February 28, 2019

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

Re: Docket No. FDA-2013-D-1445; Draft Guidance for Industry and FDA Staff on Blood Glucose Monitoring Test Systems for Prescription Point-of-Care Use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(AdvaMed), we respectfully submit these comments in response to the Food and Drug Administration’s (FDA’s or Agency’s) Draft Guidance for Industry and FDA Staff: “Blood Glucose Monitoring Test Systems for Prescription Point-of-Care Use” (hereinafter POC BGM Draft Guidance).

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

GENERAL COMMENTS

AdvaMedDx appreciates FDA’s issuance of this draft guidance, which we believe will support accuracy and reliability of blood glucose monitoring test systems while also providing for innovation and continued investment in new technology. Blood glucose monitoring test systems play an important role in managing diabetes in healthcare and assisted-use environments at the point of care, as well as in patients’ homes. We are committed to high-quality, accurate blood glucose monitoring test systems.

This draft guidance document provides recommendations to industry about the types of information to include in their premarket submissions for blood glucose monitoring systems used for diabetes management in the POC setting. This draft guidance provides important

1 AdvaMedDx also is providing comments to the counterpart draft guidance “Draft Guidance for Industry and FDA Staff on Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use”
clarifications, including ones regarding study design considerations and labeling. These proposed clarifications are important to ensuring access and innovation and are consistent with FDA’s key recommendations regarding means to support accurate, high-quality blood glucose meters.

AdvaMedDx appreciates the draft guidance and the opportunity to provide our comments. Our comments are intended to support FDA’s efforts to ensure access to safe and effective meters that meet individual needs while encouraging advancements and development of new technology. We identify in our specific comments a few areas within this draft guidance where we believe additional clarification would be helpful to achieve our shared goals. We provide in those specific comments accompanying recommendations to assist FDA.

Respectfully submitted,

/s/

Jamie Wolszon
Associate Vice President
Technology and Regulatory Affairs
**ADVA MED DX COMMENTS ON**

*Blood Glucose Monitoring Test Systems for Prescription Point-of-Care Use; Draft Guidance for Industry and Food and Drug Administration Staff*

Additions indicated in underline.
Deletions indicated in strikethrough.

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<td>1</td>
<td>723, Table 4, Hemoglobin</td>
<td>1000 g/dL, mg/dL</td>
<td>We believe that the proposed hemoglobin testing concentration is a typographical error. Our proposed hemoglobin testing concentration of 1000 mg/dL is reflected in Table 2 of Clinical &amp; Laboratory Standards Institute (CLSI) EP37: Supplemental Tables for Interference Testing in Clinical Chemistry, 1st Edition (FDA Recognition # 7-284). The Supplemental Tables provide recommended interference testing concentrations and are intended for use with the evaluation procedures in CLSI EP07: Interference Testing in Clinical Chemistry, 3rd Edition (FDA Recognition # 7-275).</td>
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<td>2</td>
<td>723, Table 4, Sodium</td>
<td>170 480 mmol/L</td>
<td>We appreciate that FDA selected a single value at an upper limit as opposed to a range. We agree that an assessment at an upper limit is appropriate, due to the variability of endogenous sodium in the population and its importance in fluid composition. However, we would propose an upper limit of 170 mmol/L. Our proposed level is aligned with the most recent edition of Tietz, widely recognized as the foremost reference for clinical chemistry, Table 2 of CLSI EP37 and other major publications. In our survey of the literature and major publications (e.g., Tietz, and Table 2 of CLSI EP37, we have found an upper limit of 170 mmol/L more than capable of covering the upper range for the vast majority of the population. We believe an upper limit of 180 mmol/L would be well above what the literature demonstrates to be an already very high range associated with poor outcomes.</td>
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<td>Tietz’s Clinical Chemistry cites a National Health and Nutrition Examination Survey III (NHANES III) that concluded that the 95% central range is 136 to 146 mmol/L with hypernatremia being defined as sodium &gt;150 mmol/L. Table 2 of CLSI EP37 also sets an upper limit for testing at 170 mmol/L, a much higher concentration than most patients already in severe hypernatremia. In a separate survey of Intensive Care Unit patients, the cutoff for defining hypernatremia was typically 150 mmol/L, in which mortality rates were high and vary between 30 to 48% for those &gt;150 mmol/L. Another publication, analyzing 151,486 ICU patients over 10 years, showed that in this group, only 0.6% (~1,000) had severe hypernatremia, defined as a concentration greater than 155 mmol/L. The percentage in this publication reflects that only an extremely small portion of the population would have this high of a sodium level. Furthermore, a vaccine trial recommendation document by the U.S. Department of Health and Human Services, already defined a threshold of &gt;150 mmol/L as potentially life-threatening. These sources suggest that values in the 150 to 155 mmol/L range are rare and considered life-threatening, making values in the 170-180 mmol/L range even less frequent. More studies continue to analyze different patient populations admitted to hospitals, both Emergency Room and non-Emergency Room, and most of those studies define hypernatremia and/or severe hypernatremia at &gt;149 mmol/L, typically accompanied by a comorbidity (e.g., cancer). Within one of these studies, the maximum sodium concentration</td>
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measured was 160 mmol/L. Even at these concentrations, mortality rates were roughly double compared to the non-hypernatremia population. Another study found that for a specific hospital population, with a range of initial sodium levels of 160 +/- 10 mmol/L, the mortality rate of many patients occurred with concentrations as low as 149 and up to 157 mmol/L. These sources all support that ranges above 170 mmol/L are highly unusual and generally linked to extreme circumstances (e.g., a child’s exposure to rock salt) or severe illness (e.g., cancer).

Based on the clinical presentation and course of treatment, it is very unlikely that a health care provider caring for a patient having plasma sodium of 180 mm/L would even be testing the patient’s blood glucose; rather, symptoms would be present requiring urgent medical attention involving intravenous fluid therapy (to prevent shock) and even dialysis. Therefore, AdvaMedDx recommends reducing this interference testing concentration to 170 mmol/L. Clinical presentation of patients with severe hypernatremia include lethargy, confusion, nystagmus, seizures, myoclonic jerks, and as discussed in the referenced studies, even death. Hypernatremia can cause cerebral contraction, resulting in vascular rupture and intracranial bleeding. The level of consciousness is correlated with the severity of hypernatremia. Severe symptoms are likely to occur with acute increases in plasma sodium levels or at concentrations greater than 160 mmol/l which is also associated with high mortality of >60%.

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<td>3</td>
<td>289-292</td>
<td>You should evaluate the accuracy of the meter using blood samples compared to results per the pre-defined acceptance criteria obtained by a comparator method (please refer to Section VI below) to ensure that accuracy is not affected by repeated cleaning and disinfection.</td>
<td>Clarifying edit. We agree with FDA that disinfection robustness is necessary to ensure that the system performance is not compromised. Since the performance is evaluated using laboratory samples using a comparator method, it would significantly benefit the reader of the guidance to understand performance expectations. Therefore, we propose adding the words “per pre-defined acceptance criteria,” which is specified in section VI.</td>
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<td>4</td>
<td>1135-45</td>
<td>None proposed</td>
<td>We understand that FDA believes it is important to have information regarding test strip lot release criteria in the premarket submissions for these products. Lot release is fundamentally a post-market function conducted under quality system regulations to assure manufacturing specifications have been met and FDA should take care before applying lot release in other premarket scenarios.</td>
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<td>5</td>
<td>145-50</td>
<td>This document is <strong>not</strong> meant to address the following types of devices: Devices used to screen for and/or to diagnose diabetes (such as clinical chemistry analyzers, including handheld glucose chemistry analyzers).</td>
<td>We appreciate the inclusion of the existing language in the guidance. We nonetheless seek additional language explicitly clarifying our understanding that FDA does not intend for the BGM POC guidance to apply to handheld POC glucose chemistry analyzers intended for screening and/or diagnosis. We seek this clarifying language because handheld POC glucose chemistry analyzers intended for screening share a product code with BGMs (LBF); however, handheld POC glucose chemistry analyzers are intended for screening and not monitoring.</td>
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