, <u>including case parts, display, buttons and labels.</u>"	It might be helpful to specifically mention each of the external meter materials.
20.	IV	161-165.	We appreciate FDA including these standards. We also recommend adding "or equivalent" for each of these standards.	Standards may evolve and are updated over time.
21.	IV	177	Revise as follows (delete stricken text and add text in underline): "You should choose worst case scenarios with regard to cleaning and disinfection frequency and end user environment to determine the number of cleaning and disinfection cycles that should be tested. <u>The disinfectant contact time in the bench studies must be identical to the contact time described in the cleaning and disinfection procedure.</u>"	It is important that the bench studies proving meter reliability mimic the manufacturers cleaning and disinfection procedure.
22.	IV	181	Clarify "exposed to in its use life" (typically 3-5 years)	This would provide helpful clarification.
23.	IV-B	185-186	Clarify that the "test strip port and all other openings" is limited to surfaces that can be	If the user cannot touch a surface, then there is no risk of contamination. As such, it is not necessary to

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			handled by the user and that it is not necessary to disinfect into the strip port but the surface around it. Alternatively, include the following statement in the labeling: "Avoid the test strip port and all other openings during your cleaning and disinfection procedures."	disinfect into the strip port, but the surface around the strip port should be disinfected. This should be clarified. The strip port cannot be sealed when using a disposable test strip. Therefore, subjecting the meter openings, such as test strip port, to cleaning and disinfection procedures will cause the disinfectant to ingress into internal parts of the meter, thereby affecting the electrical circuitry of the meter. Since disinfection efficacy studies will be conducted to demonstrate that the disinfectant is effective against the external surface of the meter, and the labeling will instruct that the meter is for single patient use (Line # 1183-1184 - 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) the risk of bloodborne pathogen transmission is minimal.
24.	IV-B	194-195	Clarify whether or not the FDA expects only accuracy to be evaluated in cleaning robustness studies or if the expectation is that other meter features be evaluated as well. Also state the following: "The manufacturer has to demonstrate that repeated cleaning and disinfection does not affect performance by comparing the performance of the system using control materials compared to devices that have not gone through the same treatment."	Currently, the guidance states that the performance of the meter should be evaluated to ensure that "repeated cleaning and disinfection does not affect performance (accuracy)." This implies that only accuracy, and no other meter features such as data downloading, should be evaluated in these studies. The method to test accuracy is not specified. A comparison of the devices that have not undergone cleaning/disinfection that have not been exposed to this treatment would adequately demonstrate the impact of cleaning/disinfection on device performance.
25.	IV	196	"reusable lancing devices"	Are these currently legally distributed in the U.S.?
26.	IV	202	Revise as follows (delete stricken text and add text in underline):	We agree that it is crucial to validate the effectiveness and clarity of the cleaning and disinfection instructions. However, we believe that usability of the C&D

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			"You should incorporate your labeling instructions for cleaning and disinfection in a ~~your~~ user study (see Section VI-C, below**)** to determine the effectiveness and clarity of the instructions in your labeling for lay users."	instructions can be validated in a user study that is separate from the Section VI.C study, allowing the VI.C study to maintain its focus on accuracy of the glucose measurement.
27.	V	216	Clarify "[m]anufacturer's performance specifications."	Does this mean the claims? Or the manufacturers internal procedures?
28.	V	220	Clarify "[d]escription of the composition and levels of control material."	Are controls required in this submission? Are controls required for SMBG? What if the controls are manufactured by a different sponsor?
29.	V	224	Request FDA provide guidance on any specific design features they consider are required.	It is unclear. Is this aside from labeling and C&D?
30.	V	237-238	Recommend that the FDA use more precise wording for its "error tolerance for user actions" description and provide clarification.	It is unclear exactly what the FDA would require in such situations. The nature of this requirement and its purpose is unclear.
31.	V	246	Clarify this paragraph.	Is this an extension of line 234?
32.	VI-A	279-280, Table 1	Update the wording in this section to indicate that, if a system does not have a measuring range below 50 mg/dL, the 30-50 mg/dL concentration interval must not be tested.	If a system does not have a claimed measuring range below 50 mg/dL, then it should not be required to test in the 30-50 mg/dL glucose concentration interval. Wording in this section could be accordingly revised.
33.	VI-A	282		Concur with this provision that "[y]ou should determine repeatability using venous blood samples. " This is particularly helpful for manufacturers with respect to contrived samples.
34.	VI-A	286-288	Revise as follows (delete stricken text and add text in underline): "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~~ or packages should be used in the study."	It appears that the sample of 500 measurements is required for each of three lots, but the proposed wording could be interpreted to mean that a total of 500 measurements are required across 3 lots (e.g., 3 vials from lot A, 3 vials from lot B, and 4 vials from Lot C). Also, the text assumes that strips are sold in vials, but this is not necessarily true for all products.
35.	VI-A	295-297	Revise as follows (add text in underline):	It is not clear whether the statistics are reported at each glucose level for the entire data set (n=300),

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			"For each glucose concentration range in Table 1, you should also provide the mean value, pooled standard deviation (with 95% confidence intervals) and pooled percent CV for data combined over all meters."	individually for each of the three lots (n=100 per lot), or the pooled (root mean square) statistics for the three lots (i.e., overall within-lot variability). ISO 15197 specifies pooled results.
36.	VI-A	298-299	Remove this sentence.	Data should not be excluded from measurement repeatability or imprecision calculations, as "outliers" contribute to such parameters as depict repeatability and imprecision. See also line 423.
37.	VI-A	304	Revise as follows (add text in underline): "Intermediate precision measurement studies are designed to measure imprecision that would be expected under normal conditions of use by the intended user (i.e., measurement by individuals over multiple days, with the same meter, and reagent system lot)."	This needs to be written so that it is clear that it is not an actual user evaluation but rather a bench study.
38.	VI-A	311-314	Revise as follows (delete stricken text and add text in underline): "Precision should be evaluated over a minimum of 10 days, taking at least 1 measurement per day per sample, for a minimum of 10 measurements per meter for each concentration (and 100 measurements per concentration). The glucose concentration intervals that should be measured are 96-144, and 280-420 mg/dL."	Recommend aligning the concentrations of the control solutions required for intermediate precision testing with those described in ISO 15197:2013. FDA guidance only recommends that manufacturers maintain two control solutions for their OTC systems, and most manufacturers do not have six control solutions at their disposable and at the FDA-specified concentrations. Therefore, it is recommended that manufacturers test only the control solutions they have available for their intermediate precision studies.
39.	VI-A	314	Revise as follows (delete stricken text and add text in underline): "You should use a minimum of 500 test strips from a minimum of 10 vials or packages ~~and 3 manufacturing lots.~~ "	"Unclear whether 500 tests include 3 lots or 500 tests should be conducted with each of 3 lots.
40.	VI-A	316-317	The FDA should specify what it considers to be "acceptable precision."	The current text indicates that, in the precision studies, acceptable precision should be demonstrated for all lots, users, and meters. However, no criteria are

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				provided by which the FDA will judge acceptability. What is “acceptable”?
41.	VI-A	321	Revise as follows (delete stricken text and add text in underline): “For each glucose concentration, you should also present the mean value, pooled standard deviation (with 95% confidence interval) and pooled percent CV using measured values from all three test strip lots.”	As stated in line 305, the purpose is to establish measurement imprecision over time with the same reagent lot. Imprecision statistics should therefore be pooled over the three lots to establish typical within-lot imprecision.
42.	VI-A	324	“you should provide all results based on all data”	This appears excessive to require line-item data for all analytical parameters. If line data is required, it should be provided only for method comparisons.
43.	VI-A	324-326	Remove this sentence regarding outliers.	Data should not be excluded from measurement repeatability or imprecision calculations, as “outliers” contribute to such parameters as depict repeatability and imprecision. See also line 423.
44.	VI-B	328 - 340	Delete Section B.	This linearity study does not provide information that is not already provided in the method comparison study (including accuracy at extreme levels) outlined in Section C.
45.	VI-B	330-331	At a minimum, clarify whether the FDA prefers “11 evenly spaced concentrations” as the guidance suggests or if they prefer 11 levels with a focus on low glucose concentrations.	In the past, the FDA has required linearity studies presented in 510(k) submissions to use 11 different glucose concentrations with an emphasis on the low glucose levels. In these studies, the glucose levels were not evenly spaced. It is unclear as to whether or not this is the FDA’s preference, given the linearity wording provided in this guidance indicates that the glucose levels should be evenly spaced across the concentration range.
46.	VI-B	331	Use of CLSI guideline	In this case, FDA’s referencing of the CLSI guideline is useful. We urge referencing of additional CLSI guidances to better promote harmonization.
47.	VI-B	334	Use of contrived samples	Concur with this provision. This is helpful for manufacturers with respect to contrived samples.

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48.	VI-C	342	Clarification and additional flexibility is needed regarding Method Comparison/User Evaluation. Remove sentence from 351-353.	While it is a challenging study design, 350 subjects total plus subgroups as necessary is acceptable. However, we appreciate clarification on why FDA is eliminating the section 6.3 study of ISO 15197: 2013. Also, FDA should allow the manufacturer to determine the appropriate comparison protocol. For example, the use of "single evaluation" is a very limiting design and does not allow any investigation or determination of root cause for any issues. Statements in this paragraph assume that manufacturers fail to perform studies in actual conditions of use or simulated use conditions in the actual or simulated environment in which the device is expected to be used.
49.	VI-C	358-359	Clarify this sentence.	It does not adequately define what testing is to be performed in each of the environmental conditions. These conditions are additionally tested in Section F.
50.	VI-C	362-365	Revise as follows (delete stricken text and add text in underline): "Fresh capillary samples should be obtained with sufficient volume to be measured on the candidate device. <u>A separate fresh capillary sample should be obtained by the medical technician for the reference method.</u> If you are planning to include claims that your device can be used at alternative sites (e.g., forearm, palm, etc.), you should obtain and evaluate 350 samples from each site. <u>Alternative site samples should be compared to the reference assay from the fingertip."</u>	It is unclear how the statement here that "fresh capillary samples should be obtained with sufficient volume to be measured on both the candidate device and the reference method" can be reconciled with the statement in line 395 that "subjects should obtain their own capillary sample." The amount of capillary blood that can be obtained by subjects lancing themselves is rarely adequate for a reference method. A special deep lancing device administered by an HCP is usually required for adequate blood to test the reference method. Also, alternative sites do not have enough capillaries to collect adequate blood for the reference method even with a deep lancing device, so a statement should be included that alternative site readings should be compared to reference method results from a fingerstick specimen.

Comment Number	Section	Line No	Change	Comment/Rationale
51.	VI-C	368-372	The samples should include 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.	As it may be difficult to obtain samples safely with glucose concentration < 80 mg/dL in diabetic subjects, fasting normal individuals may be studied.
52.	VI-C	374-375	Revise statement to read: "Data from all subjects in the study should be submitted, along with a table indicating those that have been excluded from the data analysis and the reason for the exclusion." Alternatively, state: "All data collected within the operating range of the system under investigation and the reference measurement system is included in the analysis."	The statement "Data from all subjects in the study should be submitted, and no subjects should be excluded from the data analysis" is too limiting, as there may be samples that are excluded for various approved reasons (e.g., duplicate reference values falling out of range). While all data should be provided in the submission to the FDA, the analysis should not contain such data. This statement seems more appropriate in the "Data Analyses" section beginning on line 476. At a minimum, clarify if the expectation is to include all data in analysis rather than only those data collected that are within the operating range of the system under investigation and the reference measurement system.
53.	VI-C	374	"enroll until adequate sample concentrations are collected"	Assuming that this is for the very low/very high buckets.
54.	VI-C	375	Revise as follows (delete stricken text and add text in underline): "Data from all subjects in the study <u>(even if more than 350 samples are collected)</u> should be submitted, and no subjects should be excluded from the data analysis."	Provides clarification.
55.	VI-C	379-380	The subjects you enroll in the method comparison/user study should consist of at least 20% insulin using diabetics. At least 10% of the minimum number of study participants should be naïve to SMBG devices. The naïve subjects may include non-diabetic individuals provided they	A patient when diagnosed with diabetes is ordinarily trained by the HCP on blood glucose monitoring. Hence to obtain 10% (35) of study participants being naïve to SMBG devices is impractical and unduly burdensome. The same assessment of the usability of the device (including its labeling) can be obtained

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			constitute no more than 10% of the minimum number of study participants. You should describe the inclusion and exclusion criteria for enrolling the study participants, as well as the demographic characteristics of the participants.	by testing non-diabetic subjects. Since these subjects will constitute no more than 10% of the entire population, they need not be matched for age, gender, co-morbidities, etc. The requirement that the study population should accurately reflect the intended use population is problematic because it is vague. On the other hand, it would be difficult to prescribe and difficult to recruit specific percentages of patients of a given type of diabetes, and of certain age, gender, duration of disease, complications, etc. It should be sufficient to specify a specific percentage of insulin-using patients.
56.	VI-C	384	Revise as follows (delete stricken text and add text in underline): "Prior to testing, study subjects should be given the device labeling (instructions for use, user manual etc…) that will be provided to the user with the device once on the market. Labeling may be draft and on photocopied paper**."**	Labeling may be near final draft and on photocopied paper for the purpose of the trial.
57.	VI-C	387	"translations into other languages should not be provided to these study participants"	Has the potential to leave out a huge segment of American diabetics – Spanish speakers. What will happen if the demographics are skewed because translations could not be provided?
58.	VI-C	389-390	Recommend that the FDA either impose a less restrictive reading level requirement or modify its required wording for test strip package inserts and product labeling.	The requirement that the reading grade level be at an 8th grade level or less is in direct conflict with the required wording that the FDA has described in the labeling section (section IX). For example: The intended use that the FDA has proposed (lines 1055-1059) results in a Flesch-Kincaid Reading Grade Level of 12.8. The warning that the FDA has indicated must be included on the outer box labeling and package insert

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				(lines 1065-1072) results in a Flesch-Kincaid Reading Grade Level of 20.1. The data presentation example that the FDA has provided in lines 1146-1158 results in a Flesch-Kincaid Reading Grade Level of 9.6. The warnings that the FDA has indicated must be included in the labeling (lines 1183-1186) result in a Flesch-Kincaid Reading Grade Level of 9.7. Maintaining the labeling at an 8th grade reading level while including the required information described above will not be possible.
59.	VI-C	396	Revise as follows (delete stricken text and add text in underline): "No other training <u>(other than what is routinely provided with the device)</u> 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."	The added phrase reflects ISO 15197:2013.
60.	VI-C	400-404	Revise so that it states: "Once the study participant has obtained their own result using the SMBG device, the technician should obtain an additional capillary sample from the same or a different but comparable site within 5 minutes for testing on the reference method. This reference sample should be collected in duplicate, and the difference between these duplicates should be less than ±4 mg/dL or 4% for the reference to be considered valid. Since the intended user population of SMBG devices is the layperson, it is not necessary for the technician to obtain capillary results on the SMBG device for comparison to the reference value. However, the manufacturer may wish to do so—for example, to obtain baseline performance or investigate	The statement that the technician should obtain an additional capillary sample for the reference method implies that the lancing site obtained by the user for an SMBG (typically requiring <1µL) will produce adequate blood volume for a reference method (typically requiring 100 – 200 µL of whole blood to create 50 – 100 µL of plasma for two assays). A separate deep fingerstick with a different lancing device is frequently required for the reference method. In addition, because it is important that duplicate samples be taken within a short period of time to minimize any potential changes in glucose that have occurred during the testing, a timeframe is provided. The last sentence explains why a manufacturer might choose to have the technician obtain capillary results on the SMBG device despite the fact that those results will not be considered in FDA's assessment of the

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			outliers."	device's accuracy.
61.	VI-C	406	Revise as follows (delete stricken text and add text in underline): "You should include a minimum of 3 test strip lots and a minimum of 10 test strip vials or packages <u>per lot</u> in the study."	For the sake of clarity in the design, should use 3 sensor lots with 10 vials or packages per lot. Also provide clarification if 450 tests are performed on each strip lot or one lot is tested on 1/3 of the samples.
62.	VI-C-1	407-410	Remove the requirement "All test strips used in the study should have undergone typical shipping and handling conditions from the site of manufacture to a U.S. user prior to being used in the study. You should describe these shipping and handling conditions in your premarket submission." Alternatively, revise as follows: "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" to "All test strips used in the study should have undergone typical shipping and handling conditions from the site of manufacture to a distribution center prior to being used in the study."	Given that the BGMS shipping validation report along with test strip stability is included as part of the 510(k), it is redundant to require the test strips to be subjected to typical shipping and handling conditions for the clinical study, since this does not impact the clinical study. The statement does not currently support the conduct of these studies outside the U.S. without the imposition of significant burden.
63.	VI-C	421	FDA should follow the International Organization for Standardization (ISO) analytical accuracy standard 15197 (2013), which has been recently updated and reflects the worldwide standard. Foremost, FDA must work to harmonize efforts with worldwide standards. While we do not endorse an approach inconsistent with ISO, we note that FDA might, as an alternative, consider a more reasonable approach to improve SMBG accuracy performance in the hypoglycemic range	**<u>Clinical Rationale for Recommended Criteria</u>** In a recent publication by Karon, Boyd, and Klee [Clinical Chemistry 56:7, 1091-1097 (2010)], the authors describe a tight glycemic control protocol in which all patients who have glucose <80 mg/dL are treated the same; namely, no insulin is administered and they are given a supplement to raise their blood glucose. Although the guidance described here relates to OTC systems, the concept is the same; at low glucose levels, there is not a clinically significant difference between 50 mg/dL and 62 mg/dL. Patients

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			i.e., revising the method comparison/user evaluation criteria to the following: 95% of all SMBG results must be within ±12 mg/dL of the reference at glucose concentrations <80 mg/dL and within ±15% of the reference at glucose concentrations ≥80 mg/dL. 98% of all SMBG results must be within ±15 mg/dL of the reference at glucose concentrations <75 mg/dL and within ±20% of the reference at glucose concentrations ≥75 mg/dL.	with these glucose concentrations need to have glucose administered to raise their glucose levels. The acceptance criteria described in this guidance document indicate that a bias of ±12 mg/dL at low glucose levels is clinically significant, as the allowable bias at 50 mg/dL is only ±7.5 mg/dL. This presumes that a patient with a true glucose of 50 mg/dL will act differently if he/she obtains a result of 62 mg/dL versus a result of 57 mg/dL. According to the publication by Boyd and co-workers, this is not likely. In this publication, it is indicated that a 3-category insulin dosing error can result in very dangerous, clinically significant consequences. In the low glucose range, this will occur if a sample having a true glucose of 80 mg/dL provides a meter result of 110 mg/dL, or 30 mg/dL of bias. It is recommended that, at low glucose levels (below 80 mg/dL), the allowed amount of bias only be ±12 mg/dL. This is 2/5 the allowable bias described in the publication by Boyd and co-workers, and it represents a significant accuracy requirement improvement over that which is described in the ISO 15197:2013 standard. The proposed change to ±12 mg/dL is also consistent with the recently released CLSI POCT-12 guidance for in-hospital use and provides a degree of accuracy reasonable for layperson use. That guidance stipulates an accuracy of ±12 mg/dL glucose <100 mg/dL and ±12.5% glucose ≥100. We believe that a cut point of 80 mg/dL is reasonable because FDA has expressed concern regarding accuracy at low glucose (hypoglycemia is generally defined as glucose < 70 mg/dL) and 80 mg/dL is the logical transition point since 15% (the recommendation for glucose ≥ 80 mg/dL) of 80 mg/dL= 12 mg/dL. It should also be noted that, at 80 mg/dL which is near a critical clinical decision point, the recommended criterion of ±12 mg/dL below 80 mg/dL is no different

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				than the criterion recommended by the FDA guidance document (±15% at 80 mg/dL, which is equal to ±12 mg/dL). Therefore, the proposed criteria are more technologically reasonable in the hypoglycemic range while requiring the same level of performance near the critical clinical decision point. **Clinical Considerations for the Use of Percent Bias at Low Glucose Levels** During a teleconference with industry on January 14, 2014, it was indicated that, in preparing the guidance, the FDA had consulted with clinicians who had indicated that, in a home use environment, individuals were not likely to make a different decision about what to do based on a value of 30 mg/dL vs. a value of 45 mg/dL. Given this information, it seems unlikely that these same clinicians would indicate that individuals in a home use environment would make a different decision about what to do based on a value of 50 mg/dL vs. a value of 62 mg/dL. With the current acceptance criteria, a bG value of 62 mg/dL, when the true glucose value is 50 mg/dL, would be considered an inaccurate result (the criteria require a performance of ±7.5 mg/dL at 50 mg/dL glucose). The difference between ±15% and ±12 mg/dL at low glucose values is not clinically significant for layperson use. **Reference Analyzer Considerations for the Use of Percent Bias at Low Glucose** The currently recommended method comparison acceptance criteria do not take into account that the reference method has analytical error. In the most extreme case, a measurement of 20 mg/dL would require an accuracy of ±3 mg/dL. Such a requirement is challenging the performance capabilities of even reference methods. For example, the precision of a YSI is stated as being "±2.5 mg/dL or 2%, whichever is larger." Additionally, it is commonly recognized that

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				reference measurement duplicates can differ by ±4 mg/dL or 4% (CLSI POCT-12 and ISO 15197). **Comparison of OTC and POCT Guidance Criteria** The currently recommended method comparison acceptance criteria require that the bias be no greater than ±3 to ±7 mg/dL for glucose concentrations ranging from 20 to 47 mg/dL. These criteria are more stringent than the criteria outlined in the POCT draft guidance document which require the bias to be no greater than ±7 mg/dL across the entirety of this same glucose range. It would seem illogical that an OTC BGM system would be held to a tighter accuracy requirement than a POCT system that could be used for tight glycemic control. **Proposed Criteria and Patient Considerations** It has been indicated that the use of percent bias across the entirety of the glucose range will increase patient understanding and comprehension. It is likely that, given the FDA's proposed labeling changes, this improved customer comprehension and understanding will still take place even if bias is expressed in absolute terms (mg/dL) at low glucose levels and percent terms at high glucose levels. In other words, as a result of the new labeling format, patients should still be able to adequately compare systems regardless of whether or not percent bias is used across the entirety of the glucose range. We understand that FDA chose a % rather than an absolute number [which is the standard practice] as the measure of accuracy at low glucose levels on the grounds that it would be easier for laypersons to understand a single criterion for accuracy. To our knowledge, this is supposition, not proven. Secondly, as the Agency acknowledges, it is not possible for current SMBG technology to provide a

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				glucose result within 15% of the reference at low glucose levels. By substituting an error message for an absolute value, the patient or caregiver is deprived of a specific number that may be more valuable than the recommended error message. Thirdly, few, if any, meters using current technology can achieve an accuracy of ±7.5 mg/dL at glucose = 50 mg/dL, especially if hematocrit must contribute less than 4.0 mg/dL to the error. If no meters can produce this level of accuracy, the criteria are clearly too strict.
64.	VI-C	424	Revise as follows (delete stricken text and add text in underline): "If there are any SMBG test results that are >20% relative to the reference, you should provide a justification for why the errors occurred, <u>if possible</u>. ~~and describe why the potential for that error does not render the device unsafe and ineffective, even when extrapolated to the intended use setting (e.g., when billions of tests are performed)."~~	The performance criterion is unnecessarily tight. This would require limiting the low end of the dynamic range above expected market requirements, which has been proven to be safe and effective for devices to be placed in commercial distribution, such as ISO15197:2013 (*In vitro* diagnostic test systems -- Requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus).
65.	VI-C	424	"if there are any SMBG results that are >20% relative to the reference"	"reference method" previously described as lab method (line 263), which is typically a large analyzer that uses venous, not capillary blood. Does FDA mean "predicate"?
66.	VI-C	424	"…include all results in the submission"	The need to include line-item data for analytical performance is a new requirement and unduly burdensome.
67.	VI-C	432	"The SMBG device should identify and provide an error code in situations where the measured glucose falls outside of the device's stated measuring range."	We support this proposal.
68.	VI-C	458	"…how the selected study conditions simulate intended use conditions"	Performing studies outside of a controlled environment is generally not recommended. While in an ideal world the sponsor could provide meters to anyone/everyone to test at all alternative places/sites, testing in the widely diverse possible settings and

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				would be difficult to ensure the safety and confidentiality of the study subjects if the study is not performed in a controlled environment.
69.	VI-C	462	Revise as follows (delete stricken text and add text in underline): "Patient demographics including age range, education level, race, ethnicity, ~~native language, work experience~~, disease state (type I or II) and whether they are naïve SMBG device users or not." Also request that FDA provide clearer guidance on the expected subject disease states to include in a study of this nature other than type of diabetes.	Clearer guidance will help assure understanding and consistency across manufacturers. For example, work experience is not relevant. Disease state is self-reported and can be unreliable. Given the exclusion criteria for non-English speaking, we also suggest removal of reference to native language. Also we note that FDA previously identified that all labeling must be in English only and yet is acknowledging that English might not be the native language (line 387).
70.	VI-C	472	Revise as follows (delete stricken text and add text in underline): "A user questionnaire should be provided for the ~~study participants~~ study staff to administer to the subjects after the subjects have completed the study."	The recommended wording insures more reliable data.
71.	VI-C	473	Revise as follows (delete stricken text and add text in underline): "A copy of the questionnaire and a summary of the results should be provided in the submission."	We assume this information will be submitted in a summary rather than raw data.
72.	VI-C	478	Revise as follows (delete stricken text and add text in underline): "~~All outliers that do not conform to the minimum accuracy criteria should also be included.~~ Any results outside +/- 20% should be investigated and explained when possible."	The term outlier is unclear and confusing.

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73.	VI-C	480-482	Revise as follows (delete stricken text and add text in underline): "To assist in this investigation, you should collect information regarding ~~patient medications,~~ hematocrit measurements, disease states during your study." Alternatively, revise to state: "To assist in this investigation, you should collect hematocrit information on the sample used and information (patient self- reported) regarding patient medications and disease state either during the study or retrospectively."	Including list of <u>all</u> medications will be a challenging effort in the collection, database development, source document verification (monitoring) and reporting as diabetic subjects take multiple medications. Collecting patient medications and disease states beyond diabetes for 350 subjects would increase complexity of the study documentation tremendously. This should be weighed with the amount of value it would bring to the BGM evaluation. Also to correlate outliers with medications is not a scientific method (unless the quantities of the metabolites were tested in the blood). The inclusion of medication information relates to the investigation of outlier results as part of the study design. At a minimum, FDA should allow for reliance on self-reported patient data than require physician reporting or examination of medical records. To include approaches of collecting medication and disease state information on outlier results either during or retrospectively on outlier results will also provide more flexibility for manufacturers.
74.	VI-C	486-494	Update description to include details of Bland-Altman plot and/or a linear regression plot. The current description is mixing these two concepts together.	The description here appears to be combining the requirements of a Bland-Altman plot with those of a linear regression assessment. For example, in a Bland-Altman plot, the difference is plotted versus the reference glucose and, in a linear regression plot, the meter result is plotted versus the reference result and the slope and linear regression statistics are provided. This description needs to be updated and clarified.
75.	VI-C	487	"…reference value…"	"reference method" previously described as laboratory method (line 263), which is typically a large analyzer that uses venous, not capillary blood. Please clarify. Does FDA mean "predicate"?
76.	VI-C	494	Revise as follows (delete stricken text and add text in underline):	The term outlier is unclear and confusing.

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			~~"All outliers that do not conform to the minimum accuracy criteria should also be included.~~ Any results outside +/- 20% should be included."	
77.	VI-C	502-503	Update each column header to be consistent with the acceptance criteria described in lines 416-430: "Within +/-5%/5mg/dL", "Within +/-10%/10 mg/dL", etc.	The current column headers state "Within +/-5 mg/dL", "Within +/-7 mg/dL," etc. The assessment in mg/dL is counter to the criteria described in lines 416-430, in which percent bias is used across the entirety of the glucose range.
78.	VI-C	General 506-527	Recommend placing the description of the "Accuracy at Extreme Glucose Values" and "Error Codes for Samples Outside the Measuring Range" in a section other than "Data Analyses." Also clarify whether the same number of reps (1 rep per subject) should be collected in the 'Accuracy at Extreme Glucose Values' assessment as the user study.	The "Data Analyses" section of the "Method Comparison/User Evaluation" section does not seem to be the appropriate place to describe "Accuracy at Extreme Glucose Values" and "Error Codes for Samples Outside the Measuring Range" studies. This would provide consistency among manufacturers.
79.	VI-C-2	509	Ensure that 50 sample data is tested at both <80mg/dL and >250mg/dL by either altering capillary blood samples to the desired level or collecting them naturally to be tested via the same means.	Use of the wording 'you should perform' suggests that it will be an expectation that 100 subject samples be altered and tested via this means. Please confirm whether this is the expectation. Flexibility in this part of the study design would be preferred to allow manufacturers to develop a study design to meet the needs of global regulatory requirements they are required to meet. There may be unaltered subject samples that will be collected at the extremes of glucose to address other global regulatory requirements that could also be tested to the FDA guidance requirements.
80.	VI-C-2	513	Indicate that non-diabetic subject samples can be used for the assessment of accuracy at extreme glucose values at the manufacturer's facility.	This will facilitate testing.
81.	VI-C	515	"..capillary whole blood samples should be used	The rational for this suggestion is unclear. One

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			for these studies…"	cannot typically manipulate capillary (finger stick) samples.
82.	VI-C	521	Revise as follows (delete stricken text and add text in underline): "You should analyze the data ~~using the same methods described above for~~ combined with the user evaluation studies, for a total of 450 data points."	A sample size of 50 is insufficient to accurately evaluate performance.
83.	VI-D General	529-693	In these studies the "reference method" should be replaced with the "control condition" consistent with EP7-A2.	Under the Interference Evaluation Section the Agency continually requires bias to be calculated "from the reference method". In all these tests, the samples are altered and because of this alteration could have an inherent bias from reference.
84.	VI-D	537	Revise as follows (delete stricken text and add text in underline): "Specifically, testing should be performed in samples with glucose concentrations of ~~60~~ 50-70 mg/dL, ~~120~~ 110-130 mg/dL, and ~~250~~ 225-270 mg/dL to evaluate clinically relevant decision points."	The guidance should state a tolerance around the glucose levels in the contrived samples.
85.	VI-D-1	542-544 and Table 3	Recommend that alternative descriptions be used for "Therapeutic Level" and "High Toxic Concentration." Also remove "whole" from line 544.	The terms "Therapeutic Level" and "High Toxic Concentration" are not applicable to endogenous substances such as cholesterol, sodium, uric acid, etc. Text describes the highest concentration that could potentially be observed in a whole blood sample, but the example concentration and the concentrations in Table 3 are in plasma.
86.	VI-D	550	Column Header: Therapeutic Change to: Therapeutic/Normal	Endogenous substances do not have a "therapeutic" level.
87.	VI-D	550	Column Header: High Toxic Concentration Change to: Pathological or Toxic Concentration	Endogenous substances do not have a "toxic" level.

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88.	VI-D	550	Make the units of measure of the interferents consistent. Gravimetric is preferred (mg/dL).	Inconsistent units of measure can cause confusion.
89.	VI-D	550	Revise as follows: Acetaminophen 2 mg/dL 20 mg/dL Ascorbic acid 2 mg/dL 3 mg/dL Bilirubin 1.2 mg/dL 20 mg/dL Cholesterol 154 mg/dL 309 mg/dL Creatinine 1 mg/dL 10 mg/dL Dopamine 0.04 mg/dL 0.11 mg/dL ~~EDTA~~ ~~0.1 mg/dL~~ ~~2 mg/dL~~ Galactose 0.1 mg/dL 10 mg/dL Gentisic acid 0.7 mg/dL 112 mg/dL Glutathione 0.11 mg/dL 3.07 mg/dL Hemoglobin 10 mg/dL 200 mg/dL Heparin 2016 IU/dL 10080 IU/dL Ibuprofen 7.8 mg/dL 50 mg/dL L-Dopa 0.2 mg/dL 0.5 mg/dL Maltose 100 mg/dL 480 mg/dL Methyldopa 0.5 mg/dL 1.5 mg/dL Salicylate 10 mg/dL 50 mg/dL Sodium 140 mEq/L 150 mEq/L Tolbutamide 10 mg/dL 100 mg/dL Tolazamide 4 mg/dL 40 mg/dL Triglycerides 100 mg/dL 500 mg/dL Uric acid 8 mg/dL 24 mg/dL Xylose 20 mg/dL 60 mg/dL ~~Sugar alcohols~~ ~~0.03mg/100ml~~ ~~0.09mg/100~~	• For drugs and metabolites the toxic level to test is either three times the maximum therapeutic level or the highest expected concentration per CLSI EP-7A2. • The protocol outlined in lines 568-574 is the scientifically correct method (CLSI EP-7A2) and should be used in all evaluations, not just the rare cases where the substance interferes with the reference method. • Recommend removing EDTA from Table 3. Presumably, EDTA is on this list because it can be used as an anticoagulant. However, because this guidance deals with blood glucose systems that are for self-testing only, the only claimed sample type can be capillary blood. Capillary blood is very uncommonly used with anticoagulants in a lay use environment (unless a contrived study is carried out), and, as such, it should not be necessary to force OTC systems to be compatible with a particular anticoagulant such as EDTA. Therefore, it should be removed from this list. Alternatively, revised to 201.6 mg/dL and 1008 mg/dL respectively. • The guidance document currently lists 14 g/dL and 20 g/dL as the “Therapeutic Level” and “High Toxic Level,” respectively, for hemoglobin. These values are associated with the reference range for hemoglobin for *in vitro* testing. Hemoglobin plasma concentrations, *in vivo*, are much less than these concentrations. For example, Tietz Clinical Guide to Laboratory Tests, 3rd Edition (Tietz et al., Copyright 1995 p312) indicates that the conventional reference range for hemoglobin in

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				plasma is <3 mg/dL and SI Units for Clinical Measurement (DS Young et al., Copyright 1998, p152) describes the value of hemoglobin in plasma as 1.44±0.49 mg/dL. In other sources, G.S. Lippi et al. (Haemolysis: an overview of the leading cause of unsuitable specimens in clinical laboratories. Clin Chem Lab Med 2008;46(6):764-772,2008) indicate that the upper reference limit for free hemoglobin in plasma and serum is 20 mg/dL and 50 mg/dL, respectively. Given these values, it is recommended that the "Therapeutic" and "High Toxic" concentrations for hemoglobin be updated in Table 3. The recommended "High Toxic Concentration" of 200 mg/dL is consistent with the concentration provided in Appendix D of CLSI EP7-A2. • Bilirubin levels per CLSI EP-7A2. • Recommend updating the "Therapeutic Level" of Methyldopa to 0.5 mg/dL and the "High Toxic Concentration" to 1.5 mg/dL. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics, 5th Ed. Copyright 2012, page 2182 describes the therapeutic range of methyldopa as 1-5 µg/mL (0.1-0.5 mg/dL), and the toxic concentration is described as ≥7 µg/mL (0.7 mg/dL). Adverse reactions to methyldopa administration have been reported at ~9.4 mg/L (0.94 mg/dL) [E.G.C. Clarke (ed.). Isolation and Identification of Drugs, Pharmaceutical Press, p 422-423, 1969]. V. Tamminen and A. Alha (Fatal methyldopa poisoning. Bull Int. Asso. For. Tox 7(2):2-3 1970) reported a methyldopa overdosing that resulted in death. The postmortem concentration was 9 mg/L (0.9 mg/dL). 140 mg/dL was also reported in this publication, but this was in urine and not in blood. As such, it is recommended that the concentrations at which this substance be

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				evaluated be updated to reflect this information. CLSI EP7-A2 recommends an upper testing concentration of 1.5 mg/dL. • The "Therapeutic Level" of sodium that is currently listed in the document is 120 mEq/L. This is an extreme concentration of sodium. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics indicates that hyponatremia is defined as a decreased plasma sodium concentration of <136 mmol/L while hypernatremia is defined as an increased plasma sodium concentration of >150 mmol/L. A "Therapeutic Level" of sodium exists somewhere in the interim range, and it is suggested that 140 mmol/L be listed as that level. The guidance document currently lists 175 mEq/L as the "High Toxic Concentration" of sodium. Tietz Textbook indicates that anything higher than 150 mmol/L is considered hypernatremic, and it is highly probable that only individuals who are very sick and in the hospital will have sodium concentrations beyond such a level. For example, it has been reported that the incidence of sodium concentrations >150 mmol/L among ***hospitalized*** patients ranges from 0.2 – 2.5% (KH Polderman. Hypernatremia in the intensive care unit: An indicator of quality of care, Critical Care Medicine, 1999;27(6):1041-1042) and that the incidence of sodium concentrations >155 mmol/L among ***ICU patients*** is approximately 0.6% (GC Funk, Incidence and prognosis of dysnatremias present on ICU admission, Intensive Care Med. 2010;36(2):304-311). Even in hospital and ICU settings, such elevated sodium concentrations are exceedingly rare. As such, it is recommended that the "High Toxic Concentration" for sodium be updated to 150 mEq/L. This is consistent with the concentration described in Appendix B of CLSI EP7-A2.

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				• Dopamine High Toxic level per CLSI EP-7A2 • Ibuprofen per CLSI EP-7A2 • Uric acid High Toxic level per CLSI EP-7A2 • Xylose Toxic level is three times the Therapeutic level • Sugar alcohols are not listed in the "Interference Testing in Clinical Chemistry"
90.	VI-D-1	550, Table 3	Clarification is needed that Table 3 referring to either unconjugated bilirubin or conjugated bilirubin.	Currently, it is unclear whether or not Table 3 is referring to conjugated or unconjugated bilirubin.
91.	VI-D-1	550, Table 3	Suggest that hydrogenated starch hydrolysates (HSH) be removed from the footnote in Table 3.	Hydrogenated starch hydrolysates are simply a mixture of the sugar alcohols that are already recommended for testing in Table 3. HSH is a mixture of sorbitol, maltitol, and longer chain hydrogenated saccharides. Since the guidance recommends the testing of the individual components that make up HSH, it is not necessary to test HSH itself.
92.	VI-D-1	558-560	Revise so that it reads: "Each sample should be tested on the reference method in duplicate. If the duplicate reference results differ by less than ±4%, then the average reference value should be calculated and used in the evaluation. If the duplicate reference results differ by greater than ±4%, then the associated sample should not be included in the evaluation."	In its current state, the guidance document recommends averaging the results of four different reference measurements. If each of these four reference measurements is substantially different, then the ultimate reference value includes significant variability, the true glucose concentration of the sample is not well known, and "greater confidence in the true glucose concentration of the sample" is not had. Therefore, a true assessment of the accuracy of the BGM system cannot be determined. In order to conduct an assessment of BGM system accuracy, samples in which the true glucose concentration is not accurately known should be excluded from the study.
93.	VI-D-1	561-566 and 607-616	There appears to be a contradiction in the document in that lines 561-566 seem to recommend pooling the lots together to determine	There appears to be a contradiction in the data analysis descriptions, and it is not clear whether the acceptance criteria apply to the pooled data or on a

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			acceptability while lines 607-616 recommend evaluating each lot separately. Recommend that the data analysis only describes the presentation of pooled data and not by lot.	lot-by-lot basis. Because the guidance document recommends a sample size of 10 replicates per lot per level, this sample size will likely not be robust enough to truly determine if the acceptance criteria are met robustly by each lot. Additionally, confidence intervals around the mean bias will be very wide when the n is only equal to 10. Recommend requiring a pooled estimate that is based on n=30 to provide a robust estimate of the true performance of the system. Any lot-to-lot differences will be reflected in the presented SD and confidence intervals.
94.	VI-D-1	563-564	Recommend changing the bias calculation to the following description: "Each replicate should be compared to the average BGM value of a control sample that does not contain or contains a nominal amount of the potentially interfering substance under investigation. The bias and % bias should be calculated relative to this control sample."	The current bias calculation description (comparing the BGM system results directly to the reference analyzer value) is inconsistent with the data analysis recommendations provided in the CLSI EP7-A2 guideline for interfering substance evaluation and the ISO 15197:2013 standard. These documents highlight the importance of comparing test results to those of a control sample that does not contain or contains a nominal amount of the interfering substance of interest. It is important to evaluate interfering substances using such a methodology to eliminate any systematic bias that might be present that is unrelated to the substance under investigation. For example, investigations involving interfering substances evaluate the blood only from a few donors, and these donors introduce bias into the measurement (when compared to the reference analyzer result) that is unrelated to the investigated substance. This bias is eliminated when a control or nominal sample is used in the evaluation. The use of a reference method in such studies only serves to introduce additional analytical error and, if used solely for bias determinations, misrepresents the true bias due to the analyte of interest. Section 8.5 of CLSI EP7-A2 provides further details describing the importance of using a control group in interference calculations to isolate the interference effect. For this reason, it is

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				recommended that the methodology described in the guidance document be modified. In the case of interfering substances, it is recommended that the "paired difference" method described in CLSI EP7-A2 be used.
95.	VI-D-1	568-574	Suggest determining interference relative to the measurement of an analyte in a control or base pool. This eliminates the need for this section.	If interference evaluations are conducted according to the "paired-difference" testing method, then the use of a reference analyzer, which could be susceptible to interfering substances, is not needed. This also avoids confusion as to what is meant by "rare case."
96.	VI-D	574	Add at the end of line 574: "This information may be provided as supplied by the manufacturer of the reference method."	If this section is retained, reference method manufacturer is the best source for information on interferences to the reference method.
97.	VI-D-1	594-595	Rather than state "[i]n the 510(k), you should provide your definition of "significant" interference for that substance," the provision be revised as follows: "A substance is not classed as an interferent if the average difference in bias from the reference between the test interferent agent and the control is within ±10 mg/dL at glucose values < 100 mg/dL or within ±10% at glucose levels ≥ 100 mg/dL."	Interference testing is conducted at therapeutic concentration and the concentration that is the highest that could potentially be observed in whole blood. But there is no clearly defined acceptance criteria mentioned in the guidance. This provision is highly burdensome. This can lead to subjective interpretation of the data, and therefore clarity is required in defining the acceptance criteria particularly as this interference is to be included in the labeling. This guidance will help ensure consistency and provide clearer guidance.
98.	VI-D	598-605	Revise as follows (delete stricken text and add text in underline): "As new drugs are developed or new interfering substances are identified, FDA will update the list of interferences and notify industry. ~~you should evaluate them for potential interference with your device. For example, if a new drug intended to treat cardiac complications in diabetic patients is approved, you should conduct a robust evaluation to determine whether the new drug interferes with~~	While we support clarity and robustness for testing interfering substances, FDA must provide consistent requirements across industry. Today, FDA publishes a list of interfering substances to notify industry so that manufacturers can conduct appropriate testing and revise labeling if necessary. This list creates a uniform standard and notification mechanism that is an important safety mechanism. Eliminating this critical mechanism and shifting the burden to manufacturers to self-identify interfering substances

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			~~your device. You should report to FDA if significant new interferences are observed with any cleared glucose monitoring device that is on the market You should also evaluate new drugs/potential interferents when new or significantly modified technology is introduced.~~"	does not best support the public health. This guidance is also needed to ensure consistency and provide clearer guidance. Also should remove references to reporting to FDA in lines 602-605. This is a postmarket requirement and is currently being captured and reported to the Agency, through different processes.
99.	VI-D	608	"… you should provide raw data…."	Requiring line-item data for analytical performance is unnecessary. Summary data should be sufficient.
100.	VI-D-1	614-615, Table 4	Modify the first column heading to the following: "Mean Glucose Value (Reference)".	In Table 4, the first column heading is stated as "Mean Glucose Value (YSI)." This suggests that the YSI will be the reference for all blood glucose systems, which is not true. This table should be updated to provide a general statement (such as "reference") to account for systems that do not use the YSI as the reference.
101.	VI-D	625	"… a list of all data…"	Requiring listing of all data collected is unnecessary and overly burdensome. This provision should be revised and appropriately clarified.
102.	VI-D	636	"…recommend (testing) 20-60% hematocrit…"	FDA efforts to provide protocol/study specifications that could lead to a clearance is helpful. However, 20-60% hematocrit is not as reasonable as that described later in the same paragraph (30-55%).
103.	VI, D	639	Because lay users generally have no way to adequately determine their hematocrit status, devices that cannot adequately measure glucose across the range of 30-55% hematocrit (which includes the greatest proportion of users) cannot be safely used to monitor blood glucose and may not be determined to be substantially equivalent.	We concur and support this concept.
104.	VI-D	645-656	Reconsider and reduce the number of samples. Specifically, recommend 5 hematocrit levels split over the claimed range to read as follows (delete	FDA has provided a generally reasonable protocol for the hematocrit study, including allowing contrived samples; however, the number of samples and testing at 5% intervals from 20 -60% Hct is excessive and

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			stricken text and add text in underline): "Hematocrit levels tested should span the claimed range in 5 evenly distributed ~~%~~ intervals. ~~For example, if your claimed hematocrit range is from 20-60%, you should test samples at 20, 25, 30, 35, 40, 45, 50, 55, and 60 % hematocrit.~~ The samples should also span the claimed measuring range for blood glucose. Samples should include 5 different blood glucose concentrations ~~evenly spread and~~ targeted to the following ranges: ~~30 – 50,~~ 51 – 110, 111 – 150, 151 – 250, and 251 – 400 mg/dL. If a system's measuring range extends below 50 mg/dL, then an additional sample having a glucose concentration of 30-50 mg/dL should be tested."	should be revised. The proposed size of this study (45 samples, N=1350) is overly burdensome, particularly for a system in which hematocrit sensitivity is negligible and the 20-60% claim is easily demonstrated. Data in the middle hematocrit range already is well represented in the method comparison study. In addition, 5% is close to the error of hematocrit measurement resolution. Also, it is unlikely that the hematocrit response is so non-linear that it would require 5% intervals. Also if a system does not have a claimed measuring range below 50 mg/dL, then it should not be required to test in the 30-50 mg/dL glucose concentration interval.
105.	VI-D-2	661-663	Revise so that it reads: "Each sample should be tested on the reference method in duplicate. If the duplicate reference results differ by less than ±4%, then the average reference value should be calculated and used in the evaluation. If the duplicate reference results differ by greater than ±4%, then the associated sample should not be included in the evaluation."	In its current state, the guidance document recommends averaging the results of four different reference measurements. If each of these four reference measurements is substantially different, then the ultimate reference value includes significant variability, the true glucose concentration of the sample is not well known, and "greater confidence in the true glucose concentration of the sample" is not had. Therefore, a true assessment of the accuracy of the BGM system cannot be determined. In order to conduct an assessment of BGM system accuracy, samples in which the true glucose concentration is not accurately known should be excluded from the study. Also clarify "reference method". "[R]eference method" previously described as laboratory method (line 263), which is typically a large analyzer that uses venous, not capillary blood. Does FDA mean "predicate"? Please clarify this term in this section and other references in the guidance.
106.	VI-D-2	665-670 and 678-693	Revise as follows (delete stricken text and add text in underline):	There appears to be a contradiction in the data analysis descriptions, and it is not clear whether the acceptance criteria apply to the pooled data or on a

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			"There appears to be a contradiction in the document in that lines 665-670 recommend pooling the lots together to determine acceptability while lines 678-693 recommend evaluating each lot separately. Recommend that the data analysis only describes the presentation of pooled data and not by lot."	lot-by-lot basis. Because the guidance document recommends a sample size of 10 replicates per lot per level, this sample size will likely not be robust enough to truly determine if the bias is less than the 8% criteria. Additionally, confidence intervals around the mean bias will be very wide when the n is only equal to 10. Recommend requiring a pooled estimate that is based on n=30 to provide a robust estimate of the true performance of the system. Any lot-to-lot differences will be reflected in the presented SD and confidence intervals.
107.	VI-D-2	665-676. 674-676, and 684-685	Revise as follows (delete stricken text and add text in underline): "~~A minimum of 3 test strip lots should be used to evaluate interference from hematocrit. Each test sample should be tested on your new SMBG device in replicates of 30 (10 replicates per lot of test strips, for a total of 30 replicates per sample). Each replicate should be compared to the average reference value for the sample and a~~ The mean bias and % bias should be calculated from the average reference value for the samples, and the difference between the bias of the samples and the bias of the samples with nominal hematocrit (42%) should be calculated to estimate the hematocrit effect. ~~The percent bias for each replicate should be used to produce an average percent bias for the sample (with 95% confidence intervals).~~ Because hematocrit interference is only one of the variables that will contribute to the overall analytical error of the system, it is important that it represent only a portion of the allowable error for the system. For this reason, the mean bias observed in this study should be less than or equal to ~~8%~~10% above 80 mg/dL and less than or equal to 8 mg/dL below 80 mg/dL.~~on average, and no~~	The current bias calculation description (comparing the SMBG results directly to the reference system value) is inconsistent with the data analysis recommendations provided in the CLSI EP7-A2 guideline for interfering substance evaluation and the ISO 15197:2013 standard. These documents highlight the importance of comparing test results to those of a control sample that contains a nominal amount of or does not contain the interfering substance of interest. It is important to evaluate hematocrit and interfering substances using such a methodology to eliminate any systematic bias that might be present that is unrelated to the substance under investigation. This bias is eliminated when a control or nominal sample is used in the evaluation. Section 8.5 of CLSI EP7-A2 provides further details describing the importance of using a control group in interference calculations. Additionally, the mean bias should be used and compared with nominal hematocrit to be consistent with the data analysis recommendations provided in the CLSI EP7-A2 Guideline for Interfering Substance Evaluation and the ISO 15197:2013 standard. The purpose of a hematocrit study (or any bench study, for that matter) is to evaluate the effect of particular substance/condition. Such effects are most effectively measured by evaluating the mean response, as

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			~~individual value should be greater than 15% of the reference method.~~ Additionally, to ensure that hematocrit does not adversely influence the precision of the measurement, the SD or %CV should be calculated for each tested sample and should be no greater than the precision specification for the system."	described in CLSI EP7-A2. The recommended criteria of ±8 mg/dL below 80 mg/dL and ±10% above 80 mg/dL were chosen because these allowable biases only consume a portion of the total error recommended for the user performance evaluation (±12 mg/dL below 80 mg/dL and ±15% above 80 mg/dL). By using these bias limits, only a portion of the entire allowable error budget could potentially be consumed by hematocrit interference. At low glucose levels, such as 50 mg/dL, a mean bias requirement of ±8% is overly stringent, as it only allows for an error of ±4 mg/dL. As described previously, such a stringent requirement approaches the performance expectations of reference analyzers. The guidance currently states that 100% of individual results must be within ±15%, and this is based on collecting n=10 per glucose concentration/hematocrit level with each of 3 lots. This expectation is inconsistent with the first level of the FDA-recommended acceptance criteria, that the mean bias must be less than 8% on average. For example, if 10 strips tested from one lot result in an average bias of 8% for a particular glucose/hematocrit combination and the precision associated with this measurement is a %CV of 3% (which is a fairly typical precision for handheld blood glucose meters), then the probability that all ten individual results fall within ±15% of the reference is only 91%. Of course, this percentage decreases as the %CV increases and increases as the %CV decreases but, even at a %CV of 2.5% (which is very good for a handheld bG system), the probability of all results falling within ±15% of the reference is only 97%. These probabilities decrease even further with the testing of additional lots that presumably would have comparable levels of bias and precision. Therefore, from a purely statistical

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				perspective, even a system that meets the average bias requirement and has an appropriate level of precision can fail to have 100% of the individual results within ±15%. An alternative relating to precision is proposed. It should be noted that the purpose of this hematocrit study is to evaluate the effect of hematocrit. This is most accurately characterized by evaluating mean bias and not the biases of individual data points that might fall at the edges of the bias distribution. However, it is important to ensure that the precision of the system does not erode at extreme hematocrit levels, as such an erosion in precision may lead to significantly more outliers. Therefore, it is proposed that the precision with each sample be evaluated and compared to the system precision specification. If the precision specification is not exceeded, then the system is within specification and has demonstrated a suitable precision at a particular hematocrit level. Such a requirement ensures that there is not significant erosion in precision performance that could lead to an increase in outliers at extreme hematocrit levels.
108.	VI-D-2	688-689	Update the x-axis of Figure 2 consistent with the Hct data collection.	In order to be consistent with earlier comments on hematocrit data, it is recommended that the hematocrit values described in Figure 2 be updated accordingly.
109.	VI-E	695	Revise as follows (delete stricken text and add text in underline) to add the following at the beginning of this section: "E. ~~Flex Studies~~ Stress Boundary Studies This section would include reliability (mechanical vibration, shock, EMC, etc.) stability (including open use-life stability), short sample detection, intermittent sampling, temperature and humidity and altitude.	The term "flex studies" is not widely used across the medical device industry.

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			Product misuse/abuse tests This section would include sample perturbation, testing with used test strips, and extended open vial. This section is for information only and should be used to determine labeling limitations."	
110.	VI-E-1	699-701	It is recommended that this statement be updated to the following: "You should therefore demonstrate that your SMBG device design is robust (e.g., insensitive to environmental and usage variation) and that all known sources of error have been assessed through a detailed risk assessment."	Current wording states that "all known sources of error are effectively controlled." It is not possible to control all sources of error, particularly those that are related to off-label use.
111.	VI-E	730	Remove lines 730-738.	This paragraph is a general statement and more appropriate for Life-cycle Management.
112.	VI-E	760, General	FDA should accept single certification for testing performed by outside certification agency rather than requiring data submission or specific testing at the manufacturer's facility. Also, summary table of parameter and pass/fail should be sufficient as opposed to raw data.	This is consistent with certifications currently available and used by industry. Certifications are typically referenced in the submission.
113.	VI-E	761	Mechanical Vibration Testing - The requirements in IEC 60068-2-64 apply.	A recognized standard should be cited in order to provide a consistent approach across all submissions.
114.	VI-E	762	Shock Testing - The requirements in IEC 61010-1 apply.	A recognized standard should be cited in order to provide a consistent approach across all submissions.
115.	VI-E	763	Electromagnetic compatibility (EMC) Testing - The requirements in IEC61326-1 and IEC 61326-2-6 apply.	A recognized standard should be cited in order to provide a consistent approach across all submissions.
116.	VI-E	764	Electrostatic Discharge/Electromagnetic Interference Testing - The requirements in IEC61326-1 and IEC 61326-2-6 apply.	A recognized standard should be cited in order to provide a consistent approach across all submissions.
117.	VI-E	767	"…a detailed description of the following attributes should be included…"	Should be sufficient if the manufacturer is claiming compliance to standard and/or outside certification

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				agency has passed the device. Study goals, protocol, etc. are standardized in ISO/IEC standards. A brief summary (not detailed) *may* be provided.
118.	VI-E	772-773	Recommend removing lines 772 and 773 that state "Methods used to apply samples to test strips" and "Description of sample type and any anticoagulants used."	The guidance currently indicates that the methods used to apply samples to test strips, the sample type, and any anticoagulants used should be included with each flex study description. This implies that each flex study should involve the testing of blood samples. However, some of the flex studies that are recommended in the guidance commonly do not use blood samples. For example, often control solutions or check strips are used to evaluate the effects of mechanical vibration testing or EMC testing. Check strips in particular enable the effects from such stresses to be readily isolated to the meter and eliminate the strip variability that accompanies blood testing and is not the focus of the evaluation. The use of check strips and control solutions for such evaluations is consistent with the ISO 15197 standard and has been accepted by the FDA in previous 510(k) submissions. As such, it is recommended that the wording in this section be modified so as not to imply that blood samples must be used in every flex study.
119.	VI-E	785	"… submit study protocol… and conclusions…"	New submission requirement (to submit the actual protocol rather than summary). "Conclusions" may only be intermediate dating, as stability studies may proceed for up to several years.
120.	VI-E-1	788-790	Request the FDA to clarify how real-time and accelerated aging studies are acceptable (i.e., under what circumstances).	Seeking clarification to understand how accelerated aging studies may be used in 510(k) submissions for test strip stability testing. Also, please clarify that manufacturers will continue to be able to submit with interim stability data and update through their quality system.
121.	VI-D-E-1	790-791	Clarify the following statement:	The guidance is not clear on what the accuracy study requirements are. A spiked venous study has been demonstrated to be sufficient to establish the accuracy

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			"You should perform both precision and accuracy evaluations at each identified time point as described below."	of the system at different test times. This section requires clarification since this test determines the impact of storing strips and its performance at different time points, a bias from the control condition at different test points is sufficient to demonstrate the stability.
122.	VI-E	796-806	Delete lines 796-806.	To the extent that day-to-day variability with controls occurs, this is not a factor that is related to stability. Assessing day-to-day variability in a stability study only obscures any true effect of stability on repeatability.
123.	VI-E	809-812	Recommend deleting "patient" from this statement. Revised wording should read as follows: "The study should be performed using whole blood samples that span the SMBG device's stated measuring range."	The current statement implies that samples should be collected from diabetic patients; however, since the described procedure allows the samples to be spiked or allowed to undergo glycolysis to achieve the desired concentrations, this can be done with venous blood from any person.
124.	VI-E-2	816-846	Delete lines 816-846. Alternatively, replace with the following protocol: "Temperature and Humidity Study Design You should evaluate the effect of environmental temperature and humidity on your system to assess whether the device can be used safely in the intended use population across your claimed temperature and humidity ranges. If your meter does not provide an automatic temperature lockout to prevent the system from being used outside the claimed temperature range, you should perform additional testing outside the claimed range to assess the risk of off-label use. You should evaluate temperature and humidity sensitivity by testing the system with blood	The section requires significant revision as it, as drafted, inappropriately conflates at least five distinct risk factors: 1) temperature and humidity, which are environmental conditions at the time of testing that can affect the rate of the chemical reaction; 2) normal open vial use, which is an aspect of stability and relates to the ability of the packaging to provide protection from moisture exposure during normal openings that can cause degradation of the strip chemistry due to spontaneous redox reactions; 3) short-term storage at extreme temperatures such as might happen during shipping; 4) extended open vial, which represents off-label abuse in which the design and labeling controls for product protection are circumvented; and 5) sensitivity to temperature equilibration, which is the risk of erroneous glucose readings due to inappropriate temperature compensation caused by incorrect temperature

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			samples in a validated environmental test chamber or glove box capable of maintaining temperature and humidity independently across the claimed ranges for these environmental factors. Blood samples may be adjusted (by spiking with concentrated glucose stock solution or allowing to glycolyze) to obtain four glucose concentrations targeted to the following ranges: 51 – 110, 111 – 150, 151 – 250, and 251 – 400 mg/dL. Each sample should be tested on the laboratory comparison method before and after meter testing in order to control for glycolysis that may occur during testing (particularly at high temperatures). Testing should be performed at naturally occurring temperature and humidity conditions that probe the limits of the claimed ranges. If a manufacturer chooses, it may test at combinations of the temperature and humidity range limits that never actually occur simultaneously in nature (e.g., 40°C/90% r.h.) Testing should also be performed at a normal temperature and humidity condition (23°C ±3°C, 45%RH ±10% RH). A minimum of three test strip lots should be used to evaluate temperature and humidity performance. Each test sample should be tested on your SMBG device in replicates of 30 (10 replicates per lot of test strips, for a total of 30 replicates per sample). Data Analysis Calculate the mean and standard deviation for each environmental condition, glucose level, and strip lot. If the same sample can be used for the study, the bias can be calculated from the nominal condition. If different samples are used, then calculate the bias and percent bias of each lot mean from the laboratory comparison method. Calculate the difference between the bias of each	measurement. The first three risk factors (environmental conditions, moisture exposure during normal use, and shipping simulation) represent aspects of testing which are within the intended use of the product but are independent and unrelated factors that should be evaluated separately. The proposed protocol for this section specifically addresses the effect of environmental conditions; open-use and shipping simulation are aspects of stability that should be addressed in the Stability section. The final two risk factors (extended open vial and temperature equilibration) represent testing scenarios which are outside of the intended use. Testing protocols for these factors should be designed by the manufacturer to provide sufficient data for determining the risk that is represented by these off-label uses, and the rationale for this testing can be provided to the FDA. While it is not possible for systems to maintain the same level of performance in these off-label scenarios, the outcome of such studies provide the basis for an assessment of risk and proposed design controls, which should be incorporated into the risk assessment provided with each 510(k) submission. The proposed temperature/humidity protocol compares the results at extreme conditions to results obtained at a normal environmental condition. This follows the principle used in CLSI EP7-A2 guideline for interfering substance evaluation and the ISO 15197:2013 standard. It is important to evaluate environmental effects using such a methodology to eliminate any systematic bias that might be present that is unrelated to the condition under investigation. The process of preparing artificial venous blood samples for laboratory evaluations can sometimes introduce bias in systems that are optimized for testing with fingerstick blood (e.g., oxygen effects on systems using glucose oxidase enzyme). This bias is

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			lot at each extreme condition and the bias of that lot at the normal condition. The average bias should then be calculated for each glucose concentration and environmental condition to determine the range of environmental effects. Acceptance Criterion The average bias observed in this study should be less than 8 mg/dL for glucose concentrations <80 mg/dL and less than 10% for glucose concentrations ≥80 mg/dL.	eliminated when a control or nominal condition is used in the evaluation.
125.	VI-D-E-2	846-848	Remove lines 846-848.	A requirement to include temperature and/or humidity detectors is excessive in terms of efforts and resources for the current technology available. It is also difficult to control since many OTC products are distributed by 3rd party (distributor) and will also lead to increase costs for end user. FDA should also avoid terminology such as "encourage." If FDA is requesting this information, then this should be clear.
126.	VI-E-3	850-860	Remove lines 850-860.	Verification testing should be based on an assessment of risk. This is a legacy issue and no longer a concern for modern test strips. Variations in atmospheric pressure have never been associated with either observed or theoretical SMBG error.
127.	VI-E-2 and 3	General	Specify the glucose concentrations for testing in studies VI-E-2 and 3. Recommend that these concentrations are aligned with those present for the other studies described in this section (50-65 mg/dL, 100-120 mg/dL, and 200-250 mg/dL).	Sections VI-E-4, 5, and 6 are very specific in that they recommend that glucose concentrations of 50-65 mg/dL, 100-120 mg/dL, and 200-250 mg/dL need to be tested. Sections VI-E-2 and 3 do not specify the glucose concentrations that should be tested.
128.	VI-E	862	Short samples detection: especially difficult to test in the very low sample size instruments	The impact of short sampling on sample volume, especially for strips using <1uL would present a major technical challenge.

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129.	VI-E-4	875-876	Remove the following sentence: "Results obtained from the candidate device should be compared to the reference method."	As with the interference and hematocrit studies, it is important that, for laboratory studies involving the assessment of a particular effect (whether it be interfering substances, hematocrit, sample volume, temperature, etc.), a control be used to isolate the influence under investigation. In all such studies, bias should be calculated relative to a control to eliminate any potential sources of variability that are unrelated to the analyte/condition of interest. Bias should not be calculated relative to a reference analyzer, as this introduces additional error that prevents the true effect under investigation from being evaluated.
130.	VI-E	881-895	Remove sample perturbation study.	This encompasses a concerning new submission requirement. Manufacturers should not be required to test off-label uses and abuses. The impact of perturbation on sample volume, especially for strips using <1uL, would present a major technical challenge. It is impossible to define the nature of the sample perturbation parameters (e.g., force, duration) in this flicking study. The described events ("flicking test strip") are also not typically seen, as most strips are self-contained and are in the meter at the time the sample is added. These provisions reflect excessive, non-value added requirements.
131.	VI-E	897	Consider revising and/or removing this section.	We note that the described event (short sampling) is unlikely with newer meters using very small sample volumes. Testing is excessive (all of the levels) given the low possibility of occurrence.
132.	VI-E	906-910	Revise so that it reads: "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	This test cannot be reconciled with the requirement that SMBG devices detect a short sample and not provide a result (lines 864-866). Such a device will never start reading a short sample, so applying a second sample once the first sample starts reading is impossible.

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			period of time. For systems that allow a second sample of blood, several delay times throughout the claimed period of second application should be tested."	
133.	VI-F	923	Revise as follows (delete stricken text) : "~~Calibration and External~~ Control Materials"	Unclear what "external" refers to. Do some systems have an internal control solution? Explaining "how the system compensates for differences between strip lots or strip types" does not relate to controls and should be included in a separate section.

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134.	VI-F	925-927	Revise the statement to read as follows: "Two levels of control materials should be available for all systems."	While we agree with the Agency that use of control materials is beneficial, there are numerous challenges with providing two levels of control with each vial of strips. Controlling the expiration of controls and test strips in one package is extremely difficult to manage from a logistical perspective. Additionally, we are concerned that this may discourage routine blood glucose testing by patients who do not want to encumber the additional expense of two bottles of controls with every strip vial. In this customer cost-sensitive environment, it is unlikely that a consumer will want to use up one to two of his/her strips on controls testing. Of primary importance, these controls are already available today. Customers can obtain controls at any time through retail purchases or through phone hotline requests. It is recommended that this method of providing customers with controls still be employed. We also note this recommendation seems outside the scope of this document, which states "[t]his draft guidance document describes studies and criteria that FDA recommends be used when submitting premarket notifications (510(k)s)" for SMBGs. Finally, we are concerned about the impact this requirement would have on the environment since this would increase the amount of waste generated at a time of worldwide efforts to reduce waste. For example, the draft recommendation is in conflict with Article 4 of the EU Waste Framework Directive (2008/98/EC).
135.	VI-F	947-949	Revise as follows (delete stricken text and add text in underline) : "~~You should describe how T~~the candidate system should be designed in such a way that either it recognizes and distinguishes ~~calibration or~~ control	In its current form, the statement implies that all BGM systems are able to distinguish control solutions from patient samples. While we note that is can be a useful safeguard, some systems are unable to automatically distinguish control and blood samples. This should be

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			materials from patient samples ~~as well as explain how the system compensates for differences between strip lots or strip types~~ automatically or allows the user to manually select the sample type on the device. ~~Where the system automatically recognizes control materials from patient samples, then it should correctly identify the sample type at least 99 % of the time."~~	clarified. As not all devices are capable of recognizing different sample types, allowance should be made for systems where user manually selects control solution.
136.	VII	951-987	Remove this section.	We note that lot release criteria is typically part of a PMA and BLA review, not 510(k) review. This is a postmarket, not premarket, function. Lot release testing of finished products is conducted under good manufacturing practices to assure manufacturing specifications have been met. Also, the requirement to test over 10 days is excessive and will require performance of lot release tests of hundreds of lots on any given day that will create practical issues, such as storage of large number of strip lots at the facility and supply of blood for the test lending to practical challenges. There is also no evidence that the current lot release process validated by manufacturers is inadequate nor that the proposed method would improve the detection of poor performing lots to justify the magnitude of the proposed testing. Statistically justified sample size and test duration would be adequate to detect any of the failures this method is designed to address.
137.	IX	1012-1265 General	Clarify exact labeling that is referenced throughout this section.	Given that there are many different forms of labeling (package insert, meter carton, strip vial label, etc.), it would be helpful to clarify the exact labeling that is referred to in each section (rather than using the generic "label" and "labeling" terms).
138.	IX	1012 - 1265 General	Provide information on the suitability and acceptability of electronic labeling.	It would be very helpful if the FDA could share their views and requirements relating to electronic labeling in this guidance document.

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139.	IX	1020	Revise as follows (delete stricken text and add text in underline): ~~"Symbols should not be used in the labeling of OTC devices.~~ Any symbols used must be defined in the labeling."	This is overly restrictive. For example, symbols may appear on LCD screen. Also, symbols are standard labeling items worldwide. As long as they are adequately described in labeling they should be acceptable. They also allow conveyance of information in small spaces and potentially improve messaging to non-English speaking patients.
140.	IX	1047-1050	Revise as follows (delete stricken text and add text in underline): "~~The various test system components should have the same name (ABC blood glucose test system, ABC blood glucose meter, ABC blood glucose test strips, etc.) to aid in identification of system components.~~ Various test system components should be named in such a way that they are recognized as belonging to the same overall system."	Per earlier comment, we agree with FDA's intent. However, there needs to be allowance for multiple meter types using the same test strip. Therefore, it is not possible for all meters to have the identical brand name. A common root name would be feasible.
141.	IX	1051	Specify the "label and labeling" that is being referenced here is the test strip package insert.	For some labels (such as the test strip vial label), it is not possible to fit the intended use on the label. The label and labeling referenced here should be clarified.
142.	IX	1055-1059	Recommend that the FDA provide an alternative intended use example or change the reading grade level required for over-the-counter BGM systems. An example of revised language might be (delete stricken text and add text in underline): "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 their ~~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."	The Flesch-Kincaid Reading Grade Level associated with this intended use example is 12.8. This contradicts the reading grade requirement of an 8th grade level (stated in line 390).

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143.	IX	1062-1063	Revise as follows (add text in underline): "You should include the following warning *prominently* on the meter outer box labeling and package insert."	It is indicated that the warnings should be placed on the "outer box labeling." It is assumed that this is the meter outer box labeling, as the vial outer box labeling is too small to contain such information. This should be clarified.
144.	IX	1065-1072	Recommend that the FDA provide an alternative wording for the warning or change the reading grade level required for over-the-counter BGM systems.	The Flesch-Kincaid Reading Grade Level associated with this warning is 20.1. This exceeds the reading grade requirement of an 8th grade level.
145.	IX	1074-1075	Revise as follows (add text in underline): "Labeling, such as the meter instruction manual or reagent insert, must include the chemical, physical, or biological principles of the procedure…"	Clarification is helpful in reference to labeling.
146.	IX	1080-1082	Request clarity as to which label the FDA is referring.	It is unclear as to which label the FDA is referring to in this statement.
147.	IX	1084	Revise as follows (add text in underline): "Instructions should include a statement to users on the importance of thoroughly washing the skin with soap and water and drying before taking a sample…"	We would appreciate consistent guidance regarding washing with soap and water.
148.	IX	1091	"…numbering rather than bullets should be used…"	Is there evidence that numbering is more effective than bullets?
149.	IX	1097	Revise as follows (add text in underline): "You should include testing conditions that may cause clinically significant errors (due to bias or imprecision) with your device (e.g., specific drugs, oxygen therapy, or peritoneal dialysis therapy ~~high altitude~~)."	Altitude sensitivity is no longer a concern for modern SMBG systems, so using altitude as an example is not appropriate. A better example is provided.

Comment Number	Section	Line No	Change	Comment/Rationale
150.	IX	1098	Revise as follows (delete stricken text and add text in underline): "…indicate the most extreme conditions at which device ~~should be used~~ has been tested…"	This may approximate the wide range of actual use of the device, however, the pass/fail criteria for each condition may be difficult to determine.
151.	IX	1104	Revise as follows (delete stricken text and add text in underline): "All glucose values measured below 50 mg/dL will provide ~~the following error code: "Less than 50"~~ an appropriate message indicating the results are below the meter range."	Not all meters have the capability to display this specific text. Phrases such as "LO" are common in this instance.
152.	IX	1112-1116	Revise as follows (delete stricken text and add text in underline): ~~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.~~	Unless the HCP and patient are aware of issues around comparison testing, for example, both tests must be from the same sample, completed within a certain time frame. Comparison testing to a different SMBG system is not recommended. Technique and methods are proven by testing a control solution and obtaining results with the assigned control ranges.

<table>
<tr><th>Comment Number</th><th>Section</th><th>Line No</th><th>Change</th><th>Comment/Rationale</th></tr>
<tr><td>153.</td><td>IX</td><td>1125-1127</td><td>Delete “[s]ponsors 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.” Replace with a specification table in the labeling that clearly outlines the specifications of the device that were tested in the performance studies should be sufficient.
For example:
<table>
<tr><th>Characteristics</th><th>Device has been tested</th></tr>
<tr><td>Altitude</td><td>10,000 ft</td></tr>
<tr><td>Cleaning and disinfection</td><td>522 cleaning and 522 disinfection cycles</td></tr>
<tr><td>Hematocrit Range</td><td>15-65%</td></tr>
</table></td><td>Describing all performance studies and summarizing the results on the package insert will be unrealistic for the lay user to comprehend the data.</td></tr>
<tr><td>154.</td><td>IX</td><td>1125</td><td>Revise as follows (delete stricken text and add text in underline):

“Sponsors should briefly describe ~~all~~ the <u>accuracy and precision</u> studies and summarize results in the ~~package inserts~~ user guide.”</td><td>The word “all” is too broad.

The user guide is the appropriate place to show accuracy and precision data because multiple meters often use a single test strip, so including all of the different system accuracy data in the test strip labeling will be confusing to the customer.</td></tr>
</table>

Comment Number	Section	Line No	Change	Comment/Rationale
155.	IX	1130-1137	Remove or revise the requirement to provide accuracy information on the outer box labeling so that such information is readily and appropriately understood by a lay user for meeting of their needs.	In this section, it is stated that accuracy information should be located in a prominent place so that lay users can understand the performance of the device. However, will displaying the accuracy performance on the outer labeling in the manner suggested accomplish this task? For example, if a lay user compares two BGM systems and sees that one BGM system has 330/350 results within ±10% and another has 331/350 results within ±10%, the individual may not have the understanding that there is no statistically significant difference between this performance (i.e., superior performance).
156.	IX	1136-1137	Clarify this sentence.	It is assumed that the outer box labeling referenced in this sentence is the meter box labeling. This should be specified. We also note in some cases the vial box labeling may be too small to fit such information.
157.	IX	1142-1145	Revise as follows (delete stricken text and add text in underline): "In the ~~package insert for the test strips and the~~ user manual for the SMBG device, accuracy information should be prominently and logically placed ~~within the label~~. We recommend that this information be included in the section where the manual describes how a user will obtain a result. ~~In the test strip insert, this section should be large and centrally placed so that users understand the performance of the system using these test strips.~~ We recommend the following types of presentations to represent the results of your accuracy studies in the user manual and test strip inserts."	User performance in the meter user guide is appropriate. For test strip labeling, multiple meters often use a single test strip, so including all of the different system accuracy data in the test strip labeling will be confusing to the customer.
158.	IX	1146-1158 General	Recommend that the FDA provide an alternative example for the data presentation or change the reading grade level required for over-the-counter BGM systems."	The Flesch-Kincaid Reading Grade Level associated with the accuracy labeling example is 9.6. This exceeds the reading grade requirement of an 8th grade level.

Comment Number	Section	Line No	Change	Comment/Rationale
159.	IX	1145	Revise to follow ISO 15197 tables.	It should be represented in table consistent with ISO 15197. It should be noted that all assays, including laboratory methods have error, so the value is not really "true."
160.	IX	1148	Revise as follows (delete stricken text and add text in underline): "Accuracy information should also be included on the SMBG device ~~and test strip~~ outer box ~~labeling and test strip vials as well as in the package inserts~~ and user manual." .	We like the concept of simplifying the user accuracy data and displaying it on the meter outer box so customers are better informed when making a purchasing decision. Providing the data on the system carton addresses FDA's intent to display performance data where it allows the user to choose between SMBG systems. As previously referenced, it is not reasonably practical to include this data in a format legible to the user on these items due to space constraints. This is particularly pertinent where the same brand of test strips is intended for use with multiple meters.
161.	IX	1148	Accuracy data should be represented in table consistent with ISO 15197 in strip insert.	We note that there may not be, however, sufficient room on the test strip box. User guide may also not be possible if meter accepts 2 strips. For test strip labeling, multiple meters also often use a single test strip, so including all of the different system accuracy data in the test strip labeling will be confusing to the customer.
162.	IX	1169	Clarify the reference to "label and labeling."	It is not clear what is meant by "Label and labeling". For instance, there is not sufficient room on the reagent bottle label for all the warning statements included in the user guides.
163.	IX	1171	"…contact health care provider…"	This is useful and supported.
164.	IX	1175	Revise as follows (delete stricken text and add text in underline): You should clearly and prominently state the important warnings for this device in the front of the ~~label~~ user guide, in a section containing **Important Safety Instructions.**	The "label" reference is not clear.

Comment Number	Section	Line No	Change	Comment/Rationale
165.	IX	1183-1186	Recommend that the FDA provide an alternative wording for the warning or change the reading grade level required for over-the-counter BGM systems.	Generally supportive of the concepts, but the Flesch-Kincaid Reading Grade Level associated with this warning is 9.7. This exceeds the reading grade requirement of an 8th grade level.
166.	IX	1211	"…difference between "cleaning" and "disinfection"…	Similar to earlier comment, can these (C&D) be the same, especially if the same agent is used?
167.	IX	1225	Revise as follows (delete stricken text and add text in underline): "A contact telephone number <u>(or page reference)</u> 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."	The contact information can be provided prominently in the back of the book and referred to by multiple sections of the meter user guide. In this way, there is consistency so the customer always knows where to look for information instead of searching for it if they are not following the UG page-by-page.
168.	IX	1247-1249	Recommend changing the statement to the following: "You should include the following limitations relating to AST testing in your package insert:…".	The current statement indicates that there is a possibility of success for BGM systems to provide accurate AST results when true glucose concentrations are changing rapidly. This is physiologically not possible. In other words, there is no glucose meter that will provide accurate AST results when glucose concentrations are changing rapidly. The statement should be updated so that users know that AST should not be conducted when glucose concentrations are changing rapidly.
169.	IX	1251-1253	Clarify this provision.	FDA recommends a study but does not describe how this study can be ethically performed. Finding a subject that is moving towards hypo/hyperglucemia and then repeatedly testing the subject (especially if leaving the subject untreated) raises ethical concerns.
170.	IX	1254-1262	Remove or clarify this provision.	This expansive list only excludes a sample taken in absolutely perfect conditions.

Comment Number	Section	Line No	Change	Comment/Rationale
171.	Appendix 1 Operator	1278	Remove the following: “Incorrect incorporation of results into overall treatment plan (professional use)”	This does not apply to the OTC SBGM systems.
172.	Appendix 1 Environ-mental	1278	Remove “hyperbaric conditions.”	Currently, hyperbaric conditions is associated with altitude in this section of the table. However, testing at altitude is actually testing a hypobaric (reduced pressure) condition. Hyperbaric testing represents testing at an increased pressure and is the opposite of testing at altitude.
173.	Appendix 1 Environ-mental	1278	Delete “Visible light; sunlight."	Since test strips are chemical reagents sensitive to light, the labeling already currently includes warnings to keep test strips in their original container to protect against light. A demonstration of the detrimental effects of light is unnecessary.
174.	Appendix 1 Environ-mental	1278	Environmental conditions – human factors	How do you simulate “distractions, stressful conditions…?
175.	Appendix 1 Clinical	1278	Interference from ~~other sugars~~ exogenous substances (e.g., maltose intravenous solutions or acetaminophen)	Better to align wording with ISO 15197 and wording used elsewhere in this guidance document.
176.	Appendix 2.	1327-1348	Remove requirements from Line # 1327-1348.	Under the New 510(k) Paradigm, a manufacturer can refer to 21 CFR 807.81(a)(3) and the FDA guidance document entitled, "Deciding When to Submit a 510(k) for a Change to an Existing Device" to decide if a device modification may be implemented without submission of a new 510(k). If a new 510(k) is needed for the modification and if the modification does not affect the intended use of the device or alter the fundamental scientific technology of the device, then summary information that results from the design control process can serve as the basis for clearing the Special 510(k) application.