24 October 2016

*Medical Device Alert

On October 11, 2016, the U.S. Food and Drug Administration (FDA) issued two final guidance documents describing studies and criteria that FDA recommends when submitting premarket notifications (510(k) Notices) for blood glucose monitoring systems (BGMSs). One guidance document addresses BGMSs for prescription point-of-care use by healthcare professionals (BGMS Guidance)\(^1\), while the other focuses on self-monitoring blood glucose test systems (SMBGs) intended for over-the-counter home use (SMBG Guidance)\(^2\). The guidance documents were previously issued in draft form for public comment on January 7, 2014.

While the Agency historically placed similar requirements on the two types of glucose meters, FDA notes that it has become clear that the two user groups (health professionals and patients) have different needs that can impact device design considerations. Therefore, the Agency issued separate documents allowing manufactures to take these unique needs into account when designing their devices. For example, FDA notes that under the existing regulatory scheme, BGMSs used in professional healthcare settings have not been adequately evaluated in some of the populations in which they are being used (e.g., complex physiological and pathological factors). Therefore, FDA lays out different considerations and performance criteria for devices used in different settings. This kind of risk-based approach to requiring different performance characteristics depending on use environment may appear counterintuitive, but FDA has a long history of tailoring regulatory requirements to reflect unique, specific intended uses and differentiating them from the requirements that may apply in other, general, or less risky environments or indications.

Importantly, neither guidance applies to devices used to screen and diagnose diabetes (such as clinical chemistry analyzers), implanted or external continuous glucose sensors (e.g., continuous glucose monitoring systems (CGMs) or sensors within catheters), or non-invasive glucose measurement devices.

**CLIA Waiver for Prescription Use Meters**

510(k) clearance for SMBGs intended for OTC home use allows automatic Clinical Laboratory Improvement Amendments (CLIA) waived categorization.\(^3\) However, FDA expects that clearance
of BGMSs as prescription use devices intended for point-of-care use in professional healthcare settings will be categorized as moderate complexity, thus requiring application for CLIA waiver to use them in clinics. To facilitate a CLIA waiver for such devices, FDA has proposed several studies in the BGMS Guidance that can support dual 510(k)/CLIA waiver submission or an associated application for CLIA waiver concurrently with 510(k) clearance. FDA recommends that sponsors of BGMSs used in professional healthcare settings should design their studies with CLIA-waiver in mind.

**Performance Evaluation**

The most notable aspect of both guidance documents is FDA's determination that the criteria set forth in the ISO 15197 (*In vitro diagnostic test systems—Requirements for blood glucose monitoring systems for self-testing in managing diabetes mellitus*) do not adequately protect patients using BGMSs in professional settings or SMBGs. Thus, sponsors are now advised to rely on the criteria in FDA's guidance documents instead of the ISO standard.

FDA recommends that sponsors design a performance study to accurately evaluate system performance in the hands of the intended user and in conditions that are consistent with the validated environmental conditions of the device (e.g., temperature, humidity, altitude, etc.) Both guidance documents emphasize use of method comparison studies (i.e., comparison to a laboratory-based glucose measurement method that has been well-validated for precision and accuracy.)

Specifically, for BGMSs used in professional settings, the device accuracy should be evaluated for each claimed sample type (e.g., arterial, venous, capillary, heelstick whole blood, etc.) when the device is used by a point-of-care (POC) operator (e.g., nurses, nurse assistants, etc.). Evaluation of each sample type should include a minimum of 350 patients and should be evaluated by at least 9 POC operators. For SMBGs, FDA recommends including a minimum of 350 patients for each anatomical site (e.g., finger, forearm, palm, etc.).

For each claimed sample type or anatomical site, FDA recommends that samples span the claimed glucose measuring range of the device. Studies for BGMSs used by health professionals should include at least 10 unaltered samples < 80 mg/dL and at least 10 unaltered samples between 300 mg/dL and the upper limit of the claimed range. Similarly, at least 10 unaltered samples < 80 mg/dL and at least 10 unaltered samples between 250 mg/dL and the upper limit of the claimed range should be included in studies for SMBGs.

The subjects enrolled in method comparison/user evaluation study should reflect the intended use population of your device, such as vulnerable sub-populations in BGMS studies, and naïve as well as non-naïve users in SMBG studies. In addition, both guidances recommend including a minimum of 10 test strip vials or packages from at least 3 test strip lots that have undergone typical shipping and handling conditions.
Table 1 below summarizes the criteria set in the guidances for demonstrating that a device is sufficiently accurate, in comparison to the draft guidances. The percentage values represent samples for which the difference between the device and the laboratory comparator method were within the difference range. When the draft guidances were issued in 2014, they stirred substantial controversy with the heightened accuracy requirements. While the patient community has praised FDA for going beyond the international standards, there was pushback from industry and clinicians that such stringent criteria could increase the regulatory burden and costs of these monitors. As shown below, in the finalized guidances, the criteria for BGMSs used by health professionals are lowered compared to those in the draft guidance. The criteria for SMBGs remain unchanged from the draft guidance. FDA also recommends including the accuracy data in the device labeling.

<table>
<thead>
<tr>
<th>BGMS for Prescription POC Use</th>
<th>2016 Final Guidelines</th>
<th>2014 Draft Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose Concentrations</td>
<td>Criteria</td>
<td>Glucose Concentrations</td>
</tr>
<tr>
<td>≥ 75 mg/dL</td>
<td>95% within ± 12%</td>
<td>≥ 70 mg/dL</td>
</tr>
<tr>
<td></td>
<td>98% within ± 15%</td>
<td>99% within ± 10%</td>
</tr>
<tr>
<td>&lt; 75 mg/dL</td>
<td>95% within ± 12 mg/dL</td>
<td>&lt; 70 mg/dL</td>
</tr>
<tr>
<td></td>
<td>98% within ± 15 mg/dL</td>
<td>99% within ± 7 mg/dL</td>
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<table>
<thead>
<tr>
<th>SMBG for OTC Use</th>
<th>2016 Final Guidelines</th>
<th>2014 Draft Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire claimed range</td>
<td>95% within ± 15%</td>
<td>Entire claimed range</td>
</tr>
<tr>
<td></td>
<td>99% within ± 20%</td>
<td>99% within ± 15%</td>
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<td></td>
<td>99% within ± 20%</td>
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</table>

In addition to the comparison/user evaluation study, both guidance documents include similar recommendations related to studies evaluating precision, linearity, and interference. Moreover, FDA recommends conducting flex studies that stress the operational boundaries of the device to validate the insensitivity of the test system to performance variation under stress conditions. The flex studies include test strip stability testing, system operating conditions testing, attitude effects, error codes for samples outside the measuring range, short sample detection, sample perturbation study, intermittent sampling, and testing with used test strips.

**Cleaning and Infection Control**

Both guidances address the issue of infection control, as the Centers for Medicare and Medicaid Services (CMS) and the Centers for Disease Control and Prevention (CDC) revealed concerns that blood glucose meters and lancing devices can transmit blood borne pathogens if these devices are contaminated with blood specimens and shared between users without effective cleaning, disinfecting, and appropriate infection control measures. Therefore, FDA recommends conducting validation of cleaning and disinfection procedures as well as studies demonstrating that the device is robust after multiple cleaning and disinfection cycles.

In addition, FDA describes in the two guidances specific labeling requirements with respect to the risk of infection. Specifically, labeling of BGMSs for prescription POC use should contain detailed instructions on how to perform cleaning and disinfection procedures between patients,
while labeling for OTC SMBGs should contain a warning that the meter and lancing device are for single patient use only.

**Summary**

Although not legally binding, manufacturers should use the two guidance documents as models for conducting appropriate performance studies and preparing 510(k) premarket notifications for their blood glucose meters. Although the two guidances share many specific recommendations, FDA has outlined different characteristics between BGMS and SMBG devices that should be taken into account for study design and performance criteria for the contrasting environments in which these devices are used.


3 Per 42 U.S.C. § 263a(d)(3), laboratory examinations and procedures that are approved by FDA for home use are automatically waived from CLIA requirements.

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