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Re: Docket No. FDA-2013-D-1145; Draft Guidance for Industry and FDA Staff on Blood Glucose Monitoring Test Systems for Prescription Point-of-Care Use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and Drug Administration ("FDA" or "Agency") "Blood Glucose Monitoring Test Systems for Prescription Point-of-Care Use; Draft Guidance for Industry and FDA Staff."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 the opportunity to comment on FDA's Blood Glucose Monitoring Test Systems (BGMS) for Prescription Point-of-Care Use (or "POC" guidance). BGMS play a crucial role in managing diabetes in healthcare and assisted-use environments at the point-of-care ("professional" environments), as well as in patients' homes, making their appropriate regulation of the utmost importance to the public health. While our comments are focused on this POC guidance, please note that AdvaMedDx has also provided extensive comments on the FDA "Draft Guidance for Industry and FDA Administration Staff on Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use (or "OTC" guidance).

We appreciate the opportunity to provide comments on this FDA draft guidance outlining new proposed expectations for POC BGM devices. Even though AdvaMedDx is providing specific comments on the draft guidances, we continue to have concerns about the process used to develop the standards now proposed by the Agency given the draft guidances' substantive nature, as well as their scope and potential impact. AdvaMedDx respectfully reserves for future comment and engagement its feedback on the Agency's

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approach to identifying these standards in proposed guidance documents. Meaningful review and consideration of industry comments and appropriate stakeholder engagement in this process will be critically important to assure a thorough and fair evaluation and address of issues. The impact of this particular guidance, if implemented as drafted, will likely have far reaching consequences in access and availability to blood glucose meters to healthcare professionals and the patients that they serve.

AdvaMedDx member companies have worked to support the goal of improving meter performance and supported recent updates to worldwide standards ISO 15197 and CLSI POCT 12-A3 (or "POCT 12"). Yet, this guidance– like its counterpart OTC guidance– disregards worldwide standards already in place and implemented worldwide. We note that the CLSI POCT 12 sets out the latest rigorous guidelines for hospitals and long-term facilities, including considerations of overall accuracy and tight glycemic control. FDA can and should work to better harmonize with worldwide regulatory requirements rather than impose new requirements well in excess of current stringent standards for hospital use implemented worldwide.

Importantly, any proposed changes should be scientifically grounded and must hinge on risk-based assessment with ultimate clinical importance and impact on decision making. Our comments are provided in that context with focus importantly on the way in which the device is used and clinical impact.

As noted in the guidances, FDA has often cleared the same BGMS device for the same intended use (e.g., monitoring glucose to aid in managing diabetes) in both home and professional environments. Further, clearance for professional use could be supported by studies with laypersons. This system led to efficient clearance of 510(k)s, and provided widespread access to BGMS devices to benefit patients both inside and outside the home.

With its new draft guidances, FDA proposes to change this approach by establishing markedly different 510(k) requirements for BGMS depending on their *environment* of use – a home setting versus a professional setting.[1] For each environment there would be different accuracy requirements and study requirements. In addition, home use BGMS would be required to carry a statement that the device is intended solely for use by an individual patient and <u>not</u> for use in any professional setting, effectively nullifying the automatic "CLIA Waiver" that home use tests receive upon clearance. The result is to strongly discourage the use of BGMS across a broad gamut of point-of-care settings.

We agree that pathogen exposure concerns should be considered during BGMS 510(k) reviews. It should be clear to all healthcare professionals that they must take necessary measures to prevent exposure to bloodborne pathogens; however, the proposed solution –

[1] *See* POC Guidance, 3 (Suggesting that the root cause of FDA's concerns is that"[professional healthcare] settings are often fundamentally *different than lay users using these devices at home*.")

restricting home use BGMS *solely* to layperson use in their home – goes too far.

In addition, new accuracy and study requirements and "environment of use" restrictions in labeling, create significant and unnecessary burdens that will discourage innovation, and limit access to valuable testing that can inform diabetes management. In fact, we have already seen negative consequences from the draft guidance in New York State, where the State Department of Health is now prohibiting the use of BGMS in many healthcare settings until the new standards described in the draft guidance are met.[2] As a result, fewer patients will benefit from BGMS testing, which runs contrary to the public health.

There are, however, ways to maintain access to tests and promote innovation while addressing the safety concern that FDA has raised and staying true to the law. To that end, over the next several pages we will identify where the new guidances are misaligned with the two statutes that govern BGMS – the Food, Drug, and Cosmetic Act ("FDCA") and the Clinical Laboratory Improvement Amendments of 1988 ("CLIA") – and propose changes that we believe will further the public health and bring the guidance recommendations in line with these statutes. We also review FDA's obligations to weigh all the factors associated with the significant policy changes it has proposed, and also offer specific and critical technical comments on the guidance.

510(k) Requirements under the FDCA

The 510(k) clearance of a BGMS is governed by the FDCA. When FDA clears a medical device for OTC use, it reflects the Agency's decision that the medical device is labeled with "adequate directions for use," i.e., "directions under which the layman can use a device safely and for the purposes for which it is intended" without physician oversight.[3] Relatedly, a "home use" clearance (which encompasses the use of OTC and prescription devices used by patients) reflects the Agency's determination that a person does not need special skills, expertise, or a professional environment to perform the test effectively and safely for its intended use.[4] However, "home use" does not mean that the use of the product is *actually* restricted to the home. In fact, FDA has generally defined home use devices to include "devices intended for use *in both* professional healthcare facilities and homes."[5] Consistent with that definition, FDA has historically cleared the same BGMS devices for use in both home and professional settings. Thus, a home use clearance

[2] Letter from Stephanie H. Shulman, M.P.H., M.S., M.T. (ASCP), Director, Clinical Laboratory Evaluation Program, New York State Dep't of Health (January 13, 2014).

[3] *See* 21 CFR §§ 801.4, 801.100.

[4] *See e.g.*, FDCA §§ 513, 514; *Design Considerations for Devices Intended for Home Use: Draft Guidance for Industry and Food and Drug Administration Staff* (Dec. 12, 2012), *available at* http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm331675.htm (hereinafter Home Use Guidance).

[5] Home Use Guidance, *at* 5.

(whether as an over-the-counter device or as a prescription home use device) has meant that the device could be used anywhere.

Through its draft guidances, FDA would change this approach. First, it would require different accuracies for home and professional settings even if the intended use of the product (e.g., monitoring glucose to manage diabetes) in both environments was identical.[6] Second, it would prohibit extrapolation of test performance from studies in home use populations (i.e., layperson studies) to test performance in professional settings. We have concerns about both of these changes –

- With regard to accuracy, the assumption that *all* testing in healthcare and assisted use environments requires greater accuracy than home use testing is too broad. The guidance does not delineate between any potential point-of-care uses. There is no disagreement that there are situations where greater accuracy is required, such as where tight glycemic control is otherwise required. Where a manufacturer intends its product for one of these intended uses, FDA must require better 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, there is no reason to prohibit use of the product in professional environments for the identical use.[7] While we support the FDA's desire to have improved performance in the hospital (i.e., tight glycemic control), the guidance has essentially lumped all point-of-care users into one group (e.g., clinics, doctor's office, health fairs, wellness checks, and pharmacies, along with ICU and other sites). If a test is acceptable to help inform a patient what to do in their home, it would also be acceptable if the same patient was found, for example, in a physician's office for a check-up. For example, to exclude normal and/or healthy patient use seems unwarranted. Indeed such restrictions may interfere with access and the practice of medicine.

- With regard to studies, we believe that testing in the hands of laypersons can provide adequate information to determine if a device is effective in the professional setting. As stated above, FDA has historically assumed the effectiveness of the device in a professional setting based on home use studies because professional users are likely to be at least as good, and likely better than, a layperson performing the test. Even FDA acknowledges this in its OTC Guidance, noting that "medical professionals are generally *more proficient* at performing testing and at running appropriate controls,

[6] Professional BGMS would be required to achieve results within +/- 10% of a reference method, whereas home BGMS would be held to a +/- 15% standard. POC Guidance, 13; OTC Guidance, 11.

[7] As referenced, there are, of course, instances where greater accuracy may be required, such as neonate testing or where testing is intended for tight glycemic control. In those cases it is appropriate for FDA to require greater accuracy to support the manufacturer's intended use.

and they typically have a better understanding of test limitations as compared to lay-persons" (emphasis added).[8] There is no reason to believe more expert users would achieve inferior results, so home use testing captures the minimum achievable performance of the test in a professional setting.

We do agree with the Agency that risk of bloodborne pathogen exposures varies between home and professional environments, and this is something that is reasonably considered in evaluating product *safety*. However, with respect to test performance (effectiveness), the extrapolation of home use to professional use should continue for the reasons described above.

AdvaMedDx recommends revising the draft guidances to remove the blanket restriction on the use of OTC BGMs in professional settings and recognize that these devices provide adequate performance by healthcare professionals for certain uses. AdvaMedDx also recommends clarifying that studies with laypersons reflect, and can be used to establish, the minimum performance that would be expected in a professional use setting (which may be sufficient for a professional use clearance).

CLIA Waiver Requirements

The use of a test in any clinical laboratory, including point-of-care laboratories, is governed by CLIA. CLIA requires FDA to categorize tests as "high," "moderate," or "waived" complexity, which corresponds to the laboratory environment that can use the test.[9] Most point-of-care laboratories, such as physician office laboratories, operate under a CLIA "Certificate of Waiver," meaning they can only use tests of waived complexity, and must follow the manufacturers' instructions for use.[10]

CLIA-waived tests are those tests that have an "insignificant risk of producing an erroneous result" in the hands of a user, meaning there is no need to restrict the use to more expert laboratory settings.[11] To avoid any confusion about whether home use products would meet the CLIA waiver standard, Congress expressly provided by statute that products "approved by FDA for home use" are to receive an automatic waiver.[12] Therefore, once FDA has determined that a layperson can use a test at home, the Agency cannot restrict the use of the test by a healthcare professional in a waived laboratory.

[8] Draft OTC Use Guidance at 2.

[9] 42 CFR 493.17.

[10] 42 CFR 493.15.

[11] 42 U.S.C. § 263a(d)(3).

[12] *Id. See also* H.R. Rep No. 105-310, Sec. 21 (1997) ("[W]hen a the FDA already has determined that a diagnostic product can be used safely and effectively by a layperson at home, such product should not require additional review or action [by FDA] to determine whether CLIA requirements can be waived for this product.")

This is consistent with the fact that healthcare professionals will run a test at least as well, if not better, than a layperson (see earlier discussion).

However, per FDA's OTC Guidance, BGMS labeling must include a statement that home use BGMS are not to be used in professional settings.[13] As a result, Certificate of Waiver laboratories running the home use test are deemed, albeit arguably, not following the manufacturer's instructions for use, and therefore are violating CLIA requirements; this was the argument that the State of New York recently advanced in its letter prohibiting the use of blood glucose meters in Certificate of Waiver laboratories.[14]

The OTC Guidance's restrictive approach is contrary to the legislative intent of Congress in creating the automatic home use waiver, because it renders it null and void. Further, the approach will substantially restrict the use BGMS in waived facilities, which represent the vast majority of POC testing facilities.[15] The net result is to deny patients access to important diagnostic products, which is contrary to the public health.
There is, however, an alternative approach which has been routinely used to manage dual-use environments, and which preserves access while assuring safety: create separate labeling for home use and professional use labeling for BGMS.[16] The professional labeling could provide additional information about cleaning and disinfection that is needed to assure BGMS safe use. The home use version could present a modified version of this information more appropriate for laypersons who have reduced concern with bloodborne pathogens for their personal meter. This approach is consistent with both the FDCA and CLIA, and furthers the public health.

AdvaMedDx recommends revising the draft guidance to provide for professional and home use labeling that allows automatically-waived home use products to be used in CLIA-waived environments.

<u>The Negative Impact of the Guidance Needs to be Considered</u>
Given the importance of the guidances (i.e., the significant impact they could have on public health), it is vital to keep in mind the extent to which the Agency has changed course – in this case proposing to fundamentally change the regulatory framework for

[13] OTC Guidance, 27-28 (Recommending a label statement that "[a home use] device is not intended for use in healthcare or assisted-use settings such as hospitals, physician's offices, or long-term care facilities because it has not been determined to be safe and effective for use in these settings …").

[14] *See* footnote 1, above.

[15] FDA notes that it is still possible to pursue a waiver through FDA's CLIA waiver program. However, given the current performance of the program, as well as costs and other problems with its implementation – as addressed in previous comments – this is contrary to the legal-regulatory framework, overly burdensome, and not a viable option for many innovators.

[16] FDA's approach here is reflected by the several clearances of devices that have been cleared both for BGMS devices that have been cleared for "over-the-counter" and prescription use.

BGMS regulation. FDA must consider the relevant facts, the consequences of the policy change, and reasonable alternatives, and explain why and how it reached its conclusions.[17] It cannot ignore pertinent facts in decisionmaking;[18] in fact, doing so renders the resulting decision arbitrary and capricious.[19]

Therefore, FDA must consider not just safety issues, but the impact its proposed changes will have on innovation and access to important diagnostics. When FDA imposes new, restrictive, requirements on product development, it can have a negative impact on innovation. Also, if requirements are made too burdensome, manufacturers will be discouraged from innovating currently marketed models, and access may be limited. FDA must also consider legal issues. For example, FDA must consider the intent behind automatic CLIA waivers for home use products, and the access issues it is creating by nullifying those waivers. It also must consider whether its approach is consistent with least burdensome principles.[20] Congress requires the Agency to take to the least burdensome approach to regulation to "reduce [regulatory] burdens to improve patient access to medical devices."[21] Here, FDA's standards seem to run contrary to least burdensome principles by imposing additional, unnecessary, requirements for 510(k) clearances as described above.

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[17] *See Natural Res. Def. Council v. SEC*, 606 F.2d 1031, 1053 (D.C.Cir.1979) ("[The court] will demand that the [agency] consider reasonably obvious alternative[s] ... and explain its reasons for rejecting alternatives in sufficient detail to permit judicial review."); *Greater Boston Television Corp. v. FCC*, 444 F. 2d 841, 851 (D.C. Cir. 1970) ("Its supervisory function calls on the court to intervene…if the court becomes aware, especially from a combination of danger signals, that the agency has not really taken a 'hard look' at the salient problems, and has not genuinely engaged in reasoned decisionmaking."); *Stuttering Found. of Am. v. Springer*, 498 F. Supp. 2d 203, 208 (D.D.C. 2007) ("A reviewing court must be satisfied that the agency has 'examine[d] the relevant data and articulate[d] a satisfactory explanation for its action including a rational connection between the facts found and the choice made.'").

[18] *Marsh v. Or. Natural Res. Council*, 490 U.S. 360, 378 (1989) (determining whether an agency decision was arbitrary and capricious requires the court to consider whether the decision was "based on a consideration of the relevant factors").

[19] *See American Academy of Pediatrics v. Heckler*, 561 F. Supp. 395, 399 (D.D.C. 1983) (invalidating a Department of Health and Human Services rule as arbitrary and capricious where the record "clearly establishe[d] that many highly relevant factors…were not considered prior to promulgation of the challenged rule").

[20] FDCA § 513(i)(1)(D) ("Whenever the Secretary requests information to demonstrate that devices with differing technological characteristics are substantially equivalent, the Secretary shall only request information that is necessary to making substantial equivalence determinations. In making such request, the Secretary shall consider the least burdensome means of demonstrating substantial equivalence and request information accordingly.").

[21] 158 Cong. Rec. S4618 (daily ed. June 26, 2012) (Statement of Sen. Burr).

Other 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. In all cases, care must be taken neither to jeopardize choice and access to safe and effective meters that meet patient needs nor to discourage innovation and continued investment in new technology.

As previously noted and 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 legal and substantive concerns with the framework as outlined. Furthermore, we encourage the holding of a workshop following review of comments and prior to issuance of final guidances with healthcare professionals including physician point-of-care users as well as medical centers and institutions, industry, and other stakeholders to discuss scientific and technical issues and consider risk-based approaches that do not have the unintended consequences of limiting the appropriate use of glucose meters while addressing issues of in-patient tight glycemic control.

In such time as a carefully rereviewed and revised POC guidance is issued, this draft POC guidance (and similarly its counterpart OTC guidance) should not be implemented for premarket 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 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. In addition, 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 to FDA for specific inclusion in the guidance to address concerns and provide alternative but equivalent means.

This guidance should be carefully examined and specifically integrate appropriate alternatives where at all possible and assure that a least burdensome approach is implemented that supports public health while ensuring assuring continued patient access to meters that meet their individual needs. The list of new requirements is extensive and in a number of cases not clinically grounded and/or speculative. Careful consideration is needed as the guidance includes extensive analytical tests 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 beyond worldwide product standards.

We hope the Agency will take the opportunity to consider all of these factors, in addition to those it raised in its draft guidances and other commenters identify, to develop a better final guidance that will not only protect patients, but will benefit patients by facilitating access and innovation.

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—
Blood Glucose Monitoring Test Systems for Prescription Point-of-Care 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 (e.g., in the Interference Evaluation Section the Agency continually requires bias to be calculated "from the reference method"; the "reference method" in these studies should be replaced with the "control condition" consistent with CLSI EP7-A2 (FDA recognition number 7-127). In all these tests, the samples are altered and because of this alteration could have an inherent bias from reference.
2.	II	71 and related references including title	Revise as follows (delete stricken text and add text in underline): "In order to distinguish between ~~prescription use~~ 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 use~~ point-of-care blood glucose meters, for use in ~~point-of-care~~ professional healthcare settings, and (ii) over-the-counter ~~SMBG~~ devices intended for ~~OTC~~ self-monitoring by laypersons."	Many lay-users obtain 'prescriptions' for their SBGM systems so specifying that 'prescription' use is only professional is misleading. Point-of-care meters (POC) for professional healthcare settings and over-the-counter (OTC) for self-monitoring are better choices for accurate descriptions.

Comment Number	Section	Line No	Change	Comment/Rationale
3.	II	76-83	The draft guidances must remove the blanket restriction on the use of OTC BGMS in professional settings and recognize that these devices provide adequate performance by healthcare professionals for certain uses. As outlined in the general comments, a reasonable approach can bring the guidance recommendations in line with the FDCA and CLIA to preserve access while assuring safety through providing for separate professional and home use labeling that allows automatically-waived home use products to be used in CLIA-waived environments.	As covered in detail in our general comments, the new guidances are misaligned with the Food, Drug, and Cosmetic Act (FDCA) and the Clinical Laboratory Improvement Amendments of 1988 (CLIA). In order to bring the guidance recommendation in line with these statutes, these critical changes are needed. As drafted, the Guidance's restrictive approach is contrary to 42 U.S.C. 263a(d)(3) and legislative intent of Congress in creating the automatic home use waiver because it renders it null and void. The public health is also not well served by the approach. It is also critical that FDA weigh all the significant policy changes it has proposed and consider the negative impact of this guidance as proposed. Of particular note, the guidance does not delineate between any potential point-of-care uses. There is no disagreement that there are situations where greater accuracy is required, such as where tight glycemic control is needed. Where a manufacturer intends its product for these intended uses, FDA must require better accuracy (and, appropriately, fall outside the scope of the OTC Guidance). As drafted, the guidance has essentially lumped all point-of-care users into one group and in effect prohibited appropriate use of the product in professional environments for identical uses.

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4.	IV	114-121	Add clarification on when cleaning and disinfecting is required for certain scenarios. Scenario: A manufacturer 510(k) clears a BGMS device with the appropriate Cleaning and Disinfecting data. It later decides to submit the same type of device within the same family of instruments for a device modification that does not affect the housing/materials on the device and the Intended/Indication for Use does not change. This should not require repeat cleaning and disinfecting testing.	This does not address the scenario where manufacturers have a product line family of instruments and if cleaning and disinfecting is required per each BGMS submission if the devices are made up of the same materials and maintains the same intended use/indication for use. We recommend that FDA not require repeat cleaning & disinfecting testing in these scenarios.
5.	IV	126	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.
6.	IV	130-131	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.
7.	IV	134	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).
8.	IV	140-141	Clarification of this statement.	Rather than specifying a single lancet type, could labeling be a more general reference to the gauge(s) of the lancet?
9.	IV	145-149	Labeling concerning safe device use can reduce the risk of user error. Therefore, instructions for cleaning and disinfection should be clear and detailed.	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

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			However, should 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 DEF blood glucose test strips, etc.)."	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.
10.	IV-A General	156-186	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 earlier lines, it should be clear if the intent that the disinfecting effectiveness study must only be carried out with Hepatitis B.
11.	IV	158	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 safety/efficacy.
12.	IV-A	164	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 should be permitted as long as it can be shown safe/effective.
13.	IV-A	167	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 but not limited to case parts, display, buttons and labels.</u>"	It might be helpful to specifically mention each of the external meter materials.
14.	IV-B	197	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 manufacturer's cleaning and disinfection procedure.

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15.	IV-B	201	Clarify "exposed to in its use life" (typically 3-5 years)	FDA needs to define what they consider the use life.
16.	IV-B	205-206	Clarify that the "test strip port and all other openings" is limited to surfaces that can be 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."	If the user cannot touch a surface, then there is no risk of contamination. As such, it is not necessary to 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.
17.	IV-B	214-215	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 to those that have not been exposed to this treatment would adequately demonstrate the impact of cleaning/disinfection on device performance.
18.	IV-B	222	Revise as follows (delete stricken text and add text in underline): "You should incorporate your labeling instructions for cleaning and disinfection in a ~~your~~ user study (see Section VI-C, below**)** to	We agree that it is crucial to validate the effectiveness and clarity of the cleaning and disinfection instructions. However,

Comment Number	Section	Line No	Change	Comment/Rationale
			determine the effectiveness and clarity of the instructions in your labeling for lay users."	usability of the C&D 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.
19.	V	231	Clarify "[m]anufacturer's performance specifications."	Does this mean the product specification?
20.	V and IX	234 and 1095	This bullet point should be revised to state: "Description of the format...reported in whole blood and/or plasma equivalents."	If plasma equivalents are required for results reporting, then the bullet point should be amended to reflect this.
21.	V	235	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?
22.	V	252	Recommend that the FDA remove this statement: "You should also describe the error tolerance for user actions, such as these, that are inconsistent with device operation."	The nature of this requirement and its purpose is unclear. It is not feasible to set up an expected error rate for the user issues listed.
23.	VI-A	292 and related sections	Provide CLSI Reference to EP05-A2 for the entire Precision Evaluation section.	This does not reference CLSI documentation on Precision Performance. For clarity and consistency (note: FDA Standard Recognition number 7-110).
24.	VI-A	298	Change "venous blood" to "venous whole blood" (2 locations in sentence).	This is intended for clarification.
25.	VI-A	299-300		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.
26.	VI-A	303-305	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,

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				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.
27.	VI-A	312	Revise as follows (add text in underline): "For each glucose concentration range in Table 1, you should also provide the mean value, <u>pooled</u> standard deviation (with 95% confidence intervals) and <u>pooled</u> percent CV for data combined over all meters."	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.
28.	VI-A	315	Statistical methods to identify outliers can be used and described. In some cases, it might be not possible to identify the root cause for an outlier in any case.	FDA should clarify how manufacturers should describe these types of outliers.
29.	VI-A	320-322	Clarify the following statement: "Intermediate precision measurement studies are designed to measure imprecision under normal conditions of use by the intended user (i.e., measurement by individuals over multiple days, with the same meter, and reagent system lot)."	This needs to be written so that it is clear that it is not an actual user evaluation but rather a bench study.
30.	VI-A	328	Revise reference to "minimum of 10 days" to FDA-accepted standard and allow the manufacturer to conduct the appropriate precision testing.	Reflects approach consistent with currently accepted CLSI standard.
31.	VI-A	331	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.
32.	VI-A	336	"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.
33.	VI-A	338	Revise as follows (add text in underline): "For each glucose concentration in Table 1, you should also present the mean value, <u>pooled</u> standard deviation (with 95% confidence interval) and <u>pooled</u> percent CV using measured values from all three test strip lots."	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.

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34.	VI-B	346	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.
35.	VI-B	348	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.
36.	VI-B	349	Change "venous blood" to "venous whole blood" (2 locations in sentence).	Clarification
37.	VI-B	350	Use of contrived samples	FDA's allowing the use of contrived samples is a positive for manufacturers.
38.	VI-B	351-353	Remove sentence from 351-353.	In a bench test, all samples will be altered samples.
39.	VI-B	355	Provide specific reference to CLSI EP06-A to provide a linearity measure over the claimed glucose range.	For clarity and consistency (note: FDA Standard Recognition number 7-193).
40.	VI-C	358	Clarification and additional flexibility is needed regarding Method Comparison/User Evaluation.	FDA should allow the manufacturer to determine the appropriate comparison protocol. This is a very difficult study design. 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.

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41.	VI-C-1	376 388	"…Evaluate accuracy for each claimed sample type…should include 350 patients…" "…if the ranges are not covered…additional subjects should be enrolled…"	A bridging study or method comparison between sample types should be permitted, rather than 350 patients per sample type/patient population. For example, 3 samples types/sources would be a minimum of 1050 individual test results.
42.	VI-C-1 and VI-C-2	385-387 *and* 517-519	Recommend that the number of native, unaltered samples be reduced to at least 5 for samples < 80 and > 300. This would be for all sample types. Furthermore, state that the total amount of samples should be a minimum of 50 for both unaltered and altered samples < 80 and > 300. This would also be for all sample types.	Finding native, unaltered samples for sample type < 80 and > 300 is not common. Also, there is confusion on the total number of samples required. This can be interpreted as 60 total samples required for < 80 and > 300. (50 can be contrived sample, 10 must be unaltered). Due to ethical aspects, we should provide a lower number of unaltered samples to avoid patient risk. We also recommend the ability to use altered samples when necessary.
43.	VI-C-1	390-392	Add the following sentence: "The same 9 operators can be used to test the various matrices, but there should be a minimum of 9 different operators testing each matrix." We also recommend allowing non-POC operators to complete pre-analytical steps. The POC User should only perform the blood test on the POC device. This is an important distinction for the desired non-glucose data testing (hematocrit, oxygen, etc.). We also recommend that this non-glucose data come from one POC site, instead of all 3 POC sites. We also appreciate clarification from FDA regarding the rationale for requiring 9 operators rather than at least 5.	FDA states: Testing should be performed by the intended POC (point-of-care) user (e.g., nurses, nurse assistants, etc.) to accurately reflect device performance in POC settings; at least 9 operators should participate in each study (capillary, venous, and arterial). This can be interpreted that 9 new POC operators must be used for each sample type, meaning 27 POC operators total. General comment regarding POC operators: In many hospitals, there may be separate person that conducts the pre-analytical steps than those who conduct the blood test on the POC device.

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44.	VI-C-1	392-393	FDA states: You should submit data from all subjects, and no subjects should be excluded from the data analysis. We agree that all data should be provided. However, not all data should be included in the overall analysis. Samples with pre-analytical handling problems by the operator, error messages, discrepancy between recorded results and memory of system/print out whatever is applicable, QC not in range (if later detected by the CRA), laboratory reference not obtained (e.g., handlings error Operator) must be excluded.	Recommend removing this sentence as data is covered within the data analysis section.
45.	VI-C-1	393	Add a statement at the end of the sentence to say: "See 2. Data Analysis for details."	Clarification.
46.	VI-C-1	400-406	To collect performance data in such populations, each study should include at least 100 patients from ICU. To obtain a representation of other patients in the hospital setting, the remaining 250 samples should be from in-patients dispersed throughout other hospital departments. The results should indicate which of the above categories the samples were from (ICU, and other specified hospital departments).	The guidance has to provide further clarification on whether the ICU samples are only for arterial samples or for venous and capillary samples too. Clarification has to be provided on if the arterial samples are to be collected specifically for the study or if de-identified samples can be used. Specifically, it would be problematic for a clinical study in ICU. There is no evidence that the characteristics of the sample from surgical ICU and the medical ICU have any difference in performance. It would be more appropriate to just state ICU samples without separately requiring surgical and medical ICU samples.
47.	VI-C-1	408-410	FDA needs to clarify if anticoagulant testing samples should be included in the total samples required, or these are in addition to the total samples per anticoagulant. We recommend that testing samples be included in the total samples.	This statement is unclear regarding the total sample size.
48.	VI-C-1	413-415	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.	Given that the BGMS shipping validation report along with test strip stability is included as part of the 510(k), it is

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			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."	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.
49.	VI-C-1	421	Add "or according to your facility SOPs."	Protocol including information typically required by facility SOPs (for example, how often to change gloves).
50.	VI-C-1 and IX-11	423-424 *and* 1204-1205	Align the statements captured in lines 423-424 and 1204-1205. Specifically, align the statements from lines 423-424 to match those listed in line 1204-1205. Replace 423-424 so that it reads as follows: "The study protocol should also require the trained health care professionals to change gloves between users."	The study protocol instructions for how often and when the gloves of trained health professionals should be changed between users (lines 423-424) and the FDA's recommendation for including the statement that the operator should wear a new pair of clean gloves before testing each patient (lines 1204-1205) are not aligned. Study protocol instructions should align with standard hospital practices as well as the labeling for the device when used by these operators.
51.	VI-C-1	432-438	For purposes of other outpatient uses (not for tight glycemic control), accuracy will be dependent on the intended use—regardless of user. FDA must remove the blanket restriction on the use of OTC BGMs in professional settings (which can well encompass the physician office to outpatient clinic to emergency room) and recognize that these devices provide adequate performance by healthcare professionals for certain uses. Furthermore, and rather than lumping in of all point-of-care use, the method comparison/user evaluation criteria should be aligned	The guidance does not delineate between any potential point-of-care uses. There is no disagreement that there are situations where greater accuracy is required, such as where tight glycemic control is otherwise required. While we support the FDA's desire to have improved performance in the hospital (i.e., tight glycemic control), the guidance has essentially lumped all point-

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			appropriately as follows such that in the case of hospitalized patients, any BGMs (including OTC products) meeting such criteria would be appropriate;) consistent with POCT-12: 1) Where an alternate laboratory system is available 95% of all results must be within +/-12 mg/dL of the reference at glucose concentrations <100 mg/dL and within +/-12.5% of the reference at glucose concentrations ≥100 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. 2) Where no alternate laboratory system is available 95% of all 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. You should investigate and provide a justification for any BGM test result that exceeds the above mentioned criteria, if possible.	of-care users into one group. In that vein, the recommendations outlined in #1 and #2 are intended for hospital point-of-care testing consistent with worldwide standards for blood glucose meters. Based on analysis, using the +/- 7/10 at 99% confidence interval criteria means that with 350 samples, no single test result can be outside the +/- 15/20 (Error Grid A Zone). A single outlier would show a failure. Question for FDA: - What is the rationale for such tighter criteria than the recently approved CLSI POCT12 (formerly C30-A2)? This is FDA-recognized standard number 7-133. Our understanding is that FDA was involved in the POCT12 standard development discussions. Clinical Rationale for Recommended Criteria 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. At low glucose levels, there is not a clinically significant difference between 50 mg/dL and 60 mg/dL. Patients with these glucose concentrations need to have glucose administered to raise their glucose levels.

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				The acceptance criteria described in this guidance document indicate that a bias of +/-10 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 60 mg/dL versus a result of 55 mg/dL. According to the publication by Boyd and co-workers, this is not likely. In the publication by Boyd and co-workers, 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 100 mg/dL), the allowed amount of bias only be +/-10 mg/dL. This is 1/3 of the bias described in the publication by Boyd and co-workers, and it represents a significant accuracy requirement improvement over that which is described in CLSI POCT-12. <u>Clinical Considerations for the Use of Percent Bias at Low Glucose Levels</u> In 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

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				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 60 mg/dL. With the current acceptance criteria, a BGM value of 60 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). <u>Reference Analyzer Considerations for the Use of Percent Bias at Low Glucose</u> 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 reference measurement duplicates can differ by ±4 mg/dL or 4% (CLSI POCT-12). <u>Proposed Criteria and Patient Understanding</u> 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

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				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. A bias of 5% and a precision of 3% would result in < 99% of the test results to fall within 7mg/dL or 10% from laboratory reference. Additionally, this will require the system precision to be in the order of 1.5% or less to meet the specified requirement. This is not achievable by the reference measurement systems such as Yellow Spring Instruments (YSI), since it has a standard deviation / coefficient of variation of 2.5mg/dL or 2%. Under the guidance "Recommendations: Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices", laboratory analyzers meet the glucose criteria of 95% within 6 mg/dL or 10%, whichever is greater. The proposed criteria mentioned in Lines # 432-438 are tighter than the current CLIA waiver criteria and hence this impacts both laboratory analyzers and blood glucose meters.) POCT-12 provides sufficient accuracy and

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				precision e.g., Mitsios, et. al J. Diabets Sci Technology 2013l 7(5): 1282-1287 regarding BGM use consistent with POCT 12-A3 at point-of-care in hospitals.
52.	VI-C-1	446	Revise as follows (delete stricken text): "Hematocrit ~~and sodium~~ values should be measured and recorded for each of the study participants."	If sodium is in the interference table, FDA should clarify if participants as patients, operators, or both.
53.	VI-C-1	467	It is unclear what is meant by study "participants".	While it likely means patients, FDA should clarify if participants as patients, operators, or both.
54.	VI-C-1	468-469	Revise as follows (delete stricken text and add text in underline): "Description of the patient demographics including age <u>and</u> disease states<u>,</u> ~~and all medications~~ for each patient."	Collecting patient medications 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, especially since the information would be self-reported by subjects. Also to correlate outliers with medications is not a scientific method (unless the quantities of the metabolites were tested in the blood). Beyond the scope of a BGM trial.
55.	VI-C-1	Footnote 6	Remove the footnote in this guidance.	In addition to our concerns outlined in our general comments, we note the current draft guidance is extensive and is closely aligned with the guidance "Recommendations: Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices" and therefore the consideration of "slightly increasing" the study size is redundant and unduly burdensome. The clinical study mentioned in Section VI. C. 1. General Study Design is adequate and additional data should not be required.

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56.	VI-C-2	482	Data requirements	First, this data may not be routinely collected or not available. Second, it is unclear about how this data would be used. If used to stratify patients, is there the anticipation that additional sample sizes would be necessary?
57.	VI-C-2	482-484	Remove the requirement to provide sodium levels.	Though the guidance requires collection of information on sodium, it does not specify the type of analysis that is expected to be performed with the information. This would require the blood samples to not be de-identified and investigation of the outlier may not always identify the root cause, which may prolong the clinical study to unspecified timelines. Also, due to the narrow range of sodium levels manifested in the study, a correlation may not be derived. Additionally, this analysis is being provided in the interference testing section.
58.	VI-C-2	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.
59.	VI-C-2	504-506	Correct table formatting so all text is visible in table.	Clarification to make it easier to read.

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60.	VI-C-2	508	Accuracy at Extreme Glucose Values This section should be embedded within the data analysis section of the User Evaluation and does not belong there. Create a new section.	Confusing outline structure: three separate studies are described within the "Data Analysis" section of the method comparison study.
61.	VI-C-2	526-529	It is not clear what type of Objective Evidence the FDA believes is appropriate to submit in the 510(k).	Please clarify. We assume this is part of the overall validation and verification activities and does not require separate data set listing to show these error code test results.
62.	VI-C-2	538	Revise as follows (add text in underline): "You should evaluate device performance with neonatal samples by testing 100 to 150 fresh <u>(can include leftover sample from a sample drawn for the laboratory for other reasons)</u> neonatal capillary blood specimens in direct comparison to the reference method."	Parents are unlikely to consent to a separate heelstick for a meter trial.
63.	VI-C-2	551	Revise as follows (add text in underline): "Since it may be difficult to obtain samples at the extreme ends of the measuring range using real neonatal patient samples, in order to provide a robust evaluation of the device performance in the extreme upper and lower ends of the measuring range, you should perform additional studies using blood samples (either adult blood or maternal cord blood) altered to achieve concentrations between 10 and 50 mg/dL <u>and hematocrits consistent with neonatal blood."</u>	If using adult blood to simulate neonatal blood, hematocrit should be elevated.
64.	VI-D-1	564	Revise as follows (delete stricken text and add text in underline): "Specifically, testing should be performed in samples with glucose concentrations of ~~60~~ <u>50-70</u> mg/dL, ~~120~~ <u>110-130</u> mg/dL, and ~~250~~ <u>225-270</u> mg/dL to evaluate clinically relevant decision points."	The guidance should state a tolerance around the glucose levels in the contrived samples.
65.	VI-D-1	569-571 and Table 4	Recommend that alternative descriptions be used for "Therapeutic Level" and "High Toxic Concentration." Also remove "whole" from line 571.	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

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				that could potentially be observed in a whole blood sample, but the example concentration and the concentrations in Table 3 are in plasma.
66.	VI-D-1	577	Column Header: High Toxic Concentration Change to: Pathological or Toxic Concentration	Endogenous substances do not have a "therapeutic" level.
67.	VI-D-1	550	Make the units of measure of the interferents consistent. Gravimetric is preferred (mg/dL).	Inconsistent units of measure can cause confusion.
68.	VI-D-1	577	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 201.6 mg/dL 1008 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 120 mEq/L 175 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 subsequently outlined 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. • 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 plasma is <3 mg/dL and SI Units for Clinical Measurement (DS Young et al., Copyright 1998, p152)

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				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 4. 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

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				(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 evaluated be updated to reflect this information. CLSI EP7-A2 recommends an upper testing concentration of 1.5 mg/dL.
69.	VI-D-1	577, Table 4	Clarification is needed that Table 4 is either referring to unconjugated bilirubin or conjugated bilirubin.	Currently, it is unclear whether or not Table 4 is referring to conjugated or unconjugated bilirubin.
70.	VI-D-1	577, Table 4	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 4. 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.
71.	VI-D-1	587-589	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

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				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.
72.	VI-D-1	588, 594, 595	Change average to mean as mean is used in the table.	Clarification for consistency
73.	VI-D-1	591-596 and 633-640	There appears to be a contradiction in the document in that lines 591-596 seem to recommend pooling the lots together to determine acceptability while lines 633-640 recommend evaluating each lot separately. We recommend that the data analysis only describes the presentation of pooled data and not by lot.	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 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. We 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.
74.	VI-D-1	593-594	Recommend changing the bias calculation to the following description: "Each replicate should be compared to the average bG 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. This CLSI document highlights 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

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				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 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.
75.	VI-D-1	596	Add the following after the last current sentence: "Calculate the mean of all replicates."	Table 5 has a column for Mean glucose value. The text does not match the example table. The text does not state to calculate this or other results desired by the FDA.

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76.	VI-D-1	598-604	FDA should determine 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.
77.	VI-D-1	602	Add at the end of the line: "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.
78.	VI-D-1	619-620	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.
79.	VI-D-1	628-629	Delete lines.	This is a postmarket requirement and is currently being captured and reported to the Agency through different processes. (Note: This is inconsistent with our SMBG recommendations, which call for FDA to update the list of interferences and notify industry.)
80.	VI-D-1	639	Within the Table, change "YSI" to "Reference". Change the Table Title to include "Summary".	YSI is a common reference method for glucose, but it is not always used. This document should be generic for all reference methods, as manufacturers can choose their reference method.

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				We believe this is an example of a summary table since the mean glucose value is in the table and not a single glucose value.
81.	VI-D-1	641-646	Revise to state: "We recommend you present data graphically for each observed interferent per individual test strip lot."	This section infers that FDA wants graphical data for all interferent testing. Graphs should only be provided only for those interfering substances where significant interference is observed. Providing graphs for all interferent tests does not represent a least-burdensome approach.
82.	VI-D-2 and VI-D-3	653 and 714	We recommend that FDA states that POC operators are not required to run the hematocrit or oxygen samples. These can be run by non-POC operators.	FDA requests POC operators to run sample on the candidate BGMS. It is unclear if FDA expects POC operators to also run the samples on devices that provide Hematocrit and Oxygen level results. Some of these devices can only be conducted on moderate or high complexity devices, and therefore cannot be run by a POC operator. This is also true for desired metabolite measurements.
83.	VI-D-2	672	Revise as follows (delete 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 10-60%, you should test samples at 10, 15, 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~~	The proposed size of this study (60 samples, N=1800) seems excessive, particularly for a system in which hematocrit sensitivity is negligible and the 10-65% claim is easily demonstrated. Data in the middle hematocrit range already is well represented in the method comparison study.

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			~~spread and~~ targeted to the following ranges: 30 – 50, 51 – 110, 111 – 150, 151 – 250, and 251 – 400 mg/dL."	
84.	VI-D-2	680, 686, and 688	Change average to mean as mean is used in the table.	Clarification for consistency
85.	VI-D-2	688	Add the following after the last current sentence: "Calculate the mean of all replicates."	Table 6 has a column for Mean glucose value. The text does not match the example table. The text does not state to calculate this or other results desired by the FDA.
86.	VI-D-2	683-694	Revise as follows (delete stricken text and add text in underline): "~~You should test a minimum of 3 test strip lots to evaluate interference from hematocrit. Each test sample should be tested on your new BGMS 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 ~~5%~~8% above 80 mg/dL and less than or equal to 8 mg/dL below 80 mg/dL.~~on average, and no individual value should be greater than 10% 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."	The current bias calculation description (comparing the BGMS 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

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				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 described in CLSI EP7-A2. The recommended criteria of ±8 mg/dL below 80 mg/dL and ±8% above 80 mg/dL were chosen because these allowable biases only consume a portion of the total error recommended for the user performance evaluation. 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 ±5% is overly stringent. As described previously, such a stringent requirement approaches the performance expectations of reference analyzers. The requirement that not a single reading out of a data set of 1800 readings have more than 10% deviation from the reference method is unreasonable. Meeting this statistical requirement would be virtually impossible, even in a laboratory study. An alternative relating to precision is proposed. It should be noted that the purpose of this hematocrit study is to

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				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.
87.	VI-D-2	701	Within the Table, change "YSI" to "Reference". Change the Table Title to include "Summary".	YSI is a common reference method for glucose, but it is not always used. This document should be generic for all reference methods, as manufacturers can choose their reference method. We believe this is an example of a summary table since the mean glucose value is in the table and not a single glucose value.
88.	VI-D-2	708-709	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 decribed in Figure 2 be updated accordingly.
89.	VI-D-3	714	Oxygen only impacts systems using glucose oxidase; these interference studies should only be necessary for these types of test strips.	We recommend adding a statement that this section is needed only if the BGMS utilizes glucose oxidase.

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90.	VI-D-3	715	FDA should specify that venous whole blood samples can be used for this study.	Clarification for this sample type.
91.	VI-D-2	731	Revise as follows (delete stricken text and add text in underline): "Oxygen levels tested should span the claimed range. For example, if the device's claimed oxygen range is from 40-200 mmHg, samples should be tested at ~~40, 45, 50, 55 mmHg. . . 190, 195 and 200 mmHg~~ 35, 65, 95, 145, and >200mm Hg. The samples should also span the claimed measuring range for blood glucose. You should include samples at ~~5~~ 3 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~~ 50-70, 110-130, and 225-270 mg/dL. "	It is impossible to manipulate oxygen levels at such high resolution, and there is no sound biochemical reasoning to explain why any oxygen effect would vary within such small increments of oxygen levels. Guidance suggests 33 levels of oxygen to be tested across the extreme oxygen levels of venous and arterial samples. That is 33 levels of oxygen to be prepared between 40mmHg (0.8psi) to 200mmHg (3.9psi). Covering the venous and arterial samples and attaining these levels of gas composition to prepare the test samples is not feasible and unduly burdensome. 5 mmHg of oxygen increment of gas composition is not attainable in this narrow range. Use the same 3 glucose levels as recommended for interference testing.
92.	VI-D-3	737, 744, 746	Change average to mean, as mean is used in the table.	Clarification for consistency
93.	VI-D-3	753	Change Table 6 to Table 7.	Correction.
94.	VI-D-3	753	Add the following after the last current sentence: "Calculate the mean of all replicates."	The current table has a column for mean glucose value. The text does not match the example table. The text does not state to calculate this or other results desired by the FDA.
95.	VI-D-3	754	Within the Table, change "YSI" to "Reference". Change the Table Title to include "Summary".	YSI is a common reference method for glucose, but it is not always used. This document should be generic for all reference methods, as manufacturers can

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				choose their reference method. We believe this is an example of a summary table since the mean glucose value is in the table and not a single glucose value.
96.	VI-E	770 et seq.	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.
97.	VI-E	770	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. 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."	The term "flex studies" is not widely used across the medical device industry.
98.	VI-E	770-847	Recommend that FDA state that these studies, unless otherwise stated, can be run with either control solutions or blood.	FDA provides information on why "flex studies" should be completed and included with the 510(k) submission. For electrical and stress testing, it does not state that control solutions can be used for these tests.
99.	VI-E	830	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.

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100.	VI-E	831	Shock Testing - The requirements in IEC 61010-1 apply.	A recognized standard should be cited in order to provide a consistent approach to the "flex" studies across all submissions.
101.	VI-E	832	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.
102.	VI-E	833	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.
103.	VI-E-1	859-860	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.	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 of the system at different test times.
104.	VI-E	864-876	Delete lines 864-876.	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. Precision can be assessed in the accuracy study.
105.	VI-E	878	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, which is unnecessary 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.
106.	VI-E-2	885-921	Delete lines 885-921. Alternatively, replace with the following protocol: "Temperature and Humidity Study Design	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

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			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 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 five 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 termperature 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 simulataneously 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. Calculate the bias and percent bias of each lot mean from the laboratory comparison method. Calculate the difference between the bias of each lot at	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 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

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			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 6.4 mg/dL for glucose concentrations <80 mg/dL and less than 8% for glucose concentrations ≥80 mg/dL. It should be noted that some systems may claim temperature and humidity ranges that are so wide that the combination of the extreme temperature and humidity limits (e.g., 40°C / 90%RH) never actually occur simultaneously in nature. Meeting the acceptance criterion at all extreme combinations of temperature and humidity provides confidence that the system will perform well at all conditions that would ever be encountered by the intended user."	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 eliminated when a control or nominal condition is used in the evaluation.
107.	VI-E-2	919-921	Remove lines 919-921.	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 these products are distributed by 3rd party (distributor) and will also lead to increased costs for end user.

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				FDA should also avoid terminology such as "encourage." If FDA is requesting this information, then this should be clear.
108.	VI-E-3	923-933	Remove lines 923-933.	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 BGM error.
109.	VI-E-4	935	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.
110.	VI-E-5	953	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.
111.	VI-E-6	969	Consider revising and/or removing this section.	We note that the described event (short sampling) unlikely with newer meters using very small sample volumes. Testing is excessive (all of the levels) given the low possibility of occurrence.
112.	VI-E	978-980	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,	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

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			then the other half of the sample should be applied to the strip after a set 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."	reading a short sample, so applying a second sample once the first sample starts reading is impossible.
113.	VI-E-7	988	Revise as follows (delete stricken text and add text in underline) to add at the beginning of this section: "~~If an automatic used test strip recognition function has not been incorporated into the design of the blood glucose meter, y~~ You should submit flex study results demonstrating that the insertion of used strips for glucose testing generates an appropriate error code to the user. In your submission you should provide the study protocol, acceptance criteria and results."	For better clarification. If there is no recognition, a built-in error code will not be generated.
114.	VII	1012-1060	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.

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115.	IX	1085-1089	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.
116.	IX	1091	You must include the intended use of the product. 21 CFR 809.10(a)(2) and 21 CFR809.10(b)(2). You should specify that the device is for ~~prescription use~~ POC testing.	Given comment above, if prescription use is changed, this requirement needs to be consistent.
117.	IX	1105	Revise as follows (delete stricken text and add text in underline): "Labeling should include testing conditions that may cause clinically significant errors (due to bias or imprecision) with your device (e.g., specific drugs, oxygen therapy, testing with venous, arterial, or neonatal blood~~, high altitude,~~ peritoneal dialysis therapy or EMC interference). Sponsors should indicate the most extreme conditions (e.g., highest ~~altitude~~ Uric Acid level) at which the device should be used based on the results of performance testing. "	Altitude sensitivity is no longer a concern for modern SMBG systems, so using altitude as an example is not appropriate.
118.	IX	1140	Revise as follows (delete stricken text): "We recommend the following types of presentations to represent the results of your accuracy studies ~~in user manuals and~~ package inserts."	This is appropriate to show accuracy and precision data in the package strip insert, particularly as a new meter may not be introduced with every new strip.
119.	IX	1146	Change laboratory method to reference laboratory method.	Consistency correction
120.	IX	1147	Change 2nd reference to "YSI" to "[reference device]" Place brackets around XYZ.	Clarification
121.	IX	1151	Row 1: add ABC before Laboratory. Row 2: add reference after ABC.	Clarification and consistency corrections
122.	IX	1154	Same comments as for line 1151.	Clarification and consistency corrections
123.	IX-11	1166	Revise as follows (delete stricken text and add text in underline): "Labeling must include statements of warning or precautions as appropriate to the hazard presented by the product ~~on the outer container and the insert~~. 21 CFR 809.10(b)(5)(ii), and 21 CFR	There are several safety warnings provided in the meter user guides that will not all fit on outer container and inserts.

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			809.10(a)(4).”	It is possible to include key warnings such as biohazard warning on the outer container.
124.	IX-12	1207 et seq.	Difference between “cleaning” and “disinfection”	Similar to earlier comment, can these (C&D) be the same, especially if the same agent is used?
125.	IX-12	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.”	The contact information can be provided very prominently in the back of the book and referred to by multiple sections of the meter user guide. Then there is always consistency so the customer always knows where to look for information instead of hunting if they are not following the UG page-by-page.
126.	Appendix 1	1250	Remove the following reference: “Failure to contact physician when necessary (OTC)”	Remove this bullet. Only applies to OTC.
127.	Appendix 1	1250	Interference from ~~other sugars~~ <u>exogenous substances</u> (e.g., maltose intravenous solutions)	Better to align wording with ISO 15197 and wording used elsewhere in this Guidance document.

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128.	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.