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FDA/CDRH Webinar

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Final Guidance Documents: Self Monitoring Blood Glucose Systems for Over-the-Counter Use & Blood Glucose Monitoring Systems for Prescription Point-of-Care Use

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Acronyms

- SMBG – Self Monitoring Blood Glucose

- BGMS – Blood Glucose Monitoring System

- OTC – Over-the-Counter

- POC – Point-of-Care

User Populations

- Use at home by lay users (people affected by diabetes with no experience managing the device)

- Use in health care settings by health care professionals
  - Hospitals
  - Nursing homes
  - Physician's offices
  - Emergency Departments
  - Emergency Response Units

Intended User Population

- Glucose meters manufacturers historically sought clearance for OTC use

- Designed and validated for OTC use

- Increasingly clear that these different use settings comprise distinct intended use populations with unique characteristics

Glucose Meters

Glucose Meter final guidances published

Blood Glucose Monitoring Test Systems for Prescription Point-of-Care Use

...r Industry and ...Administration Staff

...d on: October 11, 2016.

...was issued on January 7, 2014.

Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use

Guidance for Industry and Food and Drug Administration Staff

Document issued on October 11, 2016.

The draft of this document was issued on January 7, 2014.

Draft Guidance
January 7, 2014

Final Guidance
October 7, 2016

Finalized Guidance Documents

- Self-Monitoring Blood Glucose for Over-the-Counter Use
  - For self-testing by home users
  - Meters for single patient use

- Blood Glucose Monitoring Systems for Prescription Point-of-Care Use
  - For assisted testing, in health care settings (e.g., hospitals, doctor's offices, long-term care facilities)
  - Meters for multiple patient use

Guidance Documents

- These guidance documents are:
  - A description of FDA's current thinking on the information manufacturers should submit to FDA for future glucose meter submissions

- These guidance documents are NOT:
  - Guidelines or rules for how hospitals, HCPs, or patients should use glucose meters
  - Rules for how laboratories should validate glucose meters

Finalized Guidance Documents

FDA

what's new?

- Most testing is unchanged from current submissions. However, the FDA modified the following:
  - *Accuracy*
  - *Interferences*
  - *Cleaning and Disinfection*
  - *Flex Studies*
  - *Test strip manufacturing lot release criteria*

Finalized Guidance Documents

what's new?

- A few changes/clarifications from the draft

  - *Clinical Laboratory Improvement Amendments (CLIA) clarifications*

  - *Performance goals*

  - *Interference testing protocol*

Blood Glucose Monitoring Test Systems for Prescription Point-of-Care Use (BGMS POC)

- Address only those systems intended for prescription POC use in professional health care settings

- Don't address those blood glucose monitoring systems intended for OTC use by people affected by diabetes at home

BGMS POC
Intended use setting

- Intended for POC use in professional health care settings

- Studied in the intended use populations and labeled appropriately

- Performance studies should account for factors such as disease state, patient condition, physiological state and medications that might affect device performance in the intended use population for that BGMS

- Identify sub-populations in which the BGMS may function differently than in the broader intended use population

Clinical Laboratory Improvement Amendments (CLIA) Waiver of professional use meters

- BGMSs cleared as prescription-use will not be automatically waived

- FDA recognizes the importance of CLIA-waived BGMs in point-of-care settings

CLIA Waiver of professional use meters

- User studies designed to simultaneously support both clearance and CLIA waiver
    - The recommended number of samples
    - Use of untrained intended users in a CLIA waived setting

BGMS POC Performance - *Accuracy*

- 350 patient samples spanning measuring range for each claimed sample type/matrix (e.g. arterial, venous, capillary whole blood)

  - Testing should be performed by the intended user (e.g., nurses, technicians)

  - Studies should be done in patients that accurately reflect the intended use population (e.g., neonatal, ambulatory, ICU patients, etc.)

- Additional 50 high (<80 mg/dL glucose) and 50 low (>300 mg/dL glucose) samples (may be contrived)

- Test strips used in studies should undergo typical shipping and handling conditions prior to use in the study

BGMS POC Performance - _Accuracy_

- Neonatal (<28 days old)

- 100 to 150 fresh neonatal capillary blood samples compared to reference

BGMS POC Accuracy

- FDA does not recognize ISO 15197:2013
- FDA guidances address some issues not addressed by ISO 15197:2013
  - Non-OTC use
  - Design features
  - Performance by intended user
  - Improved performance in hypoglycemic range

- FDA guidances describe studies designed to be compatible with ISO 15197:2013, but not identical

(guidance studies can be done to satisfy ISO, but not always vice-versa)

BGMS POC – _Accuracy Goals_

Changed slightly from draft

Draft Guidance	Final Guidance
99% within +/-10% $\geq$70mg/dL and within +/- 7 mg/dL <70mg/dL	95% within +/-12% $\geq$ 75 mg/dL and +/- 12 mg/dL <75 mg/dL
100% within +/- 20%	98% within +/- 15% $\geq$75 mg/dL and +/- 15 mg/dL <75 mg/dL

BGMS POC – _Accuracy Goals_

- Description of the study setting including the size, type and location

- Justifications for how the study conditions simulate intended use conditions

- Description of the shipping and handling conditions of the test strips prior to use in the study

- Outliers should be specifically addressed by manufacturers in the pre-market submission

BGMS POC Performance
Potential Interferences

- Should evaluate the effect of potentially interfering endogenous and exogenous substances and conditions (e.g. lipemia, common medications, varying hematocrit levels, ascorbic acid, dopamine, L-dopa, methyl-dopa, triglycerides, uric acid, xylose)

- Conduct a risk analysis to assess commonly used drugs in the intended use population

BGMS POC Performance
Potential Interferences

- Recommend a comparison between a test sample that contains the potential interferent measured on the candidate device vs. a control sample containing solvent/vehicle also measured on the candidate device

- **_The relative bias (mg/dL) and percent bias with 95 percent confidence intervals should be provided instead of using "non-interference" criteria_**

BGMS POC Performance
Potential Interferences

- Hematocrit
  - Span claimed hematocrit range, compare to comparator method, 3 test strip lots
  - Each meter replicate compared to the average of the comparator value.
  - Bias for samples with glucose $\geq$75 mg/dL should be less than 5 percent on average, no individual value greater than 10 percent
  - For samples with glucose <75 mg/dL the absolute bias (mg/dL) should be provided with 95 percent confidence intervals with a clinical justification
  - Minimum claimed range of 10-65 percent

BGMS POC Performance
Potential Interferences

- Oxygen
  - If intended to be used in patients with a broad range of blood oxygen levels study should be conducted to demonstrate the range of blood oxygen levels device can be used with
  - Supplement with blood oxygen levels of patients in Method Comparison/User Evaluation Study
  - If blood oxygen levels do not affect performance of device comprehensive justification should be provided supported by analysis of blood oxygen levels on device performance from Method Comparison/User Evaluation Study

Infection Control

- The majority of the infection control recommendations remained the same as what manufacturers are currently doing

- *Meters should be designed such that all external materials can be cleaned and disinfected – seams, test strip port, other ports*

- Validation studies differ mainly in the number of cleaning and disinfection cycles - should be representative of the amount of cleaning and disinfection that the meter will be exposed to in its use life (typically 3-5 year use life)

- Include validated cleaning and disinfection instructions in the labeling

BGMS POC Flex Studies

- Demonstrate that the BGMS device design is robust (e.g., insensitive to environmental and usage variation) and that all known sources of error are effectively controlled

- Design test systems to incorporate fail-safe mechanisms whenever technically practicable (e.g. lock-out functions)

Flex Study Examples

- Test strip stability testing Mechanical Vibration Testing
- Temperature and humidity effects
- Altitude effects
- Short sample detection
- Sample perturbation study
- Intermittent sampling

- Used test strips
- Mechanical Vibration Testing
- Shock testing
- Electromagnetic compatibility (EMC) Testing
- Electrostatic Discharge/Electromagnetic Interference Testing

Test Strip Lot Release Criteria

- **_Test strip lot release criteria will be reviewed as part of the submission_**

- Test strip lot release criteria should be sufficient to ensure consistent quality of the test strips
  - should be designed to ensure that all released lots conform to the labeled BGMS device performance in the hands of the intended user.
  - These criteria should be more stringent than the criteria used to evaluate total error in the performance studies.
  - Criteria to assure statistical confidence for full lot

- Manufacturers should provide a description of the lot release criteria and a summary of the sampling scheme in the pre-market submission

Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use (SMBG OTC)

- Meant to address only those blood glucose monitoring systems intended for use by people affected by diabetes at home

- Encompasses individuals with wide ranges in age, dexterity, vision, training received on performing testing, and other factors that can be critical in the patient's ability to accurately use the device and interpret test results

- SMBG systems (meters and associated test strips) should be designed to be robust and reliable to accommodate actual use by people affected by diabetes (e.g. more varied storage and handling conditions compared to devices used in professional settings

- Not meant to address blood glucose monitoring systems intended for use in prescription point-of-care settings

SMBG OTC Performance - _Accuracy_

- User evaluation – assess system accuracy in the hands of intended users, labeling assessment and usability

- Under conditions reflective of the expected use

- Minimum of 350 different subjects for each claimed sample type (e.g. fingerstick, palm, thigh)

- At least 10 percent of the participants should be low awareness of SMBGs, may include non-diabetic subjects

- Test strips should have undergone typical shipping and handling conditions prior to the study.

- Additional 50 high (>250 mg/dL glucose) and 50 low (<80 mg/dL glucose) samples (may be contrived)

SMBG OTC - _Accuracy Goal_

Not changed from draft

Draft Guidance	Final Guidance
95% within +/-15%	95% within +/- 15%
99% within +/- 20%	99% within +/- 20%

SMBG OTC - *Accuracy Goal*

- Outliers, results >20 percent relative to the comparator method, should be specifically addressed by providing a clinical justification for why the errors occurred and why the errors when extrapolated to the intended use setting do not affect user safety

- Claimed measuring range should minimally span 50 – 400 mg/dL glucose

SMBG OTC Performance
Potential Interferences

- Same study design as for BGMS – common endogenous and exogenous substances

  – Comparison between a test sample on the candidate device vs. a control sample on the candidate device

  – ***The relative bias (mg/dL) and percent bias with 95 percent confidence intervals should be provided instead of using "non-interference" criteria***

SMBG OTC Performance
Potential Interferences

- Hematocrit

  - Claimed hematocrit range of 20-60 percent (ideal)

  - Minimum claimed range 30-55 percent hematocrit

SMBG OTC – Infection Control

- Similar to BGMS guidance and not much different from what manufacturers are currently doing

- Validation studies differ mainly in the number of cleaning and disinfection cycles - should be representative of the amount of cleaning and disinfection that the meter will be exposed to in its use life (typically 3-5 year use life)

- ***Meters should be designed such that all external materials can be cleaned and disinfected – seams, test strip port, other ports***

- Include validated cleaning and disinfection instructions in the labeling

SMBG OTC Performance

- Flex studies

- Test strip manufacturing lot release criteria

SMBG OTC Labeling

SMBG labeling changes added for clarity

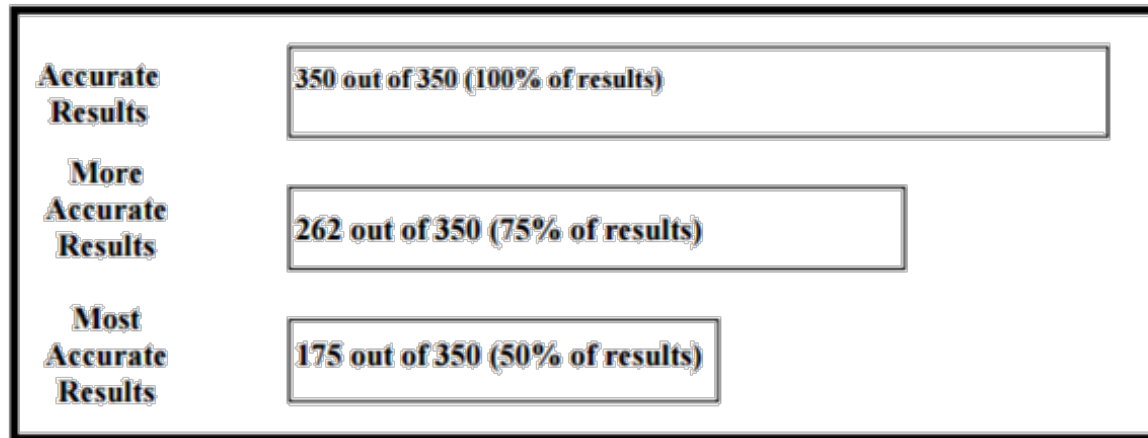Warning against use on multiple patients (due to risk of infection)

> *This device is not intended for use in health care or assisted-use settings such as hospitals, physician offices, or long-term care facilities because it   has   not   been cleared by FDA for use in these settings, including for routine assisted testing or as part of glycemic control procedures. Use of this device on multiple patients may lead to transmission of Human Immunodeficiency Virus (HIV), Hepatitis C Virus (HCV), Hepatitis B Virus HBV), or other bloodborne pathogens.*

SMBG OTC Labeling

- Accuracy information placed prominently in the labeling – on outer box label, test strip inserts and user manuals
  - Currently no way for users distinguish meters
  - Labeling aimed at allowing users and their health care professionals to ability to choose the best meter for their needs
  - Recommend data be presented in tabular format as well as graphically on the outer box
  - Examples are included in the guidance document

SMBG OTC Labeling

Outer box accuracy information to help patients choose the meter that is right for them:

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

Implementation

- Working with manufacturers on phasing in the guidance documents

Questions?

Division of Industry and Consumer Education:
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Slide Presentation, Transcript and Webinar Recording will be available at:

http://www.fda.gov/training/cdrhlearn

Under the heading: Specialty Topics; Sub-heading: Device Specific Topics