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Re: Docket No. FDA-2013-D-1446; Draft Guidance for Industry and FDA Staff on Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use

February 28, 2019

Dear Sir/Madame:

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(AdvaMed), we respectfully submit these comments in response to the Food and Drug Administration’s (FDA’s or Agency’s) Draft Guidance for Industry and FDA Staff: “Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use” (hereinafter SMBG Draft Guidance).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AdvaMedDx appreciates FDA’s issuance of this draft guidance, which we believe will support accurate, reliable blood glucose monitoring test systems while also providing for innovation and continued investment in new technology. SMBG test systems play an important role in helping patients manage their diabetes. We are committed to high-quality, accurate SMBG test systems.

This draft guidance document provides recommendations to industry about the studies and criteria to include in premarket submissions for SMBG test systems used for diabetes management in the home setting. This draft guidance provides important clarifications,

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2 AdvaMedDx also is providing comments to the counterpart draft guidance “Blood Glucose Monitoring Test Systems for Prescription Point-of-Care Use; Draft Guidance for Industry and Food and Drug Administration Staff.”
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, reliable 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AdvaMedDx appreciates the draft guidance and the opportunity to provide our comments.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**

Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use; Draft Guidance for Industry and Food and Drug Administration Staff

Line No. – Guidance line number  
Change – Proposed change to the guidance  
Comment/Rationale – Reason for proposed change

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<td>1</td>
<td>610, Table 3, 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>610, Table 3, Sodium</td>
<td>170 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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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 >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 >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 >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 >149 mmol/L, typically accompanied by a comorbidity (e.g., cancer). Within one of these studies, the maximum sodium concentration measured was 160 mmol/L. Even at these concentrations, mortality rates were roughly double compared to the

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|                |               |        | non-hypertremia 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 patient having plasma sodium of 180 mm/L would even be testing their own 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 hypertremia include lethargy, confusion, nystagmus, seizures, myoclonic jerks, and as discussed in the referenced studies, even death. Hypertremia can cause cerebral contraction, resulting in vascular rupture and intracranial bleeding. The level of consciousness is correlated with the severity of hypertremia. 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%.

For the reasons discussed above, AdvaMed recommends revising the interference testing concentration for sodium to 170 mmol/L.

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<td>3</td>
<td>222-25</td>
<td>You should evaluate the accuracy of the meter using blood samples compared to results <strong>per the pre-defined acceptance criteria</strong> obtained by a comparator method (please refer to Section VI below for the definition of comparator method) to ensure that accuracy is not affected by repeated cleaning and disinfection.</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>1040-53</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>1214-15</td>
<td>Accuracy information should also be included on the SMBG outer meter box labeling, as well as in the test strip package inserts and meter user manual. Test strip package inserts should refer the user to the meter user manual for accuracy information.</td>
<td>We appreciate that FDA is not recommending inclusion of the accuracy information on the outer packaging of the test strip. We also agree with presenting the accuracy information in the user manuals of the meters. However, instead of recommending that the test strip package insert contain the information, we would propose that the test strip package insert refer to the meter user manual, which would include the information. We believe that recommending the accuracy information on the test strip package insert would lead to complex presentation (potential patient confusion), particularly for strips that can be used with multiple meters. We believe that our proposal would allow patients to easily access the information in a clear manner. Our proposal would also facilitate changes to accommodate the addition of a meter.</td>
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