CLOSER LOOK

MEMORANDUM

FDA publishes final guidance updating SMBG, point-of-care BGM accuracy and study requirements; SMBG accuracy unchanged from draft, POC loosened - October 11, 2016

Executive Highlights

- The FDA has finalized guidances updating SMBG (home use) and point-of-care (healthcare facilities) BGM accuracy and study requirements.
- The SMBG final guidance has retained the same accuracy standards first shared in the 2014 draft: 95% of results should be within ±15% of the comparator across the entire claimed measuring range. Additionally, 99% of results should be within ±20% of the comparator method across the entire claimed measuring range.
- The point-of-care final guidance has significantly loosened the 2014 draft accuracy standards: 95% of results should be within ±12% of the comparator method (>75 mg/dl) and within ±12 mg/dl (<75 mg/dl). Additionally, 98% of values should be within ±15% (>75 mg/dl) and ±15 mg/dl (<75 mg/dl) of the comparator method.
- We see the part specifically about tighter accuracy on the SMBG side and study requirements as a positive for patients and HCPs, who can be more assured that the approved accuracy is what they will see in real-world use. We assume established industry players were largely expecting the SMBG guidance, though we believe it will have a further negative impact on innovation. As one expert told us, "the law of unintended consequences may prevail." The looser POC guidance is good news (relative to previous draft guidance) and very appropriate and positive for balancing better performance with continued innovation.
- The guidances only apply to pre-market submissions (new meters), meaning other efforts will be needed to address poorly performing, already-cleared meters. We expect it will take several years before the field's overall BGM accuracy rises. We don't expect these guidances to impact the challenging and price-sensitive payer landscape near-term. But they are just something else that adds to the extreme difficulty of the environment.

The FDA just posted long-awaited final guidances updating SMBG (home use) and point-of-care (healthcare facilities) BGM accuracy and study requirements. These follow the draft guidances released back in January 2014 (34 months ago!) that garnered hundreds of patient comments and some critical industry feedback.

The SMBG final guidance has retained the same tighter accuracy standards first shared in the 2014 draft: 95% of all measured SMBG results should be within ±15% of the comparator (across the entire claimed measuring range), including 99% of all measured results within ±20%. The new standards are noticeably tighter than the 2013 ISO standards (see table below) in hypoglycemia. We're glad to see the FDA focus on this, though some are not convinced the tighter hypoglycemia accuracy is clinically significant. The Agency does recognize that being within ±15% is difficult at very low glucose concentrations, and meters are allowed to restrict the measurement range (e.g., 50-400 mg/dl) and provide an appropriate error code (e.g., "LOW - Less than 50 mg/dl").

The point-of-care final guidance has significantly loosened the accuracy standards first shared in the draft. Now, 95% of measured values should be within ±12% (≥75 mg/dl) and ±12 mg/dl (<75 mg/dl) of the comparator method. Additionally, 98% of values should be within ±15% (≥75 mg/dl) and ±15 mg/dl (<75 mg/dl) of the comparator method. We're glad to see the FDA incorporated feedback on this front, since

many, including us, felt the draft expectations were far from appropriate (99% within ±10%/±7 mg/dl; 100% within ±20%/±15 mg/dl - no outliers!). These new standards are very much in line with the 2013 CLSI standards (see below).

One thing seems clear to us from these final guidances - the bar is certainly now higher for new BGM devices to secure clearance, which means smaller players may have a harder time getting products through the FDA - we imagine this was by design and we're very glad to see this. A cleared system needs more robust accuracy assessment (n=350 users), disinfectant efficacy data (hepatitis B), and other studies (e.g., interferences, environment), which raises the barriers to entry for any new device.

The tighter accuracy and study requirements are a positive for patients and HCPs in one sense, who can have more confidence that new meters will be more accurate for dosing insulin, calibrating a CGM, identifying hypoglycemia, and making decisions. The guidance even emphasizes that accuracy labeling should be more prominent (see picture below), a plus for helping patients choose between different products. That said, already-cleared meters will not need to meet these criteria (e.g., with a resubmission), meaning it will take several years for the field's overall accuracy to rise as older meters are phased out. Dr. Lias shared with us that the Agency is concerned about the quality of all meters currently on the market, but other efforts will be needed to make changes.

BGMs also won't have an insulin-dosing claim, a conundrum as Dexcom's G5 and presumably Abbott's FreeStyle Libre seek one. We wonder if BGMs that don't meet the accuracy bar will be explicitly labeled NOT for dosing insulin.

It will be most interesting to see what impact these standards have on the struggling BGM industry. The field has had extremely weak results in the wake of competitive bidding (see our 1H16 Roundup), and we wonder if these tighter FDA standards will further negatively impact the cadence of new products going forward. Those in industry we talked to seemed to think so (both for established players and startups seeking funding). In searching the FDA 510(k) database, there is no question that innovation has dropped over the past few years: from a high of 61 FDA 510(k) BGM clearances in 2012, the field saw just 35 in 2015 and only 17 thus far in 2016. Stronger accuracy requirements are a positive, but it does come at a tough time in the field.

- **From what we can see, the FDA has mostly made small changes from the draft guidances - e.g., moving a few sections around, changing certain data formatting in tables, etc.** We were glad to see a few more meaningful changes like expanding certain specific cutoffs to ranges. Aside from the big point-of-care accuracy change, however, the guidances look very similar to the drafts, including an entire section on lot release criteria (debated in some industry comments but retained in the final form - this is one area that will add significant expense) and a focus on reducing the risk of blood pathogen transmission.
- **We don't expect these standards will impact payers near-term, who are laser focused on cost and equate FDA clearance with "good enough." Continued payer pressure will likely still push many (not all) patients towards already-cleared, lower-cost meters.** While it's a positive for *new* meters that have to meet the higher accuracy standards, those that were cleared under the looser previous guidance will still be reimbursed and used by patients unless the FDA takes action (e.g., removing them from the market, changing labeling, etc. - we wish they would do that for some). We know this is an FDA concern, but the Agency is constrained in what it can do with the tools at its disposal and with its limited resources.
- **Like a number of experts, we believe that the market for BGM in type 1 is likely to shrink over the next few years, as the most intensive patients switch to CGM and automated insulin delivery.** This will constrain much of the remaining BGM market to patients with type 1 who monitor glucose less frequently and type 2s (many of whom are price limited by CMS' competitive bidding or who are switching to less hypoglycemia-causing agents). It's a tough time in BGM and the trends are not in the field's favor.

- **What's the impact on BGM innovation, particularly from smaller players in need of funding?** Said one expert to us, "The law of unintended consequences may prevail here." As we understand it, the investment community is looking less and less favorably at BGM, which makes raising money challenging for innovative small companies. Meanwhile, companies outside the US will continue to use ISO 15197 (2013) and may not be able to meet the FDA standards at lower glucose levels. For these players, the market incentives may not exist to meet the FDA's more accurate standards, leading to less innovation in US BGM.
- **A look at the FDA 510(k) database shows that many smaller players have gotten SMBG devices cleared this year, but the new guidance has not applied to them.** FDA-cleared meters in recent months include Infopia, iHealth/Andon, and Prodigy. However, Dr. Courtney Lias told us that the FDA has not been applying the draft guidances in its recent reviews, even though some manufacturers (e.g., Roche's Accu-Chek Guide) have chosen to perform their studies in line with the new guidance (draft at the time, now finalized). We'll be interested to see how the pace of clearances from smaller players changes in the coming months and years, given the higher FDA bar.

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New FDA Accuracy Requirements vs. ISO (2013, 2003) and CLSI

SMBG (home use)		
	Overall	**Outliers**
FDA 2016	95% within ±15% of the comparator method across the entire claimed measuring range	99% of all measured SMBG results within ±20% of the comparator method across the entire claimed measuring range
ISO 2013	95% within ±15 mg/dl of reference (<100 mg/dl) or within ±15% (≥100 mg/dl)	99% of measured SMBG values must be within zones A and B of the Consensus Error Grid (CEG) for type 1 diabetes.
ISO 2003 (previous FDA standard)	95% within ±15 mg/dl (<75 mg/dl) and within ±20% (≥75 mg/dl).	None

Point-of-Care BGM Devices (healthcare facilities)		
	Overall	**Outliers**
FDA 2016	95% within ±12% (>75 mg/dl) and ±12 mg/dl (<75 mg/dl) of the comparator method	98% within ±15% (>75 mg/dl) and ±15 mg/dl (<75 mg/dl) of the comparator method.

CLSI 2013	95% within ±12.5% (≥100 mg/dl) or within ±12 mg/dl of reference (<100 mg/dl.	98% of measurements must meet the old CLSI criteria.

- **Relative to ISO, the FDA has tightened down on hypoglycemia, requiring ±15% accuracy for SMBG devices across the entire glucose range. At a glucose level of 50 mg/dl, this means the meter can be off by just 7.5 mg/dl vs. ISO's limit of 15 mg/dl.** We commend the FDA for focusing on hypoglycemia accuracy, though some would argue there is a tradeoff: the clinical difference between FDA vs. ISO hypoglycemia thresholds may be minimal, but the innovation bar may rise considerably. Some might ask - would a patient treat a 40 vs. 50 vs. 60 mg/dl much differently? We're asking Richard Wood at dQ&A, the diabetes market research company, this same question.
    - **We wonder if new meters will begin restricting their measurement range** and displaying error messages like "LOW - Less than 50 mg/dl", which would allow companies to get a product cleared even if it doesn't meet ±15% in all hypoglycemia bins.
- **We like that the FDA's percent-only error approach is much easier to read and understand for patients relative to the ISO standard,** which mixes percentage, absolute numbers in mg/dl, and an error grid.
- **BGMs will still have an indicated use that does not include dosing insulin:** "The XYZ Blood Glucose Monitoring System is intended for use in the quantitative measurement of glucose in capillary whole blood from the finger. It is intended for use by people with diabetes mellitus at home as an aid in monitoring the effectiveness of a diabetes control program." We think this is unfortunate since everyone knows that millions of patients use these products to dose insulin.
- **The guidances do not apply to CGM directly, though we believe more accurate BGMs used for calibration would improve real-world CGM accuracy.** We've heard that some Medicare patients paying for their own CGMs out of pocket are using cheaper off-shore meters for calibration. In our view, moving better BGM accuracy forward will hopefully improve real-world MARDs to what they should be, especially for these patients using less accurate meters for calibration. Of course, these new standards won't improve the accuracy of grandfathered devices, which is a concern for years to come.
    - **This guidance may also impact the world of artificial pancreas for the same reason** - better accuracy for CGM, and thus, more accurate automated insulin delivery. We'd note that the only approved AID device, Medtronic's MiniMed 670G, is approved for use with Bayer's very accurate Contour Next Link meter.
- **Both guidances have some carve-outs if results do not fall within the above standards.** These suggest that the standards may not be black-and-white rules but interpreted in the context of a device's overall risk-benefit profile.
    - **SMBG Guidance: "FDA understands that some SMBG devices may not be able to measure reliably within 15% of the reference method at very low concentrations.** If this is the case, you may need to raise the lower end of the claimed measuring range to the concentration where your device is sufficiently accurate according to the above described criteria. We expect that to meet the clinical needs of the user population, SMBGs should minimally be able to measure blood glucose accurately between 50 mg/dL and 400 mg/dL, or a clinical justification should be provided for alternate measuring ranges. A SMBG should identify and provide an error code in situations where the measured glucose value falls outside of the device's stated measuring range. For example, meter XYZ has a measuring range that can detect glucose concentrations down to 50 mg/dL; therefore, blood samples with glucose concentrations below 50 mg/dL should provide an appropriate error code (e.g., "LOW - Less than 50 mg/dL")."

- **SMBG Guidance: "Though we expect that with the technologies available, SMBG devices will be able to meet this criteria, there may be instances where meters may be determined to be substantially equivalent even when performance does not meet these criteria** because, for example, other features of the meter or its setting of use provide benefits that compensate for different performance. For all SMBG test results that are >20% relative to the comparator method, you should provide a clinical justification for why the errors occurred and describe why the potential for that error does not affect user safety when extrapolated to the intended use setting (e.g., when billions of tests are performed). We will review any submitted justification to determine whether the data suggest that patients may be put at risk, or whether the justification and any proposed mitigation are adequate."
- **POC Guidance: "We expect that the measuring range of the meter will meet the clinical needs of the intended use population. BGMSs intended for prescription-use in the hospital setting should be able to measure blood glucose accurately down to 10 mg/dl and up to 500 mg/dl, or a clinical justification should be provided for alternate measuring ranges.** BGMSs intended for use outside a hospital setting and which will not reasonably be used to test neonatal samples should be able to measure blood glucose accurately down to 20 mg/dL. The BGMS device should identify and provide an error code in situations where the measured glucose level falls outside of the device's stated measuring range. For example, if BGMS XYZ has a measuring range that can detect glucose concentrations down to 10 mg/dL, then blood samples with glucose concentrations below 10 mg/dL should provide an appropriate error code (e.g., "LOW - Less than 10").
- **POC: "Though we expect that BGMSs will be able to meet this criteria, there may be instances where meters may be determined to be substantially equivalent when performance does not meet these criteria because,** for example, other features of the meter or its setting of use provide benefits that compensate for different performance. In instances where your BGMSs is unable to meet this criteria, you should provide a clinical justification for all test results, including those that exceed the above mentioned criteria, and describe why the potential for that error would not affect patient safety when extrapolated to the intended use setting (e.g., when extrapolated to the volume of testing performed in the intended use setting). FDA will review your justification to determine whether the data suggest that patients may be put at risk or whether your justification and any proposed mitigations are adequate."

SMBG Accuracy Labeling Examples

- **The SMBG guidance emphasizes the importance of clear, prominent labeling that allows users and HCPs to quickly understand a device's accuracy.** We're glad to see the guidance encourage the accuracy information on the outer box, which has not been done with meters and strips to date. It is very difficult to currently find a meter/strip's accuracy, since the data is buried well into the strip package insert and often not even included in the meter's user manual. We see this outer box labeling as a welcome change for SMBG users and HCPs.
- **The FDA recommends the following types of presentations to convey the results of SMBG accuracy studies:**

Suggested Representation of Accuracy for Home Use by Lay-Users - Example

Your ABC Meter result may vary slightly from your actual blood glucose value. This may be due to slight differences in technique and the natural variation in the test technology.

The chart below shows the results of a study where 350 typical users used the ABC meter to test their blood glucose level. For example, in this study, the ABC meter gave results within 15% of their true blood glucose level 340 out of 350 times.

Difference range between the true blood glucose level and the ABC meter result.	**Within 5 %**	**Within 10 %**	**Within 15 %**	**Within 20%**
The percent (and number) of meter results that match true blood glucose level within x%	57% (200/350)	94% (330/350)	97% (340/350)	100% (350/350)

Accurate Results	**350 out of 350 (100% of results)**
More Accurate Results	**262 out of 350 (75% of results)**
Most Accurate Results	**175 out of 350 (50% of results)**

Accuracy key	**Percentages listed are meter result as compared to laboratory result**
Accurate Results	Meter result is +/-15% of laboratory result
More Accurate Results	Meter result is +/-10% of laboratory result
Most Accurate Results	Meter result is +/-5% of laboratory result

Bloodborne Pathogen Transmission

- **A major focus of both guidances, similar to the drafts, is control of bloodborne pathogen transmission. This issue - an FDA and CDC focus - is discussed heavily throughout each document and has its own dedicated three-page section in each guidance (appearing before accuracy!).** Companies are expected to do disinfection efficacy studies to demonstrate effectiveness of a chosen disinfectant process against Hepatitis B virus. We're not sure exactly how much work this entails over current practices, but assume it is at least

meaningful. This issue is critical in the healthcare setting, as meters are typically shared among patients. In the SMBG home-use setting, few patients will actually disinfect their meters, but industry will need to do these studies anyways.

Close Concerns Questions

Q: How will these tighter accuracy requirements impact real-world use and safety of BGMs? Will patients and HCPs see better performance that more closely mimics FDA 510(k) data?

Q: How long will it be before the majority of meters in the field reach these higher accuracy standards? How will the FDA evaluate new meters that don't meet the standards - will they be cleared but with labeling caveats? Will the FDA eventually find a way to take poorly performing meters off the market?

Q: What is the impact of these standards on BGM innovation and the future of the field? Will big players carry on as usual and continue to mostly focus on non-accuracy enhancements to their BGMs (connectivity, dosing advice)? To what degree will smaller players be more impacted by these guidances? How much will the FDA be able to enforce with smaller players?

Q: What will BGM look like in 2020 vs. CGM? How long will it take (if ever) for most type 2s to transition to professional CGM and most type 1s to be on traditional CGM or CGM-enabled automated insulin delivery?

-- by Adam Brown and Kelly Close