Guidance for Industry and FDA Staff

Class II Special Controls Guidance Document: Newborn Screening Test Systems for Amino Acids, Free Carnitine, and Acylcarnitines Using Tandem Mass Spectrometry

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostic Device Evaluation and Safety

Preface

Public Comment

Written comments and suggestions may be submitted at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane Room 1061, (HFA-305), Rockville, MD, 20852. Alternatively, electronic comments may be submitted to http://www.fda.gov/dockets/ecomments. Please identify your comments with the docket number 2004D-0481. Comments may not be acted upon by the Agency until the document is next revised or updated.

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

1. Introduction

This guidance document was developed as a special controls guidance to support the classification of newborn screening test systems for amino acids, free carnitine, and acylcarnitines using tandem mass spectrometry into class II (special controls). These devices are intended for the measurement and evaluation of amino acids, free carnitine, and acylcarnitine concentrations from newborn whole blood filter paper samples. Quantitative analysis of amino acids, free carnitine, and acylcarnitines and their relationship with each other provides analyte concentration profiles that may aid in the screening of newborns for one or more inborn errors of amino acid, free carnitine, and acylcarnitine metabolism. This document addresses premarket submissions for newborn screening purposes only; it does not address premarket submissions for confirmatory or pre-natal screening purposes.

This guidance is issued in conjunction with a Federal Register notice announcing the classification of newborn screening test systems for amino acids, free carnitine, and acylcarnitines using tandem mass spectrometry.

Any firm submitting a 510(k) premarket notification for newborn screening test systems for amino acids, free carnitine, and acylcarnitines using tandem mass spectrometry will need to address the issues covered in the special controls guidance. However, the firm need only show that its device meets the recommendations of the guidance or in some other way provides equivalent assurances of safety and effectiveness.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

In this document we use the phrase "inborn errors of metabolism" synonymously with diseases of amino acid, free carnitine, and acylcarnitine metabolism.

The Least Burdensome Approach

The issues identified in this guidance document represent those that we believe need to be addressed before your device can be marketed. In developing the guidance, we carefully considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred in your attempt to follow the statutory and regulatory criteria in the manner suggested by the guidance and in your attempt to address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, you believe that there is a less burdensome way to address the issues, you should follow the procedures outlined in the document, "**A Suggested Approach to Resolving Least Burdensome Issues.**" It is available on our Center web page at: http://www.fda.gov/cdrh/modact/leastburdensome.html.

2. Background

FDA believes that special controls, when combined with the general controls, will be sufficient to provide reasonable assurance of the safety and effectiveness of newborn screening test systems for amino acids, free carnitine, and acylcarnitines using tandem mass spectrometry. A manufacturer who intends to market a device of this generic type should (1) conform to the general controls of the Federal Food, Drug, and Cosmetic Act (the Act), including the premarket notification requirements described in 21 CFR 807 Subpart E, (2) address the specific risks to health associated with newborn screening test systems for amino acids, free carnitine, and acylcarnitines using tandem mass spectrometry identified in this guidance, and (3) obtain a substantial equivalence determination from FDA prior to marketing the device.

This guidance document identifies the classification regulation and product code for newborn screening test systems for amino acids, free carnitine, and acylcarnitines using tandem mass spectrometry (Refer to Section 4 – **Scope)**. In addition, other sections of this special controls guidance document lists the risks to health identified by FDA and describe measures that, if followed by manufacturers and combined with the general controls, will generally address the risks associated with these systems and lead to a timely premarket notification [510(k)] review and clearance. This document supplements other FDA documents regarding the specific content requirements of a premarket notification submission. You should also refer to 21 CFR 807.87 and other FDA documents on this topic, such as the **510(k) Manual - Premarket Notification: 510(k) - Regulatory Requirements for Medical Devices**, http://www.fda.gov/cdrh/manual/510kprt1.html.

As explained in "**The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications; Final Guidance**[1]," a manufacturer may submit a Traditional 510(k) or has the option of submitting either an Abbreviated 510(k) or a Special 510(k). FDA believes an Abbreviated 510(k) provides the least burdensome means of demonstrating substantial equivalence for a new device, particularly once a special controls guidance document has been issued. Manufacturers considering modifications to their own cleared devices may lessen the regulatory burden by submitting a Special 510(k).

3. The Content and Format of an Abbreviated 510(k) Submission

An Abbreviated 510(k) submission must include the required elements identified in 21 CFR 807.87, including the proposed labeling for the device sufficient to describe the device, its intended use, and the directions for its use. In an Abbreviated 510(k), FDA may consider the contents of a summary report to be appropriate supporting data within the meaning of 21 CFR 807.87(f) or (g); therefore, we recommend that you include a summary report. The report should describe how this guidance document was used during the device development and testing and the methods or tests used. The report should also include a summary of the test data or description of the acceptance criteria applied to address the risks identified in this document, as well as any additional risks specific to your device. This section suggests information to fulfill some of the requirements of 21 CFR 807.87, as well as some other items that we recommend you include in an Abbreviated 510(k).

Coversheet

The coversheet should prominently identify the submission as an Abbreviated 510(k) and cite the title of this class II special controls guidance document.

Proposed labeling

Proposed labeling should be sufficient to describe the device, its intended use, and the directions for its use. (Refer to Section 8 for specific information that you should include in the labeling for the device type covered by this document.)

Summary report

We recommend that the summary report contain:

- A description of the device and its intended use. We recommend that the description include a complete discussion of the performance specifications and, when appropriate, detailed, labeled drawings of the device. You should also submit an "indications for use" enclosure.[2]

- A description of device design requirements.

[1] http://www.fda.gov/cdrh/ode/parad510.html

[2] Refer to http://www.fda.gov/cdrh/ode/indicate.html for the recommended format.

- Identification of the Risk Analysis method(s) used to assess the risk profile in general, as well as the specific device's design and the results of this analysis. (Refer to Section 5 for the risks to health generally associated with the use of this device that FDA has identified.)

- A discussion of the device characteristics that address the risks identified in this class II special controls guidance document, as well as any additional risks identified in your risk analysis.

- A brief description of the test method(s) you have used or intend to use to address each performance aspect identified in Sections 6 and 7 of this class II special controls guidance document. If you follow a suggested test method, you may cite the method rather than describing it. If you modify a suggested test method, you may cite the method but should provide sufficient information to explain the nature of and reason for the modification. For each test, you may either (1) briefly present the data resulting from the test in clear and concise form, such as a table, **or** (2) describe the acceptance criteria that you will apply to your test results.[3] (See also 21 CFR 820.30, Subpart C - Design Controls for the Quality System Regulation.)

- If you choose to rely on a recognized standard for any part of the device design or testing, you may include either: (1) a statement that testing will be conducted and meet specified acceptance criteria before the product is marketed, or (2) a declaration of conformity to the standard.[4] Because a declaration of conformity is based on results from testing, we believe you cannot properly submit a declaration of conformity until you have completed the testing the standard describes. For more information, please refer to section 514(c)(1)(B) of the Act and the FDA guidance, **Use of Standards in Substantial Equivalence Determinations; Final Guidance for Industry and FDA**, http://www.fda.gov/cdrh/ode/guidance/1131.html.

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If it is not clear how you have addressed the risks identified by FDA or additional risks identified through your risk analysis, we may request additional information about aspects of the device's performance characteristics. We may also request additional information if we need it to assess the adequacy of your acceptance criteria. (Under 21 CFR 807.87(l), we may request any

[3] If FDA makes a substantial equivalence determination based on acceptance criteria, the subject device should be tested and shown to meet these acceptance criteria before being introduced into interstate commerce. If the finished device does not meet the acceptance criteria and, thus, differs from the device described in the cleared 510(k), FDA recommends that submitters apply the same criteria used to assess modifications to legally marketed devices (21 CFR 807.81(a)(3)) to determine whether marketing of the finished device requires clearance of a new 510(k).

[4] See Required Elements for a Declaration of Conformity to a Recognized Standard (Screening Checklist for All Premarket Notification [510(k)] Submissions), http://www.fda.gov/cdrh/ode/reqrecstand.html.

additional information that is necessary to reach a determination regarding substantial equivalence.)

As an alternative to submitting an Abbreviated 510(k), you can submit a Traditional 510(k) that provides all of the information and data required under 21 CFR 807.87 and described in this guidance. A Traditional 510(k) should include all of your methods, data, acceptance criteria, and conclusions. Manufacturers considering modifications to their own cleared device should consider submitting a Special 510(k).

The general discussion above applies to any device subject to a special controls guidance document. The following is a specific discussion of how you should apply this special controls guidance document to a premarket notification for newborn screening test systems for amino acids, free carnitine, and acylcarnitines using tandem mass spectrometry.

4. Scope

The scope of this document is limited to the following device as described in 21 CFR 862.1055 (product code: NQL):

> 21 CFR 862.1055 –Newborn screening test system for amino acids, free carnitine, and acylcarnitines using tandem mass spectrometry
>
> A newborn screening test system for amino acids, free carnitine, and acylcarnitines using tandem mass spectrometry is a device that consists of stable isotope internal standards, control materials, extraction solutions, flow solvents, instrumentation, software packages, and other reagents and materials. The device is intended for the measurement and evaluation of amino acids, free carnitine, and acylcarnitine concentrations from newborn whole blood filter paper samples. The quantitative analysis of amino acids, free carnitine, and acylcarnitines and their relationship with each other provides analyte concentration profiles that may aid in screening newborns for one or more inborn errors of amino acid, free carnitine, and acylcarnitine metabolism.

5. Risks to Health

There are no known *direct* risks to patient health. However, failure of the test to perform as indicated or error in interpretation of results may lead to improper medical management of patients with inborn errors of metabolism. For example, a false negative (false normal) measurement could contribute to failure to detect a possible inborn error of metabolism, which could lead to functional impairment or death. A false positive (false abnormal) measurement could contribute to unnecessary additional patient testing and added concern and apprehension of parents and physicians.

In the table below, FDA has identified the risk to health generally associated with the use of newborn screening test systems for amino acids, free carnitine, and acylcarnitines addressed in this document. The measures recommended to mitigate this risk are given in this guidance document, as shown in the table below. We recommend that you conduct a risk analysis, prior to submitting your premarket notification to identify any other risks specific to your device. The

premarket notification should describe the risk analysis method. If you elect to use an alternative approach to address a particular risk identified in this document, or have identified risks additional to those in this document, you should provide sufficient detail to support the approach you have used to address that risk.

Identified risk	Recommended mitigation measures
Improper patient management	Sections 6, 7, and 8

6. Performance Characteristics

General Study Recommendations

For the pre-clinical studies described below, you may use whole blood samples spiked with known quantities of representative amino acids, free carnitine, and acylcarnitines and spotted on filter paper. You may also obtain whole blood filter paper samples from proficiency testing programs. You should design the studies so that they incorporate the effects of all preparatory steps on test performance. Although spiked whole blood filter paper samples can be used as a supplement in pre-clinical studies, we caution against using spiked samples as the only matrix in the evaluations, because spiked samples may not provide an accurate assessment of the performance characteristics. You should include patient samples derived from the intended use population (e.g., newborn screening samples) and from appropriate control groups in your clinical (method comparison) studies, with known abnormal samples interspersed randomly among the normal samples.

We recommend that you evaluate the assay in at least two external sites in addition to that of the manufacturer's site, using clinical samples from the intended use population (e.g., newborns). Generally, we recommend that you assess performance in the testing environment where the device will ultimately be used (i.e., central laboratory or reference laboratory) by individuals who will use the test in clinical practice (e.g., trained technologists). We recommend that you analyze data from the individual sites separately to evaluate any inter-site variation and include results of the analysis in the 510(k) summary report. You can pool method comparison results from the individual sites in the package insert if you demonstrate that there are no significant differences in the results among sites. It may be helpful to contact the Division of Chemistry and Toxicology Devices to discuss questions you have about a clinical study or other issues before initiating the study.

We recommend that you provide appropriate specifics concerning protocols in the 510(k) so that we can interpret acceptance criteria or data summaries during the review. For example, when referring to NCCLS protocols or guidelines, we recommend that you indicate the specific aspects of the protocols or guidelines you followed. We also recommend that you include protocol specifics in labeling, as these may be crucial to aid users in interpreting information in your labeling.

Software Validation

You should provide documentation of the software validation for all programs associated with the device. FDA guidance documents on software, "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices; Final," www.fda.gov/cdrh/ode/57.html and "Guidance for Off-the-Shelf Software Use in Medical Devices; Final," www.fda.gov/cdrh/ode/1252.html contain information about the documentation recommended for 510(k) premarket submissions.

We believe the software used in class II newborn screening test systems for amino acids, free carnitine,, and acylcarnitines using tandem mass spectrometry systems meets the definition given in these guidance documents for devices with a moderate level of concern, because they are used in the diagnosis of a condition that, if misdiagnosed, could result in a serious injury to newborns. Therefore, we recommend that you provide documentation appropriate for devices with moderate level of concern.

Specific Performance Characteristics

Reproducibility

You should characterize within-run and total imprecision for your device. We recommend using whole blood samples spotted on filter paper at three relevant concentrations, including concentrations near medical decision points and at concentrations near the limits of the reportable range (e.g., above the medical decision concentration and at a clearly abnormal concentration). We recommend that you include inter-injection as a factor of total imprecision.

Guidelines provided in the NCCLS document, "Evaluation of Precision Performance of Clinical Chemistry Devices;" Approved Guideline, EP5-A (1999), describe an acceptable approach. That document includes guidelines for experimental design, computations, and a format for stating performance claims.

We recommend that you include the following items in the description of your evaluation:

- Sample types (e.g., whole blood spotted on filter paper).
- Point estimates of the analyte concentration.
- Sites at which precision protocol was run.
- Number of days, runs, and observations.
- Standard deviations of within-run and total imprecision.
- Inter-injection variation.

We recommend that you identify which factors (e.g., instrument calibration, reagent lots, operators) were held constant and which were varied during the evaluation. You should describe the computational methods, if they are different from that described in NCCLS EP5-A.

Interference

We recommend that you characterize the effects of potential interferents on assay performance. The NCCLS document "Interference Testing in Clinical Chemistry; Approved Guideline," EP-7A (2002) describes, in detail, examples of experimental designs, including guidelines for selecting interferents for testing.

Typically, interference studies involve adding the potential interferent to the sample of whole blood spotted on filter paper and determining any bias in the recovery of analyte relative to a control sample (to which no interferent has been added).

Some known sources of interference are: improper specimen collection; certain medication treatments (e.g., valproic acid, pivalic acid); anticoagulants, such as EDTA; and other compounds, such as benzoic acid, asparagine, hydroxyproline, methionine sulfone, methionine sulfoxide, glutamate, and incomplete butylation of acylcarnitines. The compounds above may not be all-inclusive. When the assay is in widespread use, other sources of interference may become clinically apparent and should be evaluated.

We recommend that you include the following items in your 510(k):

- Types and levels of interferents tested.
- Sample type (e.g. whole blood spotted on filter paper).
- Concentrations of analyte in the sample.
- Number of replicates tested.
- Definition or method of computing interference.

If you identify any observed trends in bias (i.e., negative or positive), you should indicate the range of observed recoveries in the presence of the particular interferent. This approach is more informative than listing average recoveries alone.

Functional Sensitivity/ Limit of Detection

We recommend that you calculate the functional sensitivity of the test system. Often this is defined as the lowest analyte concentration that can be reliably (usually 95% with stated probability) detected, and for which assay bias and inter-assay precision meet your stated acceptance criteria. For amino acids, free carnitine, and acylcarnitines, the functional sensitivity must be at or below the normal endogenous concentrations.

We recommend that you describe the methodology, (e.g., sample type, measures of sensitivity, and acceptance criteria) that clarifies how you established the limit of detection of the test system.

Linearity

We recommend that you characterize the linear range of the assay by evaluating samples whose concentration levels are known relative to each other. The NCCLS document, "Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline," EP-6A (2003), describes a protocol for sample preparation and value assignment as well as a format for stating performance characteristics.

We also recommend you characterize the method(s) used to determine analyte recovery.

You should describe the sample types and preparation, concentrations and number of replicates in your evaluation. When describing your acceptance criteria or summary data, we recommend that you include the slope and intercept with confidence intervals for the estimated regression line, the range of linearity and the degree of deviations (biases) that were observed or that are considered acceptable for the various concentration levels. Often these deviations can be best described by listing observed or acceptable values relative to the expected values for each level evaluated.

Calibration and Control Materials

General Comments: You should describe the relationship of all control and calibration materials to each specific amino acid, free carnitine, or acylcarnitine tested by your device. You should also describe the traceability of your control and calibrator materials. The incorporation of newly emerging control and calibration material is desired and optimal.

Specific Recommendations: We recommend that you provide the following information about the calibrator and control materials:

- Protocols and acceptance criteria for real-time or accelerated stability studies for opened and unopened calibrators.
- Protocols and acceptance criteria for value assignment and validation, including any specific instrument applications or statistical analyses used.
- Identification of traceability to a domestic or international standard reference material.
- Protocols and acceptance criteria for the transfer of performance of a primary calibrator/control to a secondary calibrator/control.
- A table illustrating the specific substances that serve as a calibrator and or a control for each specific analyte, if there is not a one to one relationship between calibrator/control material and analyte detected by your device.

For information about calibrators marketed separately as class II devices under 862.1150, see FDA guidance "Abbreviated 510(k) Submissions for *In Vitro* Diagnostic Calibrators," http://www.fda.gov/cdrh/ode/calibrator.html. For information about control materials marketed separately as class I devices under 862.1660, see FDA guidance "Guidance for Industry, Points to Consider Guidance Document on Assayed and Unassayed Quality Control Material," http://www.fda.gov/cdrh/ode/qcmat.pdf

Carry Over and Drift

You should evaluate each amino acid, free carnitine, and acylcarnitine for any effects of carry over or drift using referenced material. We recommend that you include evaluation at low, mid, and high concentrations spotted on filter paper and assayed using your complete system. Specifically, drift is evaluated over a period of time. We recommend that you provide the statistical analyses of your results.

Cut-Off(s) / Reference Interval(s)

You should determine the cut-off values for each amino acid, free carnitine, and acylcarnitine in newborn samples spotted on filter paper. You should include a sufficiently large sample size from two or more different geographical sites in order to establish the cutoff. This is important for achieving high reliability in discerning abnormal patterns of inborn errors of metabolism. We recommend that you include the following in the description of your evaluation:

- Criteria for selecting the samples (e.g., random order, number of samples from the same infant, minimum birth weight of infant, age of infant at time of blood collection, and samples analyzed within a time frame of blood collection).
- Description of samples in the study, including relevant features listed above.
- Description of the type of site and the individual doing the testing.
- Number of samples.
- Statistical method used to analyze the data and establish the cut-off(s).

If appropriate, you should provide information on the use of an equivocal zone for testing. We recommend that you perform an initial feasibility study to determine the cut-off(s) and a larger study performed at two or more geographical sites to verify the cut-off(s).

7. Method Comparison

We recommend that you compare your device to a predicate device or an acceptable reference method. As with studies to evaluate performance characteristics, you may contact the Division of Chemistry and Toxicology Devices for input on your study plan prior to initiating comparison studies. Banked (retrospective) filter paper samples may be appropriate for some studies as long as information described below, concerning sample characterization, is available.

Specimen collection and handling conditions You should substantiate recommendations in your labeling concerning specimen collection, storage, and transport by assessing whether the device can maintain acceptable performance (e.g., precision) over the storage times and temperatures that you recommend to users. For example, an appropriate study may include an analysis of aliquots stored under the conditions of time, temperature, or allowed number of freeze/thaw cycles. NCCLS LA4-4A "Blood Collection on Filter Paper for Newborn Screening Programs; Approved Standard" – Fourth Edition (2003), addresses the issues associated with specimen collection, the filter paper collection device, and the transfer of blood onto filter paper, and provides uniform techniques for collecting the best possible specimen for newborn screening.

Sample selection, inclusion, and exclusion criteria

We recommend that you evaluate newborn whole blood filter paper samples distributed across the reportable range of the assay. Regardless of whether prospective or retrospective samples are used, we suggest that you provide a clear description of how the samples were selected, including reasons that samples are excluded. We recommend that you indicate whether samples are chosen from patients with specific clinical outcome.

Appropriate sample size depends on factors, such as precision, interference, range, and other performance characteristics of the test. We recommend that you provide a statistical justification to support the study sample size. The number of patients should be large enough so that inter-individual variation would be observed.

Presentation of Results

We recommend that you conduct separate data analyses for each group that you include in your evaluation (e.g., by age, gender, disease/non-disease, and ethnic background). We recommend that you provide quantitative and qualitative results. To summarize your quantitative analysis, we recommend that you provide the following:

- Plots of results from the new assay (y-axis) versus the reference method (x-axis), including all of the data points, the estimated regression line and the line of identity. Data points should represent individual measurements.

- A description of the analytical method used to fit the regression line.

- Results of regression analysis, including the slope and intercept with their 95% confidence limits, the standard error of the estimate (calculated in the y direction), and the correlation coefficient.

To summarize your qualitative analysis, we recommend that you provide the following:

- A 2x2 table showing qualitative agreement between the new assays (rows) and the predicate or reference method (columns).

- The percent positive, percent negative, and overall agreement between the methods, including the 95% confidence interval or other measures of robustness, where appropriate.

8. Labeling

The premarket notification should include labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e.)).[5] The following recommendations are aimed at assisting you in preparing labeling that satisfies this requirement.

Directions for use

You should include clear instructions that delineate the technological features of the specific device and how the device is to be used on patients. We recommend that your instructions encourage local/institutional training programs designed to familiarize users with the features of the device and how to use it in a safe and effective manner.

Intended use

You should specify each amino acid, free carnitine, and acylcarnitine that your device is intended to measure, the specific population (e.g., newborns) for which the test is intended, and the acceptable specimen type (e.g., whole blood filter paper).

Limitations and Precautions

We recommend that you provide the following information concerning limitations:

- Descriptions of conditions that may alter assay results (e.g., an antibiotic that will affect assay results, an incomplete butylation of acylcarnitines that may interfere with smaller chain butylated acylcarnitines).

- Statement emphasizing that this device is for screening and that a diagnostic procedure is necessary for confirmation of presumptive abnormal amino acid and acylcarnitine profiles.

- Clarification that no single metabolite will provide sufficient information about a metabolic defect, but rather that a pattern of metabolites are presumptive for a particular disorder.

- Clarification that age relative to disease state is a complicating factor for newborn screening.

- Explanations addressing rare and/or newly identified inborn errors of metabolism that may be known but not detected by your device (e.g., some forms of dicarboxylic aminoaciduria).

[5] Although final labeling is not required for 510(k) clearance, final labeling must comply with the requirements of 21 CFR 801 and 21 CFR 809.10 before a medical device is introduced into interstate commerce. Labeling recommendations in this guidance are consistent with the requirements of part 801 and section 809.10.

Quality Control

We recommend that you provide suitable control materials and provide a table showing the relationship of all control materials to each specific amino acid, free carnitine, or acylcarnitine. The incorporation of newly available control material is desired and optimal.

Expected Values and Interpretation of Results

We recommend that you emphasize in the labeling that decisions should not be made solely on the basis of results obtained with the screening device, but always in conjunction with other accepted methods of clinical assessment. You should clarify that samples found to be above the cut-off for any given analyte should be confirmed.

You should provide a table of published estimates of the physiologic and pathophysiologic ranges for the amino acids and acylcarnitines along with the cut-off values determined by your system. You should cite the published references from which you gather this information. You should include discussion of important factors in the interpretation of results, such as the correlation of diseases with expected metabolites and the age of the infant.

Performance

You should include in the package insert a description of your evaluation and results observed for all the performance characteristics discussed in sections 6 and 7 above, in order to aid the user in interpretation of results.

For the method comparison study, you should provide a description of device performance in comparison to an accepted reference method or predicate device. Typically, this is most clearly represented in the form of 2x2 tables and percent agreement. We recommend you include a table of the specific inborn errors of metabolism represented by the positive specimens your device detected during the study. We also recommend that you state how your positive specimens were identified.