DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Medicare & Medicaid Services
7500 Security Boulevard, Mail Stop C2-21-16
Baltimore, Maryland 21244-1850

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.

Issuance of the original Memorandum in November 2014 prompted considerable feedback regarding BGMS tests that are approved as waived devices under CLIA. From those comments, it is apparent that:

- Waived BGMS are being used in a variety of settings and applications, which may indicate diverse clinical utility.
- Some of these uses may constitute off-label applications (i.e., applications outside the intended uses and limitations specified in the manufacturers' instructions).
- There is risk of patient harm when off-label use has occurred without the necessary performance specifications being in place for such off-label.
- There may be significant confusion as to what hospitals, or other providers, must do to meet the CLIA requirements for off-label use of a waived test systems. This is particularly concerning as S&C Memorandum 15-11 contained no new CLIA policies -- the underlying CLIA Statute and regulations have not changed.

In the attached draft revisions, we seek to address some of these concerns, and clarify our longstanding requirements and policies where the feedback received thus far indicated that more education is warranted. But we believe there is more work to be done. We plan to create additional forums for more discussion of these issues. In the meantime we invite comments to this draft emailed to: LabExcellence@cms.hhs.gov. We look forward to further dialogue on this important issue.

/s/

Thomas E. Hamilton

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Center for Clinical Standards and Quality/Survey & Certification Group

Ref: S&C: 15-11-CLIA

DATE: **November 21, 2014,**
March 13, 2015 - Temporarily Withdrawn and Reissued as Draft Only

TO: State Survey Agency Directors

FROM: Director
Survey and Certification Group

Revised Draft 03-13-15
For Comment Only
Draft Additions in RED

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. In short, off-label use is not prohibited but does trigger additional safeguards.

- All laboratories using the device for an "off label use" must meet all applicable CLIA high-complexity requirements. Conversely, using a device within the limitations or precautions and intended use indicated by the manufacturer would not constitute off-label use, and not cause such use to constitute high complexity under CLIA.
- **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.
- **Frequently Asked Questions (FAQs):** Included with this memorandum are FAQs prepared by Centers for Medicare & Medicaid Services (CMS) and FAQs prepared by the FDA, respectively that provide responses to key questions.

Background

This memorandum is specifically directed toward a discussion of BGMS, but the information contained herein is applicable to all waived and non-waived laboratory testing and describes already existing regulations and interpretive guidance.

The CLIA statute, section 353 of the Public Health Services Act (codified at 42 U.S.C. 263a), provides that the examinations and procedures performed by a laboratory with a certificate of waiver are those that have been approved by the FDA for home use or that, as determined by the Secretary, are simple laboratory examinations and procedures that have an *insignificant risk of an erroneous result;* 42 U.S.C. § 263a(d)(3) (emphasis added). The CLIA statute further states that these include "methodologies that are so simple and accurate as to render the likelihood of erroneous results by the user negligible," or those that "the Secretary has determined pose no reasonable risk of harm to the patient if performed incorrectly." The CLIA regulations support these requirements as described at 42 CFR §493.15(b).

Laboratories issued a Certificate of Waiver (CW) have no regulatory requirements for routine surveys, personnel qualifications, experience or training, quality control (QC), proficiency testing (PT), record-keeping, quality assessment (QA), or laboratory director responsibilities. These laboratories are only allowed to perform waived tests, but they must also meet the following requirements under CLIA:

- Enroll in the CLIA program and obtain a CLIA certificate;
- Pay the applicable certificate fee of $150 biennially; and
- *Follow manufacturers' test instructions for test performance.*

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.

Since November 13, 2003, the FDA has had the authority to implement the CLIA test complexity categorization provisions and shares responsibility for determining which tests are waived vs. non-waived. *See* 68 Fed. Reg. 64,350 (Nov. 13, 2003). CMS and the FDA have very distinct and complementary regulatory responsibilities. CLIA regulations focus on ensuring that laboratories provide accurate, reliable and timely testing. For CLIA purposes, the FDA is responsible for test categorization (e.g., waived, moderate complexity, high complexity). The FDA has additional regulations beyond CLIA which govern manufacturers of medical devices, such as requirements of evidence of clinical validity.

The intended uses and appropriate patient population(s) that a test is or is not to be used for testing are found in the manufacturer instructions.

Using a waived test within the limitations, precautions and intended uses indicated by the manufacturer preserves its waived status. As such, use of a waived test within manufacturers' instructions does not constitute off-label use, and does not require compliance with the higher standards applied to high complexity under CLIA.

Modifying a waived test or using a waived test outside the limitations specified by the manufacturer is an off-label use. Off-label use of a waived test is NOT prohibited, but does require that the laboratory meet the higher standards required of high complexity testing.

The following parts of this Memorandum provide additional details and explanations.

Manufacturers' Instructions

CLIA regulations focus on the laboratories' ability to produce accurate, reliable and timely test results. The CLIA-certified laboratories must read and follow all of the manufacturer's instructions for waived test systems, including BGMS, in order for the use to retain its waived status. 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 from different manufacturers for the same type of testing may not be the same. The manufacturer's instructions may, however, include the following sections.

Intended Use

The intended use section describes the test purpose, substance detected or measured, test methodology, appropriate specimen type and the FDA-cleared or approved patient population on which the test system can or cannot be used. This section may also include if the test is diagnostic or used for screening a specific patient population and if the test system is intended for professional use or self-testing.

Limitations

The limitations section describes the conditions that can affect test results, or circumstances for which the test was not intended, such as: interference from medical conditions, drugs or other substances; limitations for testing with certain samples or populations. BGMS that prohibit use in a specific patient population (e.g., patients with circulatory problems) retain their waived complexity categorization if the facility does not test patients with these limitations.

For a more complete explanation of the common components of a manufacturer's instructions, please refer to Appendix B, in the Center for Disease Control and Prevention's *Ready? Set? Test! Booklet* at the following link,

http://wwwn.cdc.gov/clia/Resources/WaivedTests/pdf/ReadySetTestBooklet.pdf

The information in the manufacturer's instructions should be clearly communicated to users of the BGMS to ensure that blood glucose results are accurate and reliable. Please direct any questions about the manufacturer's instructions to the test system manufacturer.

Off-Label Use or Test Modification

Based on a laboratory's needs and the unique population it serves, there may be instances when a laboratory chooses to modify an FDA-approved/cleared test system 42 CFR §493.1253(b)(2)). For the purposes of this memorandum, a "laboratory modification" means any change in intended use, adjustments to the precautions, limitations or other sections of the manufacturer's instructions. These changes are considered "off-label" use of a commercial test system and are not supported by the manufacturer's clinical data or approved or cleared by the FDA.

Among other requirements, the CLIA regulations at §493.1253(b)(2) require all laboratories that modify an FDA-cleared or approved test system to establish performance specifications for that test system (i.e., accuracy, precision, analytical sensitivity, analytical specificity including interfering substances, reportable range of test results, reference intervals and any other performance characteristic required for test performance).

An example of off-label use would be using a waived BGMS test to perform a blood glucose test on a patient whose hematocrit or oxygenation level is below the range indicated in the manufacturer's instructions. If the manufacturer states that the BGMS may be used only for patients whose hematocrit is between 20 percent and 65 percent, for example, use of the BGMS outside of this hematocrit range would be considered off-label use of that BGMS. Since results of blood glucose testing in this situation may lead to clinical interventions that could cause patient harm, the hospital must establish its own performance specifications if it wishes to use the BGMS in an off-label application.

By way of additional example, some manufacturers' instructions contain limitations indicating that the BGMS has not been evaluated or cleared for use in critically ill patients. Neither the FDA nor CMS define the term "critically ill." CMS recognizes the tremendous variation of testing environments, technology, and patient clinical circumstances where BGMS devices are used. A hospital laboratory wishing to use a waived BGMS test in an off-label application must establish performance specifications for such use. This includes determining who is eligible for such testing (such as who, for the purposes of the laboratory-developed performance specifications required for off-label application, is considered in or outside the hospital's definition of "critically ill"), based on what the laboratory knows about the test system, the patients, the environments within which the testing will be conducted, and the personnel using the test.

It is also worth noting that there is an array of point of care devices that the FDA has approved for waived testing or moderate complexity testing. Hospitals in particular may find that such devices represent useful alternatives to off-label use of a waived BGMS test. Examples include iStat, Piccolo, Hemocue, etc[1]. Laboratories seeking more information about tests approved for moderate complexity may consult the FDA website at:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCLIA/search.cfm

Further information regarding performance specifications is located in the CLIA Interpretive Guidelines (IG), in Subpart K at 42 CFR §493.1253, and in CLIA Brochure Number Two (2), "Verification of Performance Specifications," available on the CMS/CLIA web site at: www.cms.hhs.gov/clia/.

[1] Note that these are simply examples, and inclusion in this list does not represent a CMS recommendation or endorsement, nor does omission of an FDA-approved device from this list represent a lack of CMS recognition.

Laboratory Options for CLIA Compliance for Waived Blood Glucose Monitoring Systems

- The laboratory and the facility may continue using their BGMS as a waived device as long as they follow the manufacturer's instructions.

- If a facility wishes to use a BGMS off-label (e.g., in a critically ill patient population when a manufacturers' instructions contain a limitation on critically ill patients), laboratories with a CW may:

    - Obtain a CoC or CoA;
    - Establish the performance specifications; and
    - Meet the additional CLIA regulatory requirements for high-complexity testing and any applicable State regulations.

  NOTE: Personnel requirements for non-waived testing are found in Subpart M. The specific requirements for high-complexity testing personnel are located at 42 CFR §493.1489.

- Identify and use a point-of-care glucose device in the FDA CLIA database without any critically ill patient population limitations in the manufacturer's instructions. The FDA CLIA database is located at the following link:

  http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCLIA/search.cfm

  NOTE: The FDA CLIA database can be used to identify systems that could potentially be used in their patient populations. Laboratories should contact the manufacturer directly to confirm that they have the most current package insert.

- Submit blood glucose specimens from patients whose clinical conditions do not meet those described in the intended use or limitations sections of the manufacturers' instructions to a CLIA-certified or –accredited laboratory capable of doing the testing.

FDA Draft Guidance for Manufacturers

On January 7, 2014, the FDA published detailed draft guidance for *manufacturers*, to advise them on how to conduct the appropriate studies and apply for clearance of their BGMS devices. **The FDA Draft Guidance is not intended for use by CLIA-certified laboratories**.
If a manufacturer seeks, and is granted, FDA clearance to add the use of the BGMS on critically ill patients to the manufacturer's instructions, and the package insert is amended by the manufacturer to provide for such use, the use of the device for this patient population will not be considered off-label use as long as a laboratory follows all of the manufacturer's instructions.

Off-Label/Modified Use of Devices Identified on Surveys

CLIA surveyors survey laboratories for compliance with the CLIA regulations. The CMS continues to use the Outcome Oriented Survey Process. If the CLIA surveyor(s) note the use of

BGMS in a facility, they will evaluate whether the BGMS is being used following the manufacturer's instructions, or being used off-label (i.e. modified).

CLIA survey types include:

- Certificate of waiver project educational visits, and
- Complaint surveys.

If any non-compliance is identified, a written statement of deficiencies (Form CMS-2567) will be issued to the laboratory and followed up by surveyors, using standard operating procedures and timeframes found in the applicable regulations and guidance documents. Laboratories receiving a standard-level citation will have a reasonable timeframe (up to 12 months) to obtain certification or accreditation for high-complexity testing and comply with the applicable high-complexity testing requirements, or switch to a BGMS appropriate to their certificate and their patient population. Note, however, that any immediate jeopardy findings will subject a laboratory to further action in addition to what is described here.

If a laboratory is accredited by a CMS approved accreditation organization (AO), the laboratory must follow the AO standards which are equivalent to or more stringent than the CLIA requirements.

These policies will allow laboratories the opportunity to determine how they wish to proceed to achieve CLIA compliance, and the time required to implement their chosen option.

Contact: If you have any questions regarding this memo, please direct them to LabExcellence@cms.hhs.gov.

Effective Date: Immediately. This policy should be communicated with all survey and certification staff, their managers and the State/Regional Office training coordinators within 30 days of this memorandum.

Draft

Thomas E. Hamilton

Attachment(s) – 2
Attachment 1: Frequently Asked Questions (FAQs) for Blood Glucose Monitoring Systems (BGMS) - CMS
Attachment 2: Frequently Asked Questions (FAQs) for Blood Glucose Monitoring Systems (BGMS) - FDA

cc: Survey and Certification Regional Office Management
Regional Office CLIA Surveyors

Attachment 1

Frequently Asked Questions (FAQs) for Blood Glucose Monitoring Systems (BGMS) - CMS

Q1: Are BGMS only supposed to be used to test diabetic patients?

BGMS are currently only indicated for monitoring known diabetic patients. Other point-of care glucose testing devices are indicated for broader use (e.g., for screening or diagnosing diabetes mellitus). Laboratories must refer to product labeling when determining the indications for their glucose measurement device. Facilities may still choose to use the BGMS in populations that are not specifically indicated in the product label (i.e. off-label use), however, when laboratories use any FDA-cleared or approved tests off-label, the CLIA categorization of that device defaults to high complexity, and the laboratory must meet the CLIA requirements for high complexity testing.

Q2: If I establish the performance specifications for my meter for off-label uses, is it still waived?

No. When a laboratory uses a device off-label, the device defaults to high complexity, and the laboratory must meet the CLIA requirements for high complexity testing. In those cases, the laboratory must establish the performance specifications (i.e. accuracy, precision, analytical sensitivity, analytical specificity including interfering substances, reportable range of test results, reference intervals and any other performance characteristic required for test performance) for use in their patient population, and it must meet the personnel and all other applicable requirements for high complexity testing.

Laboratories wishing to meet high complexity requirements so that they can continue to use BGMS in populations not specifically indicated in the product label, may obtain further information regarding performance specifications via two resources

1. The CLIA Interpretive Guidelines (IG) at 42 CFR 493.1253, and,

2. In CLIA Brochure Number Two (2), 'Verification of Performance Specifications', on the CMS/CLIA web site at:

http://www.cms.gov/Regulations-andGuidance/Legislation/CLIA/index.html?redirect=/clia/

Q3: During a laboratory survey, it is discovered that my facility is using glucose meters off-label. What will happen?

When a facility uses a device off-label, the device defaults to high complexity, and the facility must meet the CLIA requirements for high complexity testing. If the facility using the device off-label has failed to meet the requirements for high complexity testing, the facility will be issued a written statement of deficiencies (CMS Form-2567) for non-compliance with the applicable CLIA regulatory requirements.

Q4: What will happen if my facility is issued a written statement of deficiencies (CMS Form-2567) for non-compliant off-label use of a BGMS?

Absent other CLIA compliance issues, the facility will generally be given an opportunity to submit a plan of correction to come into compliance with CLIA. Laboratories receiving only standard-level citations will generally be given a reasonable timeframe (no more than 12 months) to obtain certification of compliance or accreditation for high complexity testing, or switch to a BGMS appropriate to their certificate and patient population. Laboratories receiving more serious condition-level citations will have a much shorter timeframe, as appropriate.

Q5: What requirements need to be met to allow my facility to use these BGMS off-label?

The laboratory must meet the applicable CLIA requirements for high complexity testing. This includes the establishment of performance specifications for use in their patient population, the performance of quality control (QC), the enrollment and participation in proficiency testing (PT), and compliance with the personnel qualifications and other applicable requirements for high complexity testing.

Q6: What educational requirements need to be met for personnel performing high complexity testing?

The CLIA personnel qualification requirements for high complexity testing can be found in Subpart M of the CLIA regulations and are further discussed in the CLIA IGs, http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/apcsubm.pdf.

Laboratories performing high complexity testing are required to have a qualified laboratory director, technical supervisor(s), clinical consultant, general supervisor and testing personnel. The specific requirements for high-complexity testing personnel are located at 42 CFR §493.1489.

In summation the high complexity testing personnel must:

- Have a current license in states in which licenses are required,
- Have one of the following:
  - an M.D., D.O., or D.P.M.,
  - an earned doctoral, master's or bachelor's degree in a chemical, physical, biological science, or
  - an earned associate degree in a laboratory science or medical laboratory technology from an accredited institution or have education and training equivalent to that specified in 42 CFR 193.1487(b)(2)(i)

    The training requirements for associate's degree holders can include a requirement that the individual has at least 3 months experience with the BGMS. In those instances, if the individual is new or lacks the 3 months experience, the probationary period may count towards meeting the 3 months experience as long as training is provided and competency is evaluated during the probationary period. The training and competency evaluations should be documented.

Q7: What are my options for meeting CLIA compliance if my facility continues to use BGMS to test glucose in patient populations not indicated by the manufacturer?

The facility may:

- Obtain a Certificate of Compliance (CoC) or Certificate of Accreditation (CoA), establish the performance specifications and meet the additional regulatory requirements for high complexity testing to continue using a BGMS on patient populations not indicated by the manufacturer.
- Identify a point-of-care glucose testing device that the manufacturer's instructions support using with the desired patient population limitation, or
- Refer the glucose testing to another CLIA-certified or -accredited laboratory (e.g. central hospital laboratory) that meets the requirements to perform such testing.

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

Attachment 2
Frequently Asked Questions (FAQs) for Blood Glucose Monitoring Systems (BGMS) - FDA

Q: I have been using glucose meters in this way for years. Is this limitation new?
No. This limitation is not new. The labeling for current FDA-cleared Blood Glucose Monitoring Systems (BGMS) includes limitations on the use of the system in the critically ill patient population. These statements are included because, to date, BGMS devices have not been designed for use, or studied, in this population. Glucose meter manufacturers have generally sought FDA clearance for their meters for over-the-counter use (i.e., for lay use), and the validation studies they have performed have been designed for that population. Despite this, FDA has become aware that BGMS devices are commonly being marketed by meter manufacturers for, and used in healthcare facilities on many types of patients. These devices offer benefits in terms of cost, convenience and turnaround time, making it easier for staff to timely manage blood glucose concentrations.

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, particularly in capillary blood samples, 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 lead to inappropriate treatment decisions that may put these patients at risk of serious injury or death. Use of these devices in the treatment of critically ill patients would be an off-label use and would result in facilities needing to validate such use, place appropriate controls on such use, and have such use meet CLIA's requirements for performing high complexity tests to ensure the accurate and appropriate use of these devices. **It is important to note that device labeling does not limit use of the device in non-critically ill patients, and thus those uses are not "off-label."**

Q: Are there any glucose meters cleared for use in the critically ill patient population?
As of the date of this publication, only one blood glucose meter system, Nova's StatStrip Glucose Hospital Meter System, is FDA cleared for use in critically ill patients when venous, arterial, neonatal arterial, or neonatal heelstick whole blood samples are used. Currently no other glucose meters are cleared for use in critically ill patient populations, and no glucose meters are cleared to use fingerstick capillary samples in critically ill patients.

Q: How does the FDA determine the cleared uses of BGMS?
A manufacturer submits the intended uses (at times called "claims," but not to be confused with billing claims) for which their BGMS has been designed, along with studies to support such intended uses and labeling describing both the intended uses and the limitations of the device. The FDA then performs an evaluation of those studies

as part of the device clearance process, and determines whether the studies are adequate to support the manufacturer's requested intended uses and labeling.

Q: Could a manufacturer seek an expanded list of intended uses for an already cleared glucose meter (e.g., for use in critically ill patients)?
Yes. A manufacturer could seek FDA marketing authorization for additional intended uses for their device (e.g., expanding the intended use of their device to include use with critically ill patients). To do so, the manufacturer would have to go through a design control process to determine whether their device could appropriately be used for the new intended use and make any changes they deem appropriate to the device, its specifications, and controls for the new intended use. Then they would send a regulatory submission to the FDA with studies supporting the new intended use they are seeking for their device and updated proposed device labeling.

Q: Is there anything being done to address this issue for the future?
FDA is currently working with device manufacturers to encourage them to determine whether the use is of these devices in critically ill patient populations is appropriate for their devices, and, if they determine it to be, to provide regulatory submissions that contain data that will allow for FDA marketing authorization to use these products in the critically ill.

In addition, the FDA has recently published two draft guidance documents for glucose meter manufacturers that, if finalized as written, FDA believes will help address this issue in the future. In these draft guidance documents, FDA distinguishes prescription meters intended for use in point-of-care professional healthcare settings from over-the-counter meters intended for use by lay-users in the home. The draft guidance entitled "Blood Glucose Monitoring Test Systems for Prescription Point-of-Care Use" (http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidanceocuments/ucm380325.pdf) outline the types of studies that, if finalized as written, manufacturers should perform to validate use of their device in prescription point-of-care settings, including those caring for critically ill patients. The comment period for these draft guidance documents has closed, and FDA is working to finalize them for future publication.