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Guidance for Industry

**Points to Consider Guidance
Document on Assayed and
Unassayed Quality Control Material**

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**This guidance is being distributed for comment purposes only.
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**U.S. Department Of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health**

**Chemistry, Toxicology, and Hematology Branch
Division of Clinical Laboratory Devices
Office of Device Evaluation**

Preface

Public Comment

For 90 days following the date of publication in the Federal Register of the notice announcing the availability of this guidance, comments and suggestions regarding this document should be submitted to the Docket No. assigned to that notice, Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852.

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World Wide Web/CDRH home page at <http://www.fda.gov/cdrh/ode/qcmat.pdf>, or CDRH Facts on Demand at 1-800-899-0381 or 301-827-0111, specify number 2231 when prompted for the document shelf number.

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The attached document, “Points to Consider Guidance Document on Assayed and Unassayed Quality Control Materials” is intended to provide assistance to manufacturers of In Vitro Diagnostic quality control materials. It complements the existing guidance on labeling of these devices entitled “[Points to Consider for Review of Calibration and Quality Control Labeling for In Vitro Diagnostic Devices](#)” which was first published in February 1996. FDA is actively soliciting comments on this new document for the next 90 days. Assayed Quality Control (QC) materials have analyte (substances or factors to be detected or measured, e.g. element, hormone, infectious agent) values assigned to them by the manufacturer and unassayed QC materials have no assigned analyte ranges. Both are subject to the FDA Quality System Regulations, 21 Code of Federal Regulations, Part 820

This document only applies to those regulations listed in the guidance. Although unassayed quality control materials are currently exempt from premarket review, FDA believes information in this guidance may be useful to manufacturers making these products. Exemption of these products is largely based on the fact that while the manufacturer is expected to make these products with appropriate consistency, specific performance parameters for establishing their use in individual quality control programs is clearly the responsibility of the user laboratory. FDA believes that unassayed Quality Control materials are low risk devices only requiring oversight in their manufacture. Therefore since user laboratories can detect problems in performance, and since quality systems requirements and labeling will still be in place, the review of 510(k) submissions would not add to their oversight.

As a result of FDA’s reengineering efforts, there are 510(k) submission options. One option, which is within the 510(k) Paradigm, provides manufacturers the opportunity to submit an abbreviated 510(k) for assayed QC material. This guidance document describes a standardized abbreviated submission. Manufacturers should certify conformance to the principles presented in this guidance and submit device labeling only. Please refer to the document “A New 510 (k) Paradigm; Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications” for more information on submissions <http://www.fda.gov/cdrh/ode/parad510.html>.

FDA in particular solicits input on two sections contained in this guidance: Section III D and Section III F. Section III D recommends that sponsors evaluate control materials for the effects of the materials being tested, such as blood, serum, or urine from human or non-human sources. New and unusual non-human matrices (materials such as blood, serum, or urine from animals) are becoming more common and the Agency believes it is important for the user to know if a matrix bias exists. This would provide a better understanding of the possible limitations of a control material, thereby assisting the user who is trying to trouble shoot an assay problem.

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The second area where comments are sought is section III F that suggests that each QC material be evaluated for its ability to detect variables in assay conditions that have an impact on patient sample results. As non-human material, such as blood or serum from animals have been incorporated into control materials, the Agency has observed numerous cases where the quality control material was not sensitive to all conditions which could effect patient sample results, e.g. temperature, handling or processing procedures. When these conditions exist, the QC readings have been within the expected range, yet the patient samples were erroneous.

Comments should be sent to Dr. Joseph Hackett, HFZ-440, 2098 Gaither Road, Rockville, MD 20852.

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Points to Consider Guidance Document on Assayed and Unassayed Quality Control Materials

This document presents current approaches and concerns regarding the use of assayed and unassayed quality control materials for in vitro diagnostic devices. The information in this document is based on current science, clinical experience, previous submissions by manufacturers to the Food and Drug Administration (FDA); changes resulting from reengineering, as well as the FDA Modernization Act of 1997 (FDAMA). As advances are made in science and technology, and as additional changes resulting from implementation of legislation occur, these Points to Consider will be re-evaluated and revised as appropriate.

PURPOSE:

The intent of this guidance is to provide both manufacturers and the Division of Clinical Laboratory Devices (DCLD) with a basis for improving consistency and efficiency under “[The New 510\(k\) Paradigm: Alternative Approaches to Demonstrating Substantial Equivalence.](#)”

This document is an adjunct to the Code of Federal Regulations (CFR) and to FDA Publication Number 87-4224, the manual entitled: [In Vitro Diagnostic Devices: Guidance For The Preparation of 510\(k\) Submissions](#). It is not intended to supersede these publications but to provide additional guidance and clarification concerning information to enable the FDA to clear assayed quality control materials for marketing. The FDA can make better informed decisions based on a uniform data base, and this will lead to more reliable, reproducible, and analytically useful control materials for use with in vitro diagnostic devices.

This document provides FDA’s guidance for the evaluation and labeling in support of an abbreviated premarket notification submission for assayed quality control (QC) materials. This guidance is applicable to all types of QC devices listed in the CFR that are liquid assays QC materials. It does not, however, apply to waived or home-use devices, electronic instrumentation QC materials, process controls, or products which are classified as quality control materials intended for use as calibration verification materials.

BACKGROUND

Clinical laboratory quality control is a system for assessing the quality of analytical performance. Samples used in this process include both assayed and unassayed QC materials. Quality control materials used to analyze analytical performance are critical and will become more complex as technology progresses. Various analytes are combined for analysis by diverse methodologies. For instance animal and synthetic matrices are used to protect laboratory personnel from exposure to human infectious agents. Additives, preservatives, antimicrobials, and clarifying agents may also be added to enhance the properties of a QC material.

In efforts to reduce cost and increase convenience, various components may be used for QC device methodologies. With the addition of each new component to a control product, the potential for interference with accurate measurement increases. These modifications can result in unpredictable interactions, decreased stability, and/or unexpected effects from the matrix (materials such as blood or urine from human or non-human sources containing the material to be tested), when an assay is run. Various biological or synthetic components and matrices can affect the performance of the QC material when used in different analytic methods. These effects can not be predicted. Manufacturing processes, e.g., lyophilization or

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inactivation may significantly alter the physical, chemical, or biological properties of the QC material. Many non-native control components, i.e., animal or recombinant nucleic acid sources, do not exhibit the same interactions with the reagents as does the analyte in a patient sample. A control material may only represent one strain or portion of an organism, one isoenzyme, or may be a synthetic cellular component that may not detect all analytical errors that could cause erroneous therapeutic decisions.

The manufacturer should make every attempt to consider and address these concerns through premarket testing which will characterize whether a QC material is as sensitive as the actual patient sample to all of the anticipated analytical variances. These performance characteristics should be communicated to the user in the labeling.

For FDA to assess the substantial equivalence of assayed QC material, the following should be included in all pre-market notifications.

I. Device Description

QC materials may contain biological, chemical, bioengineered, or synthetic materials in human or non-human matrices. These products may be marketed as assayed as well as unassayed controls.

Assayed QC materials have analyte values assigned to them by the manufacturer using appropriate analytical methods or procedures. Target quantitative ranges or qualitative values, e.g., positive or negative, are presented in the product labeling with stated tolerances for specific system applications. Unassayed QC materials have no assigned analyte ranges, although target concentrations may be indicated in the labeling, (e.g., low, high, normal), and system applications are not specified. Both are subject to Quality System Regulations.

QC materials are used in many types of diagnostic assays, and, therefore, have different analytical considerations which should be evaluated. Stability, matrix effects, reproducibility of expected results, and variety and number of constituents are important characteristics for each of the claimed analytes in a QC material.

REGULATION NUMBERS: 21 CFR 862.1660, 862.3280, 864.542, 864.8625, and 866.2480

- a.) 21 CFR 862.1660. A quality control material (assayed and unassayed) for clinical chemistry is a device intended for medical purposes for use in a test system to estimate test precision and to detect systematic analytical deviations that may arise from reagent or analytical instrument variation. A quality control material (assayed and unassayed) may be used for proficiency testing in interlaboratory surveys. This generic type of device includes controls (assayed and unassayed) for blood gases, electrolytes, enzymes, multi-analytes (all kinds), single (specified) analytes, or urinalysis controls. Class I.
- b.) 21 CFR 862.3280. A clinical toxicology control material is a device intended to provide an estimation of the precision of a device test system and to detect and monitor systematic deviations from accuracy resulting from reagent or instrument defects. This generic type of device includes various single, and multi-analyte control materials. Class I.

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- c.) 21 CFR 864.5425. A multipurpose system for in vitro coagulation studies is a device consisting of one automated or semiautomated instrument and its associated reagents and controls. The system is used to perform a series of coagulation studies and coagulation factor assays. Class II.
- d.) 21 CFR 864.8625. A hematology quality control mixture is a device used to ascertain the accuracy and precision of manual, semiautomated, and automated determinations of cell parameters such as white cell count (WBC), red cell count (RBC), platelet count (PLT), hemoglobin, hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC). Class II.
- e.) 21 CFR 866. 2480. A quality control kit for culture media is a device that consists of paper discs (or other suitable materials), each impregnated with a specified, freeze-dried, viable microorganism, intended for medical purposes to determine if a given culture medium is able to support the growth of that microorganism. The device aids in the diagnosis of disease caused by pathogenic microorganisms and also provides epidemiological information on these diseases. Class I, Exempt.

PANEL(S): Clinical Chemistry (75), Hematology (81), Immunology (82), Microbiology (83), and Toxicology (91).

II. Intended Use

A QC material is intended to monitor and evaluate the precision and accuracy of a test system by assessing the analytical performance of the In Vitro Diagnostic (IVD) Device. It is used to detect and estimate inaccuracy (the difference between the average values obtained when a sample is repeatedly tested and the true value) and imprecision (the extent to which results obtained when testing repeatedly agree with each other) resulting from reagent or instrument defects, or operator variation.¹ QC material may be used for internal and/or external laboratory QC programs.

III. Preclinical Data

A. For preclinical data:

- 1) The manufacturer should provide a summary description of how the control material is prepared during manufacturing.
- 2) Information on the source, i.e., human or animal species, synthetic or recombinant analyte or metabolite, organism (strain or portion of an organism if appropriate), nucleic acid segment, and specific nucleic acid sequence should be included.
- 3) Additionally, the matrix (or material in which the substance is found e.g. blood, urine), should be identified and the composition and characteristics of all components, stabilizers and preservatives, or clarifiers should be described. Information should be provided on the volumes,

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concentrations, and particle sizes of the QC materials.

Note: Safety of animal/human source components is normally satisfied through the use of certified agricultural (animal) facilities or licensed blood centers. Human blood/tissue products are commonly tested with FDA approved methods for several infectious agents (e.g., HBsAg, HCAb, HIV, HTLV, etc.). See 21 CFR Part 610.

The safety of the animal/human source materials of all applicable components should be provided.

4. If inactivation methods have been used for infectious agents, the methods should also be described
- B. For assayed QC material, the protocol that was followed during the range or value determination process should be provided.
- A description of the analytical methods, materials used, specific system applications, the number of replicates, runs and instruments, and the statistical analyses by which the range was established should be included.
 - Independent controls should be included with each value determination run in order to validate the results.
 - It may be appropriate to describe the assigned values by the clinical diagnostic procedure, e.g., disease present or absent, or the clinical relevance of the assigned value. It is desirable, when possible, to establish international consistency to a domestic or international standard material and/or method, e.g., World Health Organization standards.
- C. A description summarizing how open and closed stability of the QC material has been established, including the acceptable performance limits of the study should be provided. The term "closed" refers to shelf life stability whereas "open" refers to reconstituted or opened conditions. Stability claims should be substantiated with real time studies or accelerated studies with ongoing real time studies.
- D. The effect of the sample itself on the test results of various analytes in a human source QC material may differ from a non-human source and may require evaluation. This is dependent upon the amount of information known about the non-human source and how well its performance is understood. One suggested procedure is to add a known amount of the substance or analyte to be determined or measured (spiking) to a minimum of 5 samples each of the proposed matrix (e.g. non human blood or serum) and the matrix the QC is intended to monitor (e.g.; human blood) with equal analyte concentrations which span the clinically relevant range. This should be performed for each analyte on a number of methods consistent with the intended use and the "uniqueness" of the matrix. The performance of control material prepared in the proposed matrix and those prepared in the human matrix should be evaluated for the presence and concentration of each analyte. Plotting the two sets of values and performing a linear

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regression analysis may provide the bias of each method. Alternately bias may be evaluated by recovery studies spanning the concentrations claimed and employing all relevant analytical methods.^{2,3} A description of the procedure or protocol used to characterize the bias measurement should be provided.

- E. For assayed QC material, the levels of each constituent, and the acceptable range of the level should be furnished. The statistical parameters of coefficients of variation, standard deviations, and confidence intervals should be presented.
- F. When a QC material is unusual and/or significantly different in composition from the analyte it is intended to monitor, the manufacturer should perform a series of tests on actual clinical samples run in parallel with the QC material. This will verify that the QC material is as sensitive as actual patient samples to all anticipated analytical variables inherent to the assay system. These may include variables such as temperature variations, reagent deterioration, or pipetting or sample transfer errors. This testing assures that the same factors which affect a patient diagnostic test result would have a similar affect on the quality control result, and could, thereby, alert the user to potential problems.

SPECIAL CONSIDERATIONS:

- A. The concentrations of QC materials should be formulated such that levels of the substances or factors to be detected or measured in samples from patients span the medical decision range of the assay and should ideally target medically relevant decision points (those which result in a change of treatment). If the concentration does not stress the medical decision point of the assay, then a warning should be included in the labeling stating that the QC material is only intended to monitor for gross systematic errors.
- B. The manufacturer should submit a 510(k) or premarket notification whenever analytes are added beyond the constituents of the originally cleared assayed QC controls, or if significant changes are made in the biological source, composition of analytes, or matrix.
- C. If a distributor is simply placing their label on an already cleared QC product, without changing the product or labeling in any way, a 510(k) is not needed. See 21 CFR 807.85 for additional information.
- D. Control material, which is included as a component of an assay system, which is itself exempt by regulation, does not require a 510(k). However, the evaluation and labeling of that QC material should adhere to the recommendations made in this guidance document.

IV. Clinical Data: N/A

V. Software/Hardware Information: N/A

VI. Sterilization Information: N/A

VII. Labeling Information

Refer to 21 CFR 809.10 (b). The package insert should also include all of the following information:

- A. Intended Use: The intended use statement should define the QC material as assayed or unassayed, and for quantitative, semi-quantitative or qualitative testing, identify the matrix, and identify the analyte(s) the QC material is intended to monitor. The analytic procedure and the portion of the assay that the QC material is intended to monitor should be designated, as appropriate.

If the concentration does not challenge the medical decision point of the assay, a warning should be included in the labeling stating that the control is only intended to monitor for gross systematic errors.

- B. Reagents:

1. The following information should be provided in the description: the source of components (i.e., from human or animal species, synthetic, or purified chemicals); whether recombinant nucleic acid from an microorganism, or an entire microorganism (ATCC strain or portion of a microorganism); media or cell line used for culture; human donor characterization; nucleic acid segment and specific nucleic acid sequence; the matrix; a list of all stabilizers, preservatives, or clarifiers contained in the control mixture; volumes used ; concentrations used; particle sizes; and inactivation methods.
2. A certification statement that the animal/human source components used in the control are safe and that any blood product derived control material has been tested by FDA approved assays and found to be negative for the communicable disease agents as stated in 21 CFR Part 610 should be provided. *

- C. Procedures or instructions for use should be described, such as:

1. Handling, storage and stability for both opened and closed conditions.
2. Precautions as they apply, i.e., HBV, HIV, and sodium azide warnings should be included.

- D. Results Interpretation

Control limits and their statistical base should be clearly communicated in the Results Section. A statement should also be included which indicates that QC requirements should be performed in conformance with local, state, and/or federal regulations or accreditation requirements.

- E. Limitations

A description of any assay conditions that the control may not monitor should be included.

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F. Expected values, as appropriate.

1. The labeling for assayed QC materials should provide the established expected value(s) for the control(s), along with ranges, standard deviations, coefficients of variation, confidence intervals, and methods applications, as appropriate. Assigned values should be identified for each constituent and level. This may be furnished as an attachment to the labeling.
2. For assayed materials, the protocol used to establish the acceptable value and/or range for the QC material, e.g., low, mid or high level, should be provided. The analytical methods, number of testing replications, test runs and instruments, and the statistical analyses by which the values and/or range was established should be described.
3. If QC material is for in-house or “home brew” it should be marketed only as unassayed control material.

G. Performance characteristics, as appropriate.

1. Any significant matrix bias should be described along with a brief description of how the bias was determined.

* unless the control material is a positive control for such an agent.

2. The ability or sensitivity of the QC material to detect known analytical problems should be defined.

References:

1. National Committee for Clinical Laboratory Standards, Identification and Quantification of Matrix Effects; Proposed Guideline (1993), Document EP14-P.
2. Bruce, A. W., Basic Quality Assurance and Quality Control in the Clinical Laboratory, Boston, p. 65-75, 1984.
3. Shahangion, Proficiency Testing in Laboratory Medicine: Use and Limitations, Arch Pathol Lab Med 1998; 122: 15-30.