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FDA Public Hearing on Clinical Accuracy Requirements for Point of Care Blood Glucose Meters (BGMs)

Barriers to Overcoming Interferences and Limitations

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On Behalf of AdvaMed

BRINGING INNOVATION TO PATIENT CARE WORLDWIDE

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AdvaMed Description



- AdvaMed is the world's largest association representing manufacturers of medical devices, diagnostic products, and medical information systems
- AdvaMed member companies produce the diagnostic products, medical devices, and health information systems that are transforming health care through earlier disease detection, less invasive procedures, and more effective treatments

BGM Innovations to Improving Overall Accuracy



- AdvaMed BGM manufacturers are committed to designing and manufacturing BGMs that meet the needs of individuals with diabetes
- Industry shares the goal of advancing meter technologies and improving accuracy through innovations in meter systems that
 - Reduce use error
 - Reduce the impact of interferents
 - Improve the overall quality of testing for patients
- ISO 15197 and industry recognize the role of design to improve not only analytical performance but also usability to increase patient compliance with glucose monitoring regimens



- **Definitive Method:** (^{13}C)-Glucose Dilution Mass Spectrometry With Gas Chromatography
 - Meticulous and time-consuming **serum** sample preparation
- **Reference Method:** Double Enzymatic Conversion With Photometric Measurement
 - Prepared **serum** or **plasma**; time-consuming
- **Diagnostic Laboratory Methods**
 - Prepared **serum** or **plasma**
 - Precisely controlled sample volume, temperature, reagent pH, reaction initiation, mixing, and timing
- **Self-Monitoring of Blood Glucose Meters**
 - Capillary **whole blood**
 - Ease of use: small volumes, fast testing, varied environments
 - Performed by lay users

Laboratory Instrument

- Definitive and reference methods
- Standard reference materials
- Elimination of hematocrit effect by analysis of serum or plasma
- YSI, i-STAT, and other whole blood analyzers use membranes to
 - Eliminate hematocrit effects
 - Protect the enzyme and sensor from interfering compounds

Glucose Meter

- Ultimately traceable to definitive or reference method
- No standard reference materials
- Hematocrit effect mitigated by measurement, algorithms, etc.
- No comparable technology for SMBG
 - The presence of multiple interferences provides a considerable technical challenge



Laboratory Instrument

- >\$10,000
- Maintenance >\$1,000/year
- Plasma
- Trained technician
- Calibrated many times daily
- Controlled environment
- Controls run frequently

Glucose Meter

- <\$100
- None
- Blood → plasma equivalent
- Layperson
- No user calibration
- Variable temp, RH, altitude
- Control solution use limited



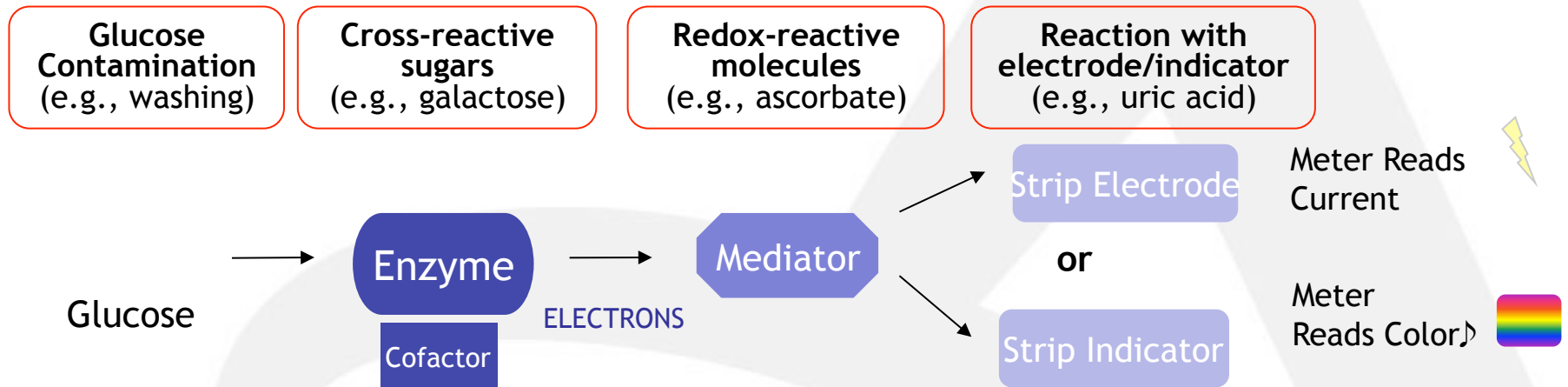
Laboratory Instrument

- Large, stationary
- Susceptible to shock, etc.
- $\geq 5000 \mu\text{L}$
- ≥ 60 secs
- Inaccuracy: $\geq \pm 4\%$,
 $\leq \pm 10\%$

Glucose Meter

- Small, portable
- Resistant to shock, etc.
- $\leq 1 \mu\text{L}$
- ≤ 10 secs
- Inaccuracy:
 - Generally $\geq 2\text{X}$ reference method (i.e., laboratory instrument)

Specific Measurement of Glucose



- Current test strip technologies use enzymes to identify glucose and produce a surrogate compound or secondary signal proportional to glucose
- Mediator molecules capture and transport electrons
- Glucose meters measure electrons or test strip color change
- Enzyme and mediator actions must be fast to yield a fast test time

Beyond Analytical Performance: Role of Interferences

- Sources of inaccuracy are analytical and non-analytical
 - Interferents
 - Endogenous: substances present in normal and disease states (e.g., hematocrit and uric acid)
 - Exogenous: compounds introduced during treatment (e.g. acetaminophen), parenteral nutrition, etc.
 - Environment: temperature*, relative humidity*, and altitude
 - Misuse (e.g., exposing test strips to high temperatures and RH*)
- Industry carefully considers all these factors and customer requirements (e.g., hospital vs. consumer) in providing devices that deliver maximum medical benefit

*FDA Patient Safety News. Advice for Patients. Getting the Most Out of Blood Glucose Meters. June 2008. <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/transcript.cfm?show=76#5>

Additional Limitations and Barriers



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- Accuracy and precision testing of individual test strips is destructive
 - Release criteria rest on sampling and statistical modeling
- Patents
- Variability in raw materials
 - Small variations may have substantial impact
 - Identification and correction of the variation often are very difficult due to limitations of analytic techniques
- Manufacturers are committed to meeting these challenges in ways that address patient needs as to
 - Cost
 - Convenience (e.g., meter size, sample size, and test time)
 - Accuracy and precision
 - Data analysis

Additional Limitations and Barriers



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- Challenge to industry: Manufacture high volumes of glucose meters and test strips
- Worldwide, in 2009, individuals with diabetes performed
 - ≈17-18 billion tests annually
 - ≈47- 49 million tests daily
- The corresponding usage in the U.S. was
 - ≈6.2 billion tests annually
 - ≈17 million tests daily

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- In addition to the many improvements to date, manufacturers believe further progress is possible through
 - Addressing the different profiles of home and hospital customers
 - Performing hazard analyses for each customer group/user profile
 - Working with and encouraging CLSI to finalize POCT 12
 - Creating a standardized list of BGM interferents to test
 - Primary list for self-testers
 - Compounds, concentration levels, and glucose levels
 - Additional provisions for hospital setting
 - Periodic updates
 - Manufacturers test every compound or justify not testing

Further Harmonize Study Design And Presentation



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- ISO 15197 can be revised to support further harmonization in
 - Study design and
 - Data presentation

Further Harmonize Labeling Statements



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- Common labeling language for residual risks
 - FDA published *Guidance on Medical Device Patient Labeling; Final Guidance for Industry and FDA* in 2001
 - Appendix E addresses Warnings and Precautions
 - Appendix F describes methods of pretesting
- While all manufacturers use this guidance, opportunities exist for further harmonization within the BGM industry

- SMBG technology is limited by a variety of factors, including
 - Use of whole blood
 - Potential interference from endogenous and exogenous substances
 - Environmental variability
 - Misuse outside the manufacturer's control
 - Constraints of cost and test convenience
 - Meter size, sample size, test time, etc.
- Industry is working to co-optimize across these spaces, and determine the best tradeoffs to deliver maximum medical benefit and patient value
- Further harmonization of study design, data analysis/presentation, and labeling statements can
 - Facilitate comparison of labeling claims and
 - Provide increased transparency to the intended user



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