FDA Evaluation of Point of Care Blood Glucose Meters

Patricia Bernhardt, M.T.(ASCP), Scientific Reviewer

- Office of in Vitro Diagnostic Device Evaluation and Safety
- Center for Devices and Radiological Health

FDA Regulation of Medical Devices

- Federal Food, Drug, and Cosmetic Act (The Act)
- Medical Device Amendments of May 28, 1976
  - Risk based regulation by intended use
    - Class I - low risk, usually exempt from Premarket review
    - Class II - moderate risk, requires “substantial equivalence” to predicate device (510(k) clearance)
    - Class III – high risk and novel intended uses, require premarket approval (PMA)

What is an IVD?

"Reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae in man…. for use in the collection, preparation, and examination of specimens from the human body."

[21 CFR 809.3]

- Used in clinical laboratories
- Other settings (e.g., Point-of-Care/Over-the-Counter)
- FDA regulates IVDs by the intended use and risk of incorrect result
- All IVDs must establish adequate analytical and clinical performance
- Labeling (21 CFR 809.10)

FDA Evaluation of POC BGMS

- Class II device (moderate risk)
- Requires 510(k)
- substantial equivalence to predicate
- FDA evaluates intended use, performance, labeling

FDA Evaluation of POC BGMS

- Intended use - Quantitative measurement of glucose in whole blood by lay users at home or by healthcare professionals in clinical settings to assist in the ongoing evaluation and management of individuals with diabetes
- For monitoring
- Not for diagnosis or screening
- Currently no distinction between performance requirements for OTC and professional use

FDA Evaluation of POC BGMS

- System components
  - Meter
  - Test strips
  - Quality control solutions
  - Sometimes lancing devices, lancets and alcohol wipes

  - Each meter and test strip when used together is a “system”, requiring separate performance testing of that “system”, regardless of prior regulatory status of individual components

FDA Evaluation of POC BGMS

- Each sample type requires FDA review and clearance
  - Typically capillary whole blood from fingersticks
  - Some use arterial, venous, or neonatal
  - Alternative sites (AST) such as forearm, upper arm, palm, thigh, calf

FDA Evaluation of POC BGMS

- FDA Guidances

  Total Product Life Cycle for Portable Invasive Blood Glucose Monitoring Systems (1997)

  Points to Consider for Portable Blood Glucose monitoring Devices Intended for Bedside Use in the Neonate Nursery (1996)

  Guidance for Content of Pre Market Submissions for Software Contained in Medical Devices

- International Standards Organization (ISO) standard

  ISO 15197, In vitro diagnostic test systems -Requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus (2003)

- Clinical Laboratory Standards Institute (CLSI) guidelines

FDA Evaluation of POC BGMS

- Factors for evaluating BGMS performance
  - Precision
  - Accuracy
  - Linearity
  - Interferences
  - Environmental
  - Software
  - Cleaning/Disinfection
  - Labeling

BGMS Performance

- Precision
  - Repeatability
    - evaluate concentrations spread across measuring range (e.g. 30-50, 51-110, 111-150, 151-250, 251-400 mg/dL)
    - multiple meters, one day
    - mean, SD, CV for each meter
  - Intermediate
    - multiple meters, multiple days, multiple strip lots
    - usually control solutions

BGMS Performance

- Method Comparison
  - to recognized reference method (such as YSI)
    - well validated for precision and trueness
    - traceable to a recognized glucose standard (such as NIST Standard Reference Material)
  - minimum of 100 capillary samples
    - spanning measuring range

BGMS Performance

- Method comparison, continued
  - Evaluation of plots of subject device vs reference device
    - Bias plots
    - Regression analyses
    - Difference plots
  - Determine system accuracy

BGMS Performance

- Current FDA minimum acceptable system accuracy and accuracy in the hands of users
  - 95 % of individual glucose results shall fall within ± 15 mg/dL of the results of the reference measurement at glucose concentrations < 75 mg/dL
  - 95% of individual results shall fall within ± 20 % at glucose concentrations ≥75 mg/dL

Format for Presentation of Accuracy Data

Table 4 — Example of presentation of system accuracy results for glucose concentration < 4,2 mmol/L (75 mg/dL)

Within ± 0,28 mmol/L (Within ± 5 mg/dL)	Within ± 0,56 mmol/L (Within ± 10 mg/dL)	*Within ± 0,83 mmol/L (Within ± 15 mg/dL)*
18/40 (45 %)	28/40 (70 %)	*38/40 (95 %)*

Table 5 — Example of presentation of system accuracy results for glucose concentration ⩾ 4,2 mmol/L (75 mg/dL)

Within ± 5 %	Within ± 10 %	Within ± 15 %	*Within ± 20 %*
36/160 (22 %)	78/160 (49 %)	136/160 (85 %)	*156/160 (97 %)*

A recent evaluation of glucose meters cleared in last 2 years showed that approx. 72% would meet ± 10 mg/dL at <75 mg/dL and approx. 50% would meet ± 15% at ≥75 mg/dL

BGMS Performance

- User Performance
  - Evaluate whether intended users can operate and obtain correct results using only instructions to be provided when device is marketed
  - Lay users obtain and run own samples
  - Compare lay user results to reference
  - Questionnaire to assess understanding

BGMS Performance

- Alternative Site Testing
  - steady state
  - lay users obtain and run own samples
  - each claimed site compared to capillary finger on recognized reference (YSI)
  - meet minimum acceptable accuracy criteria
  - appropriate instructions and limitations in labeling

BGMS Performance

- Other sample types
  - Venous and arterial
    - matrix study - samples collected in anticoagulant
    - span measuring range
    - compare to reference
  - Neonatal
    - FDA guidance
    - 10-50 mg/dL glucose
    - 45-65% hct

BGMS Performance

- Linearity
  - CLSI EP6-A
  - multiple points across entire claimed measuring range
  - multiple replicates
  - line of regression
  - difference plots

BGMS Performance

- Interference
  - CLSI EP-7A
  - Common endogenous and exogenous
    - Hemolysis
    - Icterus
    - Lipemia
    - Sugars other than glucose
    - Common OTC substances
    - Frequently administered diabetes drugs

BGM Performance

- Interference, continued
  - Endogenous
    - Highest levels at which may occur
  - Exogenous
    - Therapeutic levels and highest levels at which toxic doses may occur
  - Samples representing clinical decision points
  - Typical bias ± 10%

  - Hematocrit
    - compared to normal Hct (~40%) and reference
    - Individual bias ± 15%

BGM Performance

- Other factors evaluated
  - Environmental effects
    - Temperature
    - Humidity
    - Altitude
  - Conformance to IEC Medical Electrical Equipment standards
  - Electromagnetic Compatibility
  - Software

FDA Evaluation of POC BGMS

- Labeling
  - User manual
  - Test strip insert
  - Quality control solutions insert
  - Quick Reference Guide, if applicable
  - Box and container labels
  - 21 CFR 809.10
    - OTC labeling at 8th grade reading level

FDA Evaluation of POC BGMS

- Cleaning/disinfection
  - Single or multi-patient
  - Protocol
  - Estimation of number of uses over life of meter
  - Robustness testing
    - Performance
    - Physical integrity of meter components
  - Disinfection effectiveness and validation

FDA Evaluation of POC BGMS

- Many factors affect BGMS
- Each factor currently evaluated separately
- User experiences cumulative effect

What happens when things go wrong??

Post-market signals and adverse reports

- FDA MedWatch Program
- MedSun Program
- Listserv
- Other signals

FDA Evaluation of POC BGMS

Total Product Life Cycle