Use of Glucose Meters in Critically Ill Patients

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Objectives

- Describe the limitations of glucose meters
- Recognize FDA, CMS and other regulations for use of glucose meters in critically ill patients
- Identify CLSI POCT17 White Paper as a resource
- Review the top AACC government affairs committee priorities for Capital Hill Visits this year

POCT Glucose

A glucose test is not necessarily a glucose test

This fact has been known for many years

Glucose Testing Methods

- Core Laboratory – glucose hexokinase
- POCT – glucose oxidase, glucose dehydrogenase
- Critical Care – glucose oxidase

- Method differences
- Calibration differences
- Whole blood to plasma considerations

Blood Glucose Meter Precision

- 95% of results fall within ± 2SD
- Core Lab

  93.7 ± 0.9 mg/dL (1.0% CV)

  282.7 ± 1.9 mg/dL (0.7% CV)
- POCT

  49.0 ± 9.2 mg/dL (18.6% CV)

  283.0 ± 15.0 mg/dL (5.3% CV)
- Clinically the ADA has recommended glucose meters to have CV's of <5% at all levels and accuracy to within 5% of a lab result. (1987)

Blood Glucose Meter

- 95% of results within ± 20% if >100 mg/dL
- 95% of results within ± 20 mg/dL if <100 mg/dL
- Most recent evaluation by FDA on patient samples:

	<100 mg/dL		>100 mg/dL	
	<20mg/dL	>20mg/dL	<20%	>20%
Meter A	0%	22%	0%	24%
Meter B	0%	14%	0%	0%
Meter C	2%	6%	0%	0%
Meter D	4%	10%	4%	0%

- Currently marketed glucose meters fail to meet consensus criteria in the hypoglycemic range.

Chen ET, Nichols JH, Duh SH, Hortin G. Performance evaluation of blood glucose monitoring devices. *Diabetes Technol Ther* 2003;5:749-68.

Glucose Meter Potential Interferences

- Environmental
  - Air, exposure of strips
  - Altitude
  - Humidity
  - Temperature
- Operational
  - Hemolysis
  - Anticoagulants
  - Generic test strips
  - Amniotic fluid/Animal
  - Arterial and catheter
  - Volume of sample
  - Reuse of strips
- Physiologic
  - Hematocrit (neonates)
  - Prandial state
  - Hyperlipidemia
  - Oxygenation
  - pH
- Drugs
  - Maltose
  - Acetaminophen
  - Ascorbate
  - Mannitol
  - Dopamine

Table 1—*Confounding variables in glucose measurement*

Variable	Methodology affected* GO	GD
Hematocrit		
Anemia	↑	↑
Polycythemia	↓	↓
Oxygen concentration		
Hypoxia	↑	—
Oxygen therapy	↓	—
pH (6.8–7.55)	—	—
Low pH	−/↓	—
High pH	−/↑	—
Hypothermia	↑	↓/↑
Hypotension	↑	↑/↓
Drugs		
Ascorbic acid	↓	↑/−
Acetaminophen	↓	↑
Dopamine	—	↓
Icodextrin	—	↑
Mannitol	↑	—

*Change relative to venous plasma measured at central laboratory. GO, glucose oxidase.

Glucose Measurement: Confounding Issues in Setting Targets for Inpatient Management

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JOHN BUSE, MD, PHD[3]

source of the sample, and specimen matrix (i.e., plasma versus whole blood). This study will review assay principles

DIABETES CARE, VOLUME 30, NUMBER 2, FEBRUARY 2007

The Hospital Issue

- The critical nature of hospitalized patients presents extreme conditions to bedside glucose meters in terms of PO2 and hematocrit, and increasing the potential for interferences from drugs and hospital therapies like intralipid nutrition. Because of these circumstances, the same meters utilized for home self-testing do not always perform well when applied to hospitalized patients.

Table 1. COMPARISON OF HOME AND HOSPITAL POINT-OF-CARE GLUCOSE TESTING

Home POCT Glucose	Hospital POCT Glucose
Single operator	Multiple operators
Single meter	Multiple meters
Serial monitoring on one meter	Single samples on multiple meters
Ambulant patient	Bedridden patient
Relatively healthy patient	Acute and chronic illnesses
Capillary samples only	Noncapillary samples possible

Clarke W, Nichols JH. Bedside Glucose Testing : Applications in the Home and Hospital. *Clinics in Laboratory Medicine: Point-of-Care Testing.* Lewandrowski K editor. June 2001.

Glucose Meters

- FDA clears glucose meters for the following intended uses:
  - For quantitative measurement of glucose in whole blood (e.g., capillary, venous, arterial)
  - For use by healthcare professionals or lay users
  - A few are cleared for use on neonates

  For the following indications:
  - As aid in monitoring the effectiveness of diabetes control program
  - Not intended for the diagnosis of or screening for diabetes

Other ways they are also used (off-label):

- Glycemic control protocols in hospitals (diabetics and non-diabetics)
- Critically ill patients
- Anything they are needed for in the hospital

Glucose Meters

- Manufacturers submit the meters to FDA with home use claims even when they intend to sell them as hospital use meters
- They submit validation data suitable for home use capillary self testing, and minimal validation in arterial and venous blood (if claimed)
- This submission strategy allows the hospital meters to be waived (due to OTC status) without the need for CLIA waiver studies

Glucose Meters

- In recent years concerns have been raised citing the inability of currently cleared glucose meters, if not adequately validated and controlled by the hospital, to perform effectively in critical care settings, given that these devices were not originally designed or evaluated for this type of use.

- Patients in critical care settings can be more acutely ill and medically fragile, and are more likely to present physiological, pathological and pre-analytical factors that could interfere with glucose measurements as compared to other types of users.

- For critically ill patients who by their very nature tend to be more seriously ill, any inaccuracies in the meters could further increase the risk to these patients.

Glucose Meters

- For many years, FDA has requested that all labeling for glucose meters include a statement in their device labeling indicating that the system is not intended to be used in the critically ill patient population.

- FDA requested this statement because the device has not been designed for use in, or studied in this population.

- By including the statement in the Limitation section, FDA hoped to clarify that use in the critically ill population is an off label use and hospitals need to validate that use and place appropriate controls to assure the accurate and appropriate use of the device.

Off Label Use

- Hospitals are recently becoming more aware of these limitation statements

- FDA has been receiving more questions about these limitations, including whether use of meters in the ICU would be off label use

- Because off-label use would void the waived status, facilities would technically need CLIA high complexity certification to use these meters:
  - In critically ill patients
  - In people without diabetes
  - Health fairs and screening the general public for diabetes

- **Challenge** – abrupt disruption of glucose meter use in hospital settings may adversely affect patient safety

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

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Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.
Document issued on: January 7, 2014

You should submit comments and suggestions regarding this draft document within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document, contact Patricia Bernhardt at patricia.bernhardt@fda.hhs.gov, or at 301-796-6136.

NEW YORK
state department of
HEALTH

Nirav R. Shah, M.D., M.P.H.
Commissioner

Sue Kelly
Executive Deputy Commissioner

January 13, 2014

Re: Off-label Use of Glucose Meters

Dear Laboratory Director:

As laboratory director, you are jointly and severally responsible with the owner for the maintenance and operation of the clinical laboratory (Article 5, Title V of New York State Public Health Law). This includes testing that is performed at the point-of-care (POCT) or as part of a health fair or other community screening event.

The US Food and Drug Administration (FDA) is responsible for approving medical devices, including glucose meters, based upon the performance characteristics established by the manufacturers (validation data) and submitted by the manufacturers to the FDA.

New York State Department of Health

- FDA has approved glucose meters for quantitative measurement of whole blood glucose for use by healthcare professionals or lay users as an aid in monitoring the effectiveness of a diabetes control program
- Glucose meter manufacturer validation data has not been sufficient for FDA to extend approved intended use to other patient populations or settings (concerns about accuracy and reliability in hospitals)
- FDA reminds clinical laboratory regulatory agencies that intended use does not include:
  - Diagnosis or screening for diabetes
  - Monitoring glycemic control in non-diabetic hospitalized patients
  - Use in critically ill patients
  - Health fairs or other community events to screen the public for diabetes

Off-Label Use –New York State DOH

- Glucose meter defaults to CLIA high complexity
- For New York State, requires a New York State clinical laboratory permit in category of Clinical Chemistry
- Personnel licensed by New York State Education Dept are eligible to perform testing
- Fully establish analytic and clinical performance specifications
  - Risk-based evaluation of appropriate populations/settings for use
  - Design of studies to establish analytical and clinical performance of glucose meter used for anything other than intended use in pkg insert
  - Consideration of populations/settings where use of glucose meters may not be appropriate and have been documented to cause patient morbidity/mortality

Intended Use

Intended use

The ACCU-CHEK Inform II test strips are for use with the ACCU-CHEK Inform II meter to quantitatively measure glucose (sugar) in venous whole blood, arterial whole blood, neonatal heelstick, or fresh capillary whole blood samples drawn from the fingertips as an aid in monitoring the effectiveness of glucose control. The system is not for use in diagnosis or screening of diabetes mellitus, nor for testing neonate cord blood samples.

- Off-label use: (for this system)
  - Glucose tolerance testing
  - Diagnosis or screening for gestational diabetes
  - Health-fair screening
  - Capillary blood drawn from alternative sites (not fingertip)

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CMS
CENTERS FOR MEDICARE & MEDICAID SERVICES

Center for Clinical Standards and Quality/Survey & Certification Group

Ref: S&C: 15-11-CLIA

DATE: **November 21, 2014**

TO: State Survey Agency Directors

FROM: Director
Survey and Certification Group

SUBJECT: Directions on the Off-Label/Modified Use of Waived Blood Glucose Monitoring Systems (BGMS)

Memorandum Summary

- **"Off-Label Use" of BGMS:** Using a test outside of its Food and Drug Administration (FDA)-approved/-cleared intended use, limitations or precautions, as indicated in the manufacturer's instructions, is considered "off-label use." "Off-label use" applies whether the test is waived or non-waived and it means that the test is considered modified and therefore defaults to a high-complexity test under the Clinical Laboratory Improvement Amendments (CLIA) regulations. This will require all laboratories using the device for an "off label use" to meet all applicable CLIA high-complexity requirements.
- **Surveyors Will Document Off-Label Use:** If any non-compliance is identified, a written statement of deficiencies (Form CMS-2567) will be issued and followed up using standard operating procedures and timeframes found in the applicable regulations and guidance documents.

Laboratory Test Limitations

- Lab tests are not fool-proof!
- There is no “perfect” device, otherwise we would all be using it!
- Any device can and will fail under the right conditions
- Those conditions are listed in the limitations section of the package insert, policy and training materials

ACCU-CHEK® Inform II

Test Strips and 1 Code Key

PROFESSIONAL USE

Cat. No. 05942861001

Limitations

- The ACCU-CHEK Inform II test strips are for testing fresh capillary, venous, arterial, or neonatal whole blood. Cord blood samples cannot be used.
- Hematocrit should be between 10–65 %.
- Lipemic samples (triglycerides) in excess of 1800 mg/dL may produce elevated results.
- Blood concentrations of galactose >15 mg/dL will cause overestimation of blood glucose results.
- Intravenous administration of ascorbic acid which results in blood concentrations of ascorbic acid >3 mg/dL will cause overestimation of blood glucose results.
- If peripheral circulation is impaired, collection of capillary blood from the approved sample sites is not advised as the results might not be a true reflection of the physiological blood glucose level. This may apply in the following circumstances: severe dehydration as a result of diabetic ketoacidosis or due to hyperglycemic hyperosmolar non-ketotic syndrome, hypotension, shock, decompensated heart failure NYHA Class IV, or peripheral arterial occlusive disease.
- This system has been tested at altitudes up to 10,000 feet.

Current Vanderbilt Glucose Procedure

12.0 **PROCEDURE LIMITATIONS**

12.1 Patient hematocrit should be between 10–65 %. Samples outside this hematocrit range will yield inaccurate results.
12.2 Lipemic samples (triglycerides) in excess of 1800 mg/dL may produce elevated results.
12.3 Blood concentrations of galactose >15 mg/dL will cause overestimation of blood glucose results.
12.4 Intravenous administration of ascorbic acid which results in blood concentrations of ascorbic acid >3 mg/dL will cause inaccurate glucose results.
12.5 If peripheral circulation is impaired, collection of capillary blood from the approved sample sites is not advised as the results might not be a true reflection of the physiological blood glucose level. This may apply in the following circumstances: severe dehydration as a result of diabetic ketoacidosis or due to hyperglycemic hyperosmolar non-ketotic syndrome, hypotension, shock, decompensated heart failure NYHA Class IV, or peripheral arterial occlusive disease.
12.6 This system has been tested at altitudes up to 10,000 feet.
12.7 Refer to Accu-Chek Inform II strip package insert for complete listing of limitations and interfering substances

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- This system has been tested at altitudes up to 10,000 feet.
- The performance of this system has not been evaluated in the critically ill.

This limitation is new as of December 2012 for all glucose meters!

Definition of Critically Ill

- No universal definition of critically ill exists
- Critical illness is any disease process which causes physiological instability leading to disability or death within minutes or hours.(1)
- All inpatients, by virtue of their hospitalization, may be considered “critically ill”. So, critically ill patients are not just those patients in the ICU
  - Consider the OR, ED, Trauma, Sepsis, and others
- CMS and FDA indicate that the definition of what constitutes “critically ill” must be defined by each institution.

British Journal of Hospital Medicine, October 2007, Vol 68, No 10

The BGMS that have been cleared by the FDA as waived for home use were originally designed as consumer devices, intended for use in monitoring glucose levels in an individual patient diagnosed with diabetes. However, over time, the use of BGMS has expanded to include use in healthcare facilities and, in turn, use in patient populations that the manufacturer's studies and performance standards, which were used to evaluate these BGMS for home use, did not address.

Manufacturers' Instructions

The CLIA-certified laboratories must read and follow all of the manufacturer's instructions for waived test systems, including BGMS. This includes any instructions that the manufacturer may include regarding the system's intended use, limitations and precautions. Note that manufacturers' instructions vary in format, and some information may be found in different sections. Moreover, manufacturers' instructions may be updated or changed, and instructions

This means that, when the manufacturer's instructions contain limitations indicating that the BGMS has not been evaluated or cleared for use in critically ill patients, the use of BGMS on critically ill patients will be considered "off-label" use, and, for purposes of the CLIA regulations, will automatically default to high-complexity testing. Facilities may continue to use their waived BGMS on patients as long as they are following the manufacturer's instructions.

Revised Vanderbilt Glucose Procedure

12.0 PROCEDURE LIMITATIONS

12.1 The manufacturer, Roche Diagnostics, has indicated that the performance of the Inform II meter has not been evaluated in critically ill patients. For the purpose of point-of-care glucose testing, Vanderbilt has defined and interprets this "critically ill" testing limitation such that use of the Inform II meter is prohibited for testing in patients with any of the following conditions:

12.1.1. Hematocrits less than 10% or greater than 65%.

12.1.2. Triglyceride levels greater than 1800 mg/dL.

12.1.3. Blood concentrations of galactose >15 mg/dL.

12.1.4. Intravenous administration of ascorbic acid resulting in blood concentrations of ascorbic acid >3 mg/dL.

12.1.5. Use of capillary blood collected by fingerstick in patients with peripheral circulation impairment to include severe dehydration resulting from diabetic ketoacidosis, hyperglycemic hyperosmolar non-ketotic syndrome, hypotension, shock, decompensated heart failure NYHA Class IV, or peripheral arterial occlusive disease.

12.1.6. Cord blood samples

Do not use the ACCU-CHEK Inform II for testing patients exhibiting any of these conditions. Instead, collect venous or arterial blood and send to the clinical laboratory for testing with STAT orders as indicated

12.2 This system has been tested at altitudes up to 10,000 feet.

12.3 Refer to Accu-Chek Inform II strip package insert for complete listing of limitations and interfering substances

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CMS
CENTERS FOR MEDICARE & MEDICAID SERVICES

Center for Clinical Standards and Quality/Survey & Certification Group

DATE: **March 13, 2015**

Ref: Temporary Withdrawal-S&C: 15-11-CLIA and Reissuance as Draft, with Draft Clarifications

TO: State Survey Agency Directors

FROM: Director
Survey and Certification Group

SUBJECT: Reissuance of S&C 15-11 As DRAFT ONLY – FOR COMMENT
Off-Label/Modified Use of Waived Blood Glucose Monitoring Systems (BGMS)

We are temporarily withdrawing S&C Memorandum 15-11, which was previously issued on November 21, 2014, and reissuing it in draft-only form in order to:

- Obtain more feedback regarding the use of waived BGMS, the environments in which BGMS are currently used, and any issues that hospitals and other providers have identified with such use;
- Promote added education regarding the current CLIA requirements.

Use of Glucose Meters for Critically Ill Patients

This white paper includes an overview of glucose meter limitations with practical advice for use of glucose meters in critically ill patients

CLINICAL AND LABORATORY STANDARDS INSTITUTE®

Options to Address CMS Changes

- Proposed Policy Change
- Change to a meter cleared for “critically ill” use
- Use an “alternative” method for “critically ill” patients
- Use glucose meters “off-label”

Proposed Policy Change

- Least disruptive
- No change in practice, staff already trained and doing this
- Meets letter of the regulatory change by defining what “critically ill” means for this device – the pkg insert limitations – so not testing under “off-label” uses

Use FDA Cleared Meter

- Requires venous or catheter blood collection
- Caution! No meter is cleared for use of capillary samples in critically ill patients!
- Patients with poor peripheral circulation physiologically have differences between central and peripheral circulation
- Not unique to glucose meters (consider coag, blood gases, electrolytes, and other POCT)

Use “Alternative” Method

- Requires more costly Blood Gas testing
- The number of blood gas analyzers may limit patient access to testing
- Core lab testing has delays in results that could impact care

Off-Label Use

- CLIA high-complexity testing with required performance validation in critically ill patients
- Consequences for staff educational background, licensure (med director), and ongoing documentation.
- Personnel may not meet specific CLIA/State requirements
  - Current license (if required) by state
  - MD, doctor of osteopathy, doctor of podiatric medicine
  - Doctorate, master's, bachelor's in chemistry, physical or biological science
  - Maintain documented training and competency records
  - Some nursing or other healthcare professionals may not have the required education to meet CLIA high-complexity requirements – some states may further reduce eligible staff that can perform glucose testing

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Center for Clinical Standards and Quality/Survey & Certification Group

Ref: S&C: 16-18- CLIA
REVISED 05.03.16

DATE: **April 1, 2016**

TO: State Survey Agency Directors

FROM: Director
Survey and Certification Group

SUBJECT: Personnel Policies for Individuals Directing or Performing Non-waived Tests
Revised due to typographical error under citation of §493.1443(b)(3)

CMS Personnel Policies Update

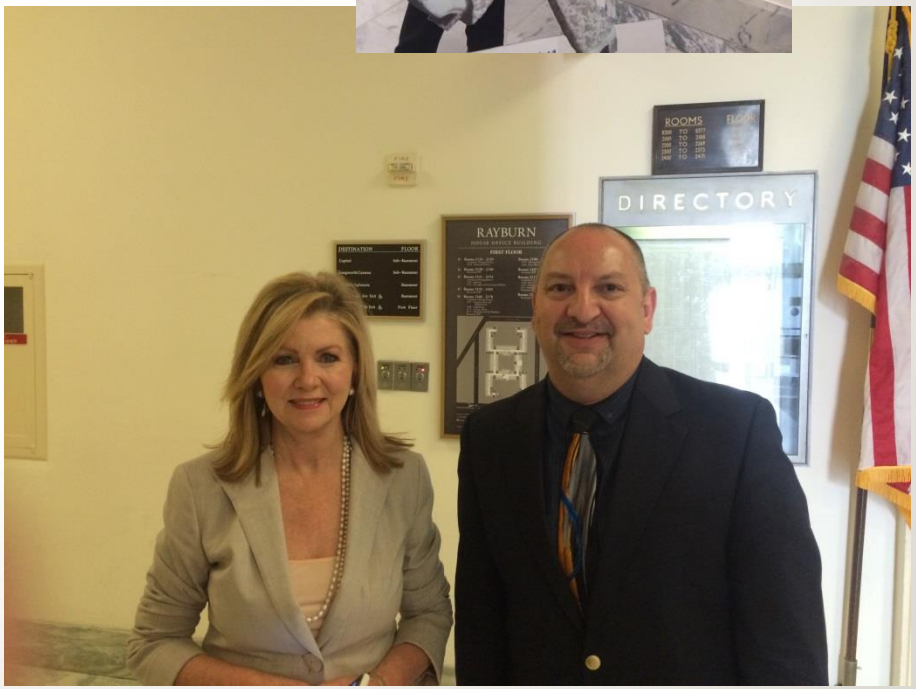
- CLIA surveyors will now accept Primary Source Verification company evidence of personnel qualification compliance
- PSV confirms applicant's credentials by verifying degree, certificate, or diploma received, licenses granted and confirming work history and positions held
- Bachelor's and Associate's degrees in nursing meet the requirement for earning a degree in a biological science for CLIA high and moderate complexity testing personnel

AACC Government Relations Committee

- To monitor and make recommendations on legislation, regulations, and legal actions pertaining to the clinical laboratory
- To ensure that the interests of AACC members are served.
- To promote member involvement in government relations issues.
- GRC has transitioned to the new AACC Core Committee on Policy & External Affairs

AACC Government Affairs Committee Capital Hill Visits

- The value of laboratory testing
  - Role in patient care
  - Who are laboratory specialists?
- Test harmonization
- 21st Century Cures – LDT position statement
- Newborn screening and children's health



VANDERBILT UNIVERSITY MEDICAL CENTER

AACC Capital Hill Briefing

- Precision Medicine vs Personalized Medicine
- Direct to Consumer Testing
- Test Harmonization
- CLIA modernization and LDT regulation

Summary

- Recognize glucose meter limitations
- Use glucose meters within the package insert limitations to maintain CLIA waived status
- Otherwise must perform studies to prove validity and reliability of results (off-label use)
- AACC Government Relations Committee is a resource for voicing your opinion on changing lab regulations
- I want to thank and acknowledge Courtney Lias and Alberto Guitierrez (FDA) and Karen Dyer (CMS) for borrowing several slides