Guidance for Industry and FDA Staff

Class II Special Controls Guidance Document: Drug Metabolizing Enzyme Genotyping System

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Preface

Public Comment

Written comments and suggestions may be submitted at any time for Agency consideration to 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 No. 2005D-0068. Comments may not be acted upon by the Agency until the document is next revised or updated.

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Guidance for Industry and FDA Staff

Class II Special Controls Guidance Document: Drug Metabolizing Enzyme Genotyping System

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 number listed on the title page of this guidance.

1. Introduction

This document was developed as a special control to support the classification of drug metabolizing enzyme (DME) genotyping systems into class II (special controls). A DME genotyping system is a device intended for use in testing DNA to identify the presence or absence of human genotypic markers encoding a drug metabolizing enzyme. This device is used as an aid in determining treatment choice and individualizing treatment dose for therapeutics that are metabolized primarily by the specific enzyme about which the system provides genotypic information.

This guidance is issued in conjunction with a *Federal Register* notice announcing the classification of DME genotyping systems. Any firm submitting a 510(k) premarket notification for a DME genotyping system will need to address the issues covered in the special control 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.

The Least Burdensome Approach

The issues identified in this guidance document represent those that we believe should 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, provide reasonable assurance of the safety and effectiveness of DME genotyping systems. A manufacturer who intends to market a device of this 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 DME genotyping systems 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 DME genotyping systems. (Refer to Section 4 – **Scope.)** In addition, other sections of this guidance document list 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 assays 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 either a Traditional 510(k) or an Abbreviated 510(k). FDA believes an Abbreviated 510(k) provides the least burdensome means of demonstrating substantial equivalence for a new device, particularly when FDA has issued a guidance document that provides recommendations on what should be addressed in a submission for the device. Alternatively, 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

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

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 generally 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 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 10 for specific information that you should include in the labeling for this type of device.)

Summary report

We recommend that the summary report contain the following:

- A description of the device and its intended use. You should also submit an "indications for use" enclosure.[2] (Refer to Section 6 for specific information that you should include in the intended use and device description for this type of device.)

- A description of the device design. We recommend that the description include a complete discussion of the performance specifications and, when appropriate, detailed, labeled drawings of the device.

- 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.)

- 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 7 and 8 of this 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) present the data resulting from the test in clear and concise form, such as a table, **or** (2) describe the acceptance criteria

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

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.

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 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 devices should consider submitting Special 510(k)s.

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 DME genotyping systems.

4. Scope

The scope of this document is limited to the following devices as described in 21 CFR 862.3360 (product code NTI):

21 CFR 862.3360 Drug metabolizing enzyme genotyping system

[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.

A drug metabolizing enzyme genotyping system is a device intended for use in testing DNA to identify the presence or absence of human genotypic markers encoding a drug metabolizing enzyme. This device is used as an aid in determining treatment choice and individualizing treatment dose for therapeutics that are metabolized primarily by the specific enzyme about which the system provides genotypic information.

DME genotyping systems that are multiplex tests may be run on instrumentation for clinical multiplex test systems. Instrumentation for clinical multiplex test systems is regulated under 21 CFR 862.2570. Guidance for such instrumentation is available in the FDA Guidance for Industry and FDA Staff "*Class II Special Controls Guidance Document: Instrumentation for Clinical Multiplex Test Systems*." If your device includes a DME genotyping assay with instrumentation for clinical multiplex test systems for that assay, you may submit the information for both devices within one 510(k). Although instrumentation for clinical multiplex test systems (a Class II device) may be used with a DME genotyping system, the guidance document, "*Replacement Reagent and Instrument Family Policy"*, (available at http://www.fda.gov/cdrh/oivd/guidance/950.pdf) does not apply to DME genotyping systems for use with instrumentation for clinical multiplex test systems.

5. Risks to Health

Failure to correctly identify the DME genotype could result in incorrect patient management decisions. In these situations a patient might be prescribed an incorrect drug or drug dose with concomitant increased risk of adverse reactions due to increased or decreased drug metabolism. Likewise, failure to properly interpret genotyping results could lead to incorrect prediction of phenotype and result in incorrect patient management decisions.

The information provided by this type of genetic test should only be used to supplement other tools for therapeutic decision-making in conjunction with routine monitoring by a physician. The effect that a specific DME allele has on drug metabolism may vary depending on the specific drug, even for drugs within a specific class. Effects of specific alleles on drug metabolism are well-documented for some drugs; for other drugs, they are less well-documented. Therefore, clinicians should use professional judgement when interpreting results from this type of test. In addition, results from this type of assay should not be used to predict a patient's response to drugs in cases where either, 1) the drug metabolizing enzyme activity of the allele has not been determined, or 2) the drug's metabolic pathway has not been clearly established.

In the table below, FDA has identified the risks to health generally associated with the use of DME genotyping systems addressed in this document. The measures recommended to mitigate these identified risks 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
Failure to correctly identify genotype encoding for a DME	Sections 7, 8, and 9
Failure to properly interpret genotyping results	Section 10

6. Device Description

You should describe the following information in your 510(k).

Intended Use

The intended use should specify the genotype(s) the test is intended to detect, the general clinical utility of detecting the genotype, and the specific populations to which the test is targeted. The intended use should specify the drug metabolizing enzyme encoded by the genotype.
Some tests may have multiple intended uses (e.g., multiple DME's). When separate studies are needed to support the multiple intended uses, you should submit separate 510(k) applications for each intended use. You should consult the appropriate review divisions in OIVD for advice on submitting applications for test systems with multiple intended uses.

Test Methodology

You should describe in detail the methodology used by your device to detect genotypes. For example, you should describe the following elements, where applicable for your device:

- Test platform[5] (e.g., flow cytometry, instrumentation for clinical multiplex test systems).
- Composition and spatial layout of arrays or other spatially fixed platforms.
- Methods used in attaching the probe material to a solid surface, if applicable.
- Sequence or identity of oligonucleotides, primers, probes, or other capture elements.
- Hybridization conditions, washing procedures and drying conditions (e.g., temperature, length of time).
- Specificity of probes for the sequence of interest, especially when pseudogenes or sequence-related genes exist.
- Methodology for DNA extraction that you provide or that you recommend for users.
- Assay components such as buffers, enzymes, fluorescent dyes, chemiluminescent reagents, other signaling and signal amplification reagents, instruments.
- External controls that you recommend or provide to users.
- Any internal controls, including those that mitigate miscalls (inaccurate results) due to genotypes that your device does not detect.

[5] Some of the elements listed in this section are applicable to instrumentation. If you are submitting a separate 510(k) for your instrumentation, you can describe the elements specific for instrumentation in that 510(k).

Where applicable for your device, you should describe the quality control design specifications in place to address the following:

- Correct placement and identity of instrument features (e.g., probes).
- For multiplexed tests in which the target molecules will contact a number of different probes, the potential for specific and non-specific probe cross-hybridization.
- Prevention of probe cross-contamination, for multiplexed tests in which many probes are handled during the manufacturing process.

Illustrations or photographs of non-standard equipment or methods can be helpful in understanding novel methodologies.

Test Algorithms

Because of the large number of polymorphisms found within some DME genes, and the fact that some polymorphisms may be common to various alleles, you should explain how the test algorithms were developed to report DME genotype, if applicable.

Test Results

You should provide examples of the test reports (e.g., printouts) that are generated for the clinician. These reports should be consistent with current recommendations of genetics professional societies, if applicable, and should contain adequate interpretation guidelines for the use of the ordering physician/counselor.

Where applicable, reports should describe the polymorphisms identified by your test and the methodology and technology used for detection. You should identify representative literature references describing genotypic interpretations, or phenotypic predictions, if applicable, to enable users to access information about specific genotypes. We expect that for most 510(k) applications, appropriate literature references will be available. If such supporting information is not available, you should provide information based on the clinical studies you conducted to address clinical validity of your device.

7. Performance Characteristics

In your 510(k), you should detail the study design you used to evaluate each of the performance characteristics outlined below. This should include information such as:

- Description of the samples you used in testing (including types of samples, preparation or origin, number of samples and how the samples specifically represent your intended use samples).
- Descriptions of the computations and statistical analyses you used to evaluate your data.
- Explanations, if there were any deviations from your protocol.

For each of the performance characteristics described below, you should also provide a clear description of all results and acceptance criteria in your 510(k).

The issues described below generally apply, regardless of the technology used by the device to detect the DME genotype. If you make additional claims for other performance characteristics not mentioned below, you should describe the study designs and results you used to support them.

Preanalytical Factors

Consideration of preanalytical factors is critical for high-quality genetic tests. If you intend to provide reagents for extraction and preparation of DNA for testing, you should validate each step in the preanalytical process for its effects on reproducibility, accuracy, and stability of product and describe study design and results addressing this issue in the 510(k). Your external site studies (e.g., reproducibility, method comparison) should include evaluation of the preanalytical process.

If you do not intend to provide reagents for DNA extraction and preparation as part of the assay, you should provide specifications for the reagents needed and for assessing the quality of the assay input DNA, so that the user can select appropriate reagents. You should describe, in your 510(k), the study design and results you used to determine these specifications. In this case, we recommend that in studies establishing the performance of your device, you permit sites to use any extraction method they choose, provided that it meets your test's specifications. In this way, you can evaluate any effect of variations in preanalytical processes on your device performance.

You should evaluate the accuracy and precision of your assay, including DNA extraction, from all the sources of DNA that you recommend for your assay (e.g., blood, PBMC, buccal swab). You should also evaluate all sample collection and storage options you recommend (e.g., heparin-preserved vs. EDTA-preserved blood, stored vs. fresh sample). Your validation of appropriate storage conditions should include both the sample and the extracted product.

You should evaluate the stability of all of your reagents and recommended samples.

Quality Control

DME genotyping systems should include both positive and negative controls. Controls should approximate sample composition and DNA concentration in order to adequately challenge the system.

You should describe the following concerning quality control and calibration material:

- The nature and the function of the various controls that you include with, or recommend for, your system. These controls may differ between individual technologies, but they should enable the user to determine if all steps and critical reactions have proceeded properly and without contamination or cross-hybridization.
- Your methods for value assignment and validation of control and calibrator material.

- Your methods for establishing quality control and calibration procedures, including your recommended frequency.

We recommend that you provide for the calibration of DME genotyping systems where appropriate.

Analytical Factors

Analytical Sensitivity and Assay Limits

You should validate the analytical sensitivity of your test. This may be defined as the lowest amount of genomic DNA for which the assay can detect genotypes with a given accuracy and precision. You should also approximate the volume of the clinical sample required to generate this minimum input. We recommend that you determine analytical sensitivity using samples containing genomic DNA at varying concentrations. You should test a statistically determined number of replicates at each DNA level. Similarly, you should determine the upper limit of the assay, in terms of DNA concentration and sample volume.

Interference

Where applicable, you should evaluate cross-contamination of your device. In particular, you should perform studies to characterize potential carryover by alternating specimens of known genotype. You should also evaluate homologous gene sequences for cross-reactivity.

Potential interfering substances may not always be removed by sample preparation, and may also interfere with sample preparation. Therefore, we recommend that you characterize the effects of potential interfering substances on assay performance. Examples of experimental designs, including guidelines for selecting interfering substances for testing, are described in detail in "Interference Testing in Clinical Chemistry; Approved Guideline" (NCCLS document EP7-A, 2002). Potential interfering substances can include compounds normally found in serum, such as triglycerides, hemoglobin (for specimens other than blood), bilirubin, lipids, and exogenous compounds such as common drugs.

Precision (Repeatability/Reproducibility)

You should fully examine the reproducibility of your DME genotyping system. "Evaluation of Precision Performance of Clinical Chemistry Devices" (NCCLS Document EP5-A) and "User Protocol for Evaluation of Qualitative Test Performance" (NCCLS EP-12A) include guidelines for experimental design, computations, and a format for stating performance claims. We recommend that you incorporate the following in the design of your reproducibility studies:

- Design the study so that you can characterize intra- and inter-assay reproducibility.
- Use appropriate test samples at multiple DNA concentrations, similar to the concentrations in the procedure you recommend to users. You should include both wild-type and mutation sequences. In addition, the genotype of samples or sample panels you test should, as much as possible, reflect all the alleles that are included in the test.
- Ensure that samples used in reproducibility testing are processed from "real" samples (e.g., whole blood, buccal swabs, or other intended use matrices) at the test site and that processing mimics the procedure you plan to recommend in the test labeling.

- Include 3 or more sites with multiple operators at each site. Operators should reflect potential users of the assay, in terms of education and experience. If training will be necessary for users to perform the test once it is marketed, you should provide information on operator training. If such training is not expected to be provided for users, you should not provide additional training (other than the proposed labeling, such as the package insert) at the testing sites.

- Ensure that procedures used in the reproducibility studies are the same as the procedure that you will recommend to users in the package insert.

- Include multiple product lots, and multiple instruments (if instruments are part of the test system), to adequately test the expected performance of the system.

In the study design description in your 510(k), you should identify which factors (e.g., instrument calibration, reagent lots, and operators) were held constant and which were varied during the evaluation, and describe the computations and statistical analyses used to evaluate the data.

8. Method Comparison

You should perform method comparison studies that demonstrate that your device detects the genotypes it claims to detect, and does not detect mutations when none are present. Samples used in these studies should be patient samples derived from the intended use population, in order to show that the device will perform as claimed in a clinical setting. We recommend that you perform method comparison studies at 3 or more sites that reflect potential users of the assay, in terms of experience and education.

Because of the abundance of technologies that could be used to genotype a patient's drug metabolizing enzyme(s), assays may vary significantly in terms of methodology, instrumentation, and sample source, making direct comparison difficult. You should compare results of your device to bidirectional DNA sequence analysis.

You should describe the protocol and results of your method comparison in your 510(k). You should submit, along with your comparative sequence data, a measure of sequence quality such as a phred score or percent correct sequence calls. You can then use this information to calculate the percent correct genotype calls of your device, relative to the bidirectional sequence data. We recommend that you tabulate all results and indicate the percent correct calls for the various genotypes. We recommend that you resolve and explain all discrepant results in the 510(k); however, you should use original unresolved results for all performance calculations, in order to avoid bias. You should include failed assays (e.g., inability to correctly determine genotype within a sample, reporting of an incorrect result, instrument failure, or reagent failure) in your description of results. Any incorrect or absent genotype determinations should be considered disagreements for the purposes of reporting performance characteristics.

Clinical Validation

Prospective clinical testing to determine clinical validity may not be necessary for validation of DME genotyping systems, if there is an established scientific framework and sufficient body of evidence supporting the clinical validity and utility of your device. In this case, you should

provide the relevant peer-reviewed references. These should include multiple studies that test appropriate populations. In cases where the literature does not sufficiently support your indications for use, you should conduct studies (usually prospective studies) to support claims for your device. In either case, you should demonstrate the association between the drug metabolizing enzyme genotype and the drug metabolic profile based on clinical testing (such as enzymatic rate studies) of study subjects.

Study Samples

While prospective samples are preferred, well-characterized samples from banks can be used in your method comparison study, if clinical utility and validity are already established in the literature. You should use clinical samples from all matrices you claim in your intended use to demonstrate that correct results can be obtained from clinical material. You should fully describe selection (inclusion/exclusion) criteria and characterize any relevant features of the samples (whether prospective, or from banks). You should also provide clear information supporting sample integrity.

Appropriate sample size depends on factors such as reproducibility, interference, and other performance characteristics of the test. We recommend that you provide a statistical justification to support your study sample size.

We recommend that you evaluate test samples that encompass all genotypes in the test system. For rare mutant alleles, genomic DNA samples or clone blends may also be used, but the composition of the test samples generated from these clones should resemble, as closely as possible, the protein and DNA content and concentrations of real clinical samples. If you use clones, you should test them in combination with various other alleles or genetic backgrounds, so that they reflect heterozygous, as well as homozygous samples. In cases where you cannot obtain multiple samples of a rare genotype, you should test a statistically determined number of replicates so that you can calculate a meaningful reproducibility value for that allele.

Sample collection and handling conditions

We recommend that you validate statements in your labeling about sample storage and transport by assessing sample stability and recovery over the storage times and temperatures recommended to users. For example, an appropriate study may include an analysis of aliquots stored under the conditions of time, temperature, or specified number of freeze/thaw cycles. We recommend that you state your acceptance criteria for the sample stability parameters.

9. Software

If your system includes software, you should submit software documentation detailed in accordance with the level of concern (See: *Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices* (http://www.fda.gov/cdrh/ode/57.html)). You should determine the Level of Concern prior to the mitigation of hazards. In vitro diagnostic devices of this type are typically considered a moderate level of concern, because software flaws could indirectly affect the patient and potentially result in injury because of the action or inaction of a healthcare provider who does not get accurate information.

You should include the following points, as appropriate, in preparing software documentation for FDA review:

- Full description of the software design. Your software should not include utilities that are specifically designed to support uses beyond those in your intended use. You should also consider privacy and security issues in your design. Information about some of these issues may be found at the following website regarding the Health Insurance Portability and Accountability Act (HIPAA) http://aspe.os.dhhs.gov/admnsimp.

- Hazard analysis based on critical thinking about the device design and the impact of any failure of subsystem components, such as signal detection and analysis, data storage, system communications and cybersecurity in relationship to incorrect patient reports, instrument failures, and operator safety.

- Documentation of complete verification and validation (V&V) activities for the version of software that will be submitted to demonstrate substantial equivalence. You should also submit information regarding validation of the compatibility of assay software with any instrumentation software.

- If the information you include in the 510(k) is based on a version other than the release version, identification of all differences in the 510(k) and detail how these differences (including any unresolved anomalies) impact the safety and effectiveness of the device.

Below are additional references to help you develop and maintain your device under good software life cycle practices consistent with FDA regulations.

- General Principles of Software Validation; Final Guidance for Industry and FDA Staff; available on the FDA Web site at: http://www.fda.gov/cdrh/ode/510kmod.pdf.
- Guidance for Off-the-Shelf Software Use in Medical Devices; Final; available on the FDA Web site at: http://www.fda.gov/cdrh/ode/guidance/585.pdf.
- 21 CFR 820.30 Subpart C – Design Controls of the Quality System Regulation.
- ISO 14971-1; Medical devices - Risk management - Part 1: Application of risk analysis.
- AAMI SW68:2001; Medical device software - Software life cycle processes.

10. Labeling

The premarket notification should include labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e). The following suggestions are aimed at assisting you in preparing labeling that satisfies the requirements of 21 CFR 807.87(e). Although final labeling is not required for 510(k) clearance, final labeling for in vitro diagnostic devices must comply with the requirements of 21 CFR 809.10 before an *in vitro* diagnostic device is introduced into interstate commerce.

Directions for use

You should present clear and concise instructions that delineate the technological features of the specific device and how the device is to be used. Instructions

should encourage local/institutional training programs, if available, that are designed to familiarize users with the features of the device and how to use it in a safe and effective manner.

If you do not intend to provide reagents for DNA extraction and preparation as part of the assay, you should provide specifications for reagents needed and for assessing the quality of the assay input DNA, so that the user can select appropriate reagents.

Interpretation of Results

You should clearly define any phenotype definitions (e.g., Extensive, Intermediate, Poor, or Ultrarapid Metabolizers in the case of cytochrome P4502D6). We recommend that you provide a section in your package insert to aid users in interpreting test results. The results should be consistent with current recommendations of genetics professional societies, if applicable, and should contain adequate interpretation guidelines for the use of the ordering physician. See ***Test Results*** in Section 6. Where applicable, reports should describe the polymorphisms identified by your test and the methodology and technology used for detection. You should identify representative literature references describing genotypic interpretations, or phenotypic predictions, if applicable, to enable users to access information about specific genotypes.

Expected Values

You should provide data concerning prevalence for specific alleles, including, where appropriate, allele prevalence according to ethnicity and race.

Quality Control

You should include a description of quality control recommendations in the package insert. This should include a clear explanation of what controls are to be used in the assay and the expected results for the control material.

Precautions for interpretations

You should clearly describe any assay limitations in the labeling. Most drug metabolizing enzyme genotyping systems should contain the following limitations:

- Results provided by this type of genetic test should only be used to supplement other tools for therapeutic decision-making in conjunction with routine monitoring by a physician.

- The effect that a specific DME allele has on drug metabolism may vary depending on the specific drug, even for drugs within a specific class. Effects of specific alleles on drug metabolism are well-documented for some drugs; for other drugs, they are less well-documented. Therefore, clinicians should use professional judgment when interpreting results from this type of test.

- Results from this type of assay should not be used to predict a patient's response to drugs in cases where either 1) the drug metabolizing enzyme activity of the

allele has not been determined, or 2) the drug's metabolic pathway has not been clearly established.

Performance Characteristics

You should include in the package insert all study designs and results for studies described in Sections 7 and 8 of this guidance document that would aid users in interpreting test results. For the method comparison, you should describe device performance in comparison to a gold standard method, such as bi-directional DNA sequencing. We recommend that you present results in the form of tables (e.g., n x n tables), descriptions of percent correct genotype calls relative to sequence analysis, and a list of the nature of any miscalls (e.g., correct sequence versus one predicted by device). We recommend that you present results for specific genotypes, in addition to overall results.