This guidance was written prior to the February 27, 1997 implementation of FDA's Good Guidance Practices, GGP's. It does not create or confer rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. This guidance will be updated in the next revision to include the standard elements of GGP's.

POINTS TO CONSIDER FOR PORTABLE BLOOD GLUCOSE MONITORING DEVICES INTENDED FOR BEDSIDE USE IN THE NEONATE NURSERY

This document presents approaches to addressing the current major concerns about blood glucose monitoring devices intended for bedside use in the neonate nursery (BGM-N). It is based on: 1) current science; 2) clinical experience; 3) previous submissions from manufacturers to the Food and Drug Administration (FDA); 4) the Safe Medical Devices Act of 1990; and 5) regulations in the Code of Federal Regulations (CFR). So that we may revise the draft as necessary, please send your comments to the address given below.

Cornelia Rooks
Chief, Clinical Chemistry and Toxicology Branch
Division of Clinical Laboratory Devices HFZ-440
2098 Gaither Road
Rockville, Maryland 20850

I. PURPOSE

This document is an adjunct to the CFR and FDA publication no. 87-4224, the manual entitled: "In Vitro Diagnostic Devices: Guidance for the Preparation of 510(k) Submissions"(1). It is not to supersede these publications, but is to provide additional guidance and clarification for information that should be provided in the premarket notifications for these devices.

The performance of portable blood glucose monitoring devices can be established by comparison of the device to the reference method or a well-characterized comparative method. The National Committee for Clinical Laboratory Standards (NCCLS) is a good source for information concerning definitive methods, reference methods, designated comparative methods and well-characterized comparative methods.

The premarket notification [510(k)] must provide evidence that the device is substantially equivalent to a predicate device legally marketed in the United States and that the device is safe and effective.

II. DEFINITION OF THE DEVICE

Blood glucose monitoring systems that consist of glucose test strips read with a software-driven, portable meter are regulated as Class II devices under section 862.1345 of the CFR. Both the

strips and meters are the subject of this regulation. Such devices, when intended for bedside monitoring of neonates diagnosed by laboratory glucose measurement, may be determined substantially equivalent based on the criteria set forth in this document.

A. PRODUCT CODES

CFR Hexokinase, Glucose
CGA Glucose Oxidase, Glucose

B. REGULATION

21 CFR 862.1345 Glucose Test Systems

(a) *Identification.* A glucose test system is a device intended to measure glucose quantitatively in blood and other body fluids. Glucose measurements are used in the diagnosis and treatment of carbohydrate metabolism disorders including diabetes mellitus, neonatal hypoglycemia and idiopathic hypoglycemia, and pancreatic islet cell carcinoma.

(b) *Classification.* Class II

III. BACKGROUND

Screening for neonatal hypoglycemia has become a routine clinical practice. Neonatal hypoglycemia, if untreated, may result in neurological damage. However, the impact on long term development is not well understood(2,3). Controversy exists over the definition of neonatal hypoglycemia, with many clinicians using a blood glucose value of 40 mg/dL as the medical decision level for the institution of therapy(4). Therapeutic responses consist of prophylactic feeding or parenteral glucose administration and require frequent blood glucose determinations(5).

Clinical studies have shown that portable reflectance meters may lack precision and accuracy around the 40 mg/dL medical decision level. This may be due to user error(6), interference from high hematocrit levels typically seen in neonate specimens(7), or the performance limitations of the meter. It is generally agreed that these devices should not be a substitute for laboratory glucose determinations in the diagnosis of neonatal hypoglycemia in the neonatal intensive care unit, nor should they be used with high risk or pre-term infants (8,9).

IV. PERFORMANCE CONSIDERATIONS

Portable blood glucose reflectance meters and reagent strips have been available for many years. Most are intended for self-monitoring by individuals with diabetes. Professional use bedside glucose monitoring of neonates, however, is a critical intended use requiring specific performance

considerations in a premarket notification. As with all microprocessor-controlled instruments for in vitro diagnostic use, software verification and validation requirements should be addressed.

Studies should be conducted which directly support the claim for use with neonate specimens. These studies are described below. Additionally, all manufacturers should conduct the analytical studies recommended for all blood glucose meters in the FDA guidance: Review Criteria for Assessment of Portable Blood Glucose Monitoring in vitro Diagnostic Devices Using Glucose Oxidase or Hexokinase Methodology(10).

A. Precision Studies

Because the most commonly used medical decision level when monitoring neonatal hypoglycemia is 40 mg/dL, specific data demonstrating the precision and accuracy of the system in the range of 10 to 50 mg/dL should be submitted. Provide data from precision studies using suitable, matrix-compatible control material, representing a value in this low glucose range, along with control precision data at higher glucose levels as recommended in other FDA guidance(10), or NCCLS Tentative Guideline EP5-T2.

B. Comparison Studies

That neonatal blood differs from adult blood in a number of ways is well known. Two of the primary characteristics of neonatal blood which are different from adult blood, and which may have a direct impact on the efficacy of blood glucose monitoring, are higher hematocrit (51 to 65%) (13) and lower blood glucose concentrations (20 to 80 mg/dL) (14) seen in neonatal bloods.

In samples from polycythemic neonates, the blood glucose results would be high in those cases where the sample color intensity affects the meter readings and low in those cases where the specimen RBC numbers negatively impact on plasma diffusion into the reagent area. Falsely low glucose results are often obtained from healthy neonates with elevated hematocrits using portable, blood glucose monitors. The following mechanisms have been proposed for some of these observations(7):

1. An increased number of erythrocytes in a blood sample may mechanically impede diffusion of glucose from plasma into the test pad.

2. Polycythemic blood may discolor the test pad more intensely, interfering with a reflectance reading calibrated for normal levels of color intensity.

3. Characteristics of neonatal blood, such as larger red cell diameter, increased mean corpuscular volume and morphological differences in the red cell membrane structure, may be contributing factors.

4. Due to the nature of polycythemic blood, there is less plasma in the blood available to absorb into the reactive area of the strip, thereby creating a dilution effect.

These effects, and the critical nature of the intended use, dictate that different studies be conducted to support a claim for use with neonates than studies for a claim of monitoring adult diabetes. A clinical study of the subject device should be submitted in the premarket notification. In order to meaningfully evaluate the hematocrit effects and impact of low glucose concentrations with blood glucose monitors in neonatal applications, representative specimens should be obtained. Performance of BGM-N should be evaluated, as much as reasonable, with fresh neonatal capillary blood specimens in a direct comparison to the well-characterized comparative method used routinely in the hospital laboratory (15). This serves as the comparison with the predicate device. These performance evaluation data should be submitted for heelstick samples obtained from a statistically significant number of neonate patients. Report the hematocrit for each patient in this study. Tabulate the glucose results from the subject and predicate devices, along with the hematocrit result. Perform a regression analysis of the glucose method comparison data. Calculate bias and total error at 40 mg/dL from the data. A separate analysis of the data for hematocrit effect should be submitted. For example, one may submit an additional regression analysis of only the samples with abnormal hematocrit.

If sufficient patient specimens with glucose levels of less than or equal to 50 mg/dL cannot be obtained, at least 20 independent samples should be prepared reflecting low glucose concentrations, (10-50 mg/dL), split and run with the meter and the predicate device. Appropriate specimens with high hematocrits and low glucose concentrations can be prepared using either pools of fresh adult blood, or maternal cord bloods. These specimens can provide additional information about hematocrit effect, linearity, and interference without endangering or inconveniencing neonates. These specimens must be prepared, however, in a manner which provides representative high hematocrits and low glucoses seen in the neonatal population of hospital maternity wards. Hematocrit results from these prepared specimens should be tabulated and the data analyzed separately from the clinical study.

In order to demonstrate the absence of a hematocrit effect on accuracy in neonatal blood glucose monitoring, FDA recommends an additional correlation study conducted in the 10-50 mg/dL glucose range, with prepared samples enriched for at least two different hematocrit levels, at or near 45% and 65%. These specimens may also be prepared as noted above.

V. LABELING CONSIDERATIONS

In meeting the requirements of the in vitro diagnostics labeling regulations (21 CFR Part 809.10b), special consideration should be given to the following points in the package insert:

A. Intended Use

The intended use statement should indicate that this product is for monitoring hypoglycemia in neonates diagnosed with laboratory glucose methods.

B. Quality Control

Quality control at the bedside is as important as in the laboratory. Labeling should reflect this, and provide appropriate instructions for quality control procedures and calibration checks.

C. Limitations

State in this section that the device may not be used in screening for neonatal hypoglycemia.

D. Precision

Present precision data for at least two different glucose levels, one of which should be less than 50 mg/dL for the neonate use claim. Additional precision data may be necessary for other claims, as described in other FDA guidance(1, 10).

E. Accuracy

Accuracy data from neonate specimens less than or equal to 50 mg/dL, and from the entire clinical study, should be provided in the package insert. Comparative study data obtained using prepared specimens should be presented separately.

VI. CONCLUSION

Frequent monitoring of blood glucose has been recommended for many years for use in the management of individuals with diabetes. It has also been shown that the portable blood glucose monitors typically utilized by these individuals can be very effective in the management of blood glucose in the hospitalized patient. Portable instruments used for this purpose in the hospital often are more sophisticated in their capabilities. They not only have the capability to test the concentration of blood glucose in these patients, but also provide and store QC information, store patient results, print out information for the health care professional, and generally serve as a reliable point of care system to support the clinical laboratory.

It has been shown that portable blood glucose monitors provide a very effective means for assisting in the health care management of neonatal patients. However, it is also recognized that a neonatal patient, particularly an ill neonate, has many unique physiologic and biochemical characteristics which are important points for consideration by the manufacturer of blood glucose monitors and reagent strips. Most of these parameters have been addressed in this document to

provide guidance to industry in the manufacture and testing of portable blood glucose monitors which will find utility in the neonatal nursery. Submissions to FDA for these systems (monitors and reagent strips) should address the concerns discussed here, and provide appropriate data in the premarket notification demonstrating that the new system is safe and effective for use in the neonatal nursery, and that the labeling claims for this use are well supported.

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Appendix I Checklist for Premarket Notifications for Portable Blood Glucose Monitoring Devices Intended for Bedside Use in the Neonate Nursery

Instructions: The checklist is divided into three sections, File, Studies and Labeling. Please check the box next to the items below that you have included in the premarket notification. Please note that some are required while others are only suggested. Those required are identified as such.

File:

☐ CDRH Premarket Submission Cover Sheet

☐ Truthful and Accurate statement verbatim as required by 21 CFR 807.87(j). Additions and deletions are not permitted.

☐ 510(k) summary **or** statement as required by 21 CFR 807.92 or 21 CFR 807.93 respectively.

Studies:

☐ Precision studies at least two levels, one of which must be in the 10 to 50 mg/dL range.

☐ Correlation study with neonate specimens against the clinical laboratory predicate device. Tabulation and regression analysis of these data. Bias and total error at 40mg/dL calculated from these data.

☐ If sufficient patient samples in the 10 to 50 mg/dL range were not available for the above study, additional correlation data from appropriately prepared samples in this range tabulated and analyzed separately from patient comparison study.

☐ Study of the hematocrit effect using prepared samples with glucose values ranging 10 to 50 mg/dL at two hematocrit levels, approximately 45% and 65%.

- [ ] Linearity and interfering substance data as described in other FDA guidance: Review Criteria for Assessment of Portable Blood Glucose Monitoring in vitro Diagnostic Devices Using Glucose Oxidase or Hexokinase Methodology(10).

Labeling:

- [ ] Draft package insert (labeling) as described by 21 CFR 809.10 Subpart B.

In addition to the labeling requirements of 21 CFR 809.10

- [ ] Intended use statement comprised of monitoring hypoglycemia in neonates diagnosed with laboratory glucose methods.

- [ ] Limitations excluding device use in screening for neonatal hypoglycemia.

- [ ] Precision data for at least two levels, one < 50mg/dL.

- [ ] Correlation (accuracy) data from neonate specimens less than or equal to 50 mg/dL, and from the entire clinical study. Correlation data obtained using prepared specimens should be presented separately.