Guidance for Industry and FDA Staff

Assayed and Unassayed Quality Control Material

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U.S. Department of Health and Human Services
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Center for Devices and Radiological Health
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. When submitting comments, docket number 98D-1232. 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.

I. Introduction

This guidance document provides recommendations to manufacturers regarding preparation of premarket notifications and labeling for quality control (QC) material. These materials are intended to monitor reliability of a test system and help minimize reporting of incorrect test results. These materials are often the best source of ongoing feedback that a laboratory has to monitor whether results reported to physicians are sufficiently reliable. QC materials may be marketed together with a specific test system, or alternatively, for more general use.

Both assayed and unassayed QC materials are discussed in this guidance document. Both types of QC materials are subject to the Quality System Regulation (QSR), 21 CFR, Part 820, and labeling regulation 21 CFR 809.10. However, most types of unassayed QC materials are exempt from premarket notification (see Section II below for exceptions). Although premarket notifications are not required for unassayed QC materials, some aspects of this guidance document such as labeling, stability, and matrix effects are still relevant for these materials. Assayed QC materials have analyte values[1] or ranges assigned by the manufacturer and presented in the labeling. Unassayed QC materials do not have manufacturer-assigned values or ranges; rather, only the end user laboratories assign values and ranges. These two categories of QC materials are further described in Section III. When QC materials are included as a component of a test system that is itself exempt from premarket notification, the QC materials also do not need premarket notification. However, as with unassayed QC materials, many of the

[1] In this guidance document we use the term “values” to refer to units of assay output, or other units from which assay output could be inferred by an end user.

recommendations in this guidance document for evaluation and labeling still apply.

This guidance addresses external QC material. It is not intended to address internal controls, process controls (such as control lines on single use devices) or, electronic QC. This guidance does not address calibrators. A separate guidance is available for calibrators at, http://www.fda.gov/cdrh/ode/calibrator.pdf. This guidance also does not address QC materials for genetic tests for heritable diseases or pharmacogenetic testing. These types of materials will be addressed in other OIVD (Office of In Vitro Diagnostic Device Evaluation and Safety) guidance documents. This guidance is not intended to apply to QC materials for use with donor screening tests. These materials are regulated by Center for Biologics Evaluation and Research (CBER).

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.

Abbreviated 510(k) Submissions

As explained in "The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications" (http://www.fda.gov/cdrh/ode/parad510.html), a manufacturer may submit either a Traditional 510(k) or an Abbreviated 510(k). An Abbreviated 510(k) provides a means to streamline the review of data in a 510(k) through a reliance on FDA-recognized consensus standards, special controls, or FDA guidance documents. Guidance on the content and format for Abbreviated and Traditional 510(k)s is available at http://www.fda.gov/cdrh/ode/guidance/1567.html. Also, see Section 514(c)(1)(B) of the Act and the FDA guidance, "Use of Standards in Substantial Equivalence Determinations" http://www.fda.gov/cdrh/ode/guidance/1131.html on use of standards in an abbreviated 510(k).

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 guidance and 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.

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II. Classification and Identification of QC Materials

The various types of QC materials are identified, and classified, as follows in the CFR:

a.) 21 CFR 862.1660 Quality control material.
(a) Identification. 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.
(b) Classification. Class I (general controls). Except when used in donor screening tests, unassayed material is exempt from premarket notification procedures, subject to 21 CFR 862.9.

b.) 21 CFR 862.3280. Clinical toxicology control material.
(a) Identification. 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.
(b) Classification. Class I (general controls). Except when used in donor screening tests, unassayed material is exempt from premarket notification procedures in subpart E of part 807 of this chapter subject to Sec. 862.9.

c.) 21 CFR 864.5425. Multipurpose system for in vitro coagulation studies.
(a) Identification. 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.
(b) Classification. Class II (performance standards).

d.) 21 CFR 864.8625. Hematology quality control mixture.
(a) Identification. 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).
(b) Classification. Class II (performance standards).

e.) 21 CFR 866.2480. Quality Control Kit for Culture Media.

(a) Identification. 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.

(b) Classification. Class I (general controls). The device is exempt from the premarket notification procedures in subpart E of part 807 of this chapter subject to the limitations in Sec. 866.9.

III. Assayed and Unassayed QC Material for Qualitative and Quantitative Assays

A. Assayed QC Materials

Assayed QC materials have analyte values specified in the labeling by the manufacturer. These analyte values and associated ranges are provided as guidelines to the end user; the clinical laboratory establishes its own ranges based on its own test system and criteria. QC materials for qualitative tests, as well as quantitative tests may be "assayed".

When QC materials are marketed for a specific assay, or assays, the manufacturer should assign analyte values of the QC material, relative to the medical decision points associated with that assay. Therefore, we consider all QC materials recommended by the manufacturer for a specific assay, (or those included as part of an assay system) to be "assayed" QC material.

The following are types of labeling information that might render a control an assayed control:

- Units are assigned to the control(s) in your labeling (examples of units include, but are not limited to, IU/mL, copies/mL and mg/mL).

- Units are used to describe the preparation of the control(s) in your labeling, such that an assay's expected value might be inferred by the user.

- The controls are described in the labeling as for use with one or more specific assays.

External QC materials for qualitative tests marketed to waived test sites should be assayed by the manufacturer and appropriately labeled, since these types of testing sites do not typically assign control values. Labeling should include the expected target value, the relationship of this value to the cut-off point of importance in the assay being controlled, and estimates of performance around the target value.

B. Unassayed QC Materials

Unassayed QC materials do not have assigned analyte values provided by the manufacturer and are not linked to specific assays/assay systems by labeling or other means. The end user, rather than the manufacturer assigns expected results to unassayed QC material. The manufacturer may indicate whether a specific analyte is present or absent in the QC material preparation without indicating an expected assay result.

While manufacturing of a QC material should include some type of analyte level assessment as part of the production process, for unassayed QC material you should not provide end users with values from which they might mistakenly infer expected assay results.

The following are examples of types of label information that **alone** would not render a control an assayed:

- Relative dilutions (e.g., linear dilutions ranging from 1:2 to 1:20) are specified, but the absolute and/or source concentration is unspecified and it is clear that the user laboratory is responsible for determining the value of the control.

- Relative levels such as high, medium and low are provided, but without any specific values or concentrations and it is clear that the user laboratory is responsible for determining the value of the control.

- For assays that target infectious microorganisms, specific protein(s) or nucleic acid sequence(s) that make up the QC material are specified but do not provide information on likely test performance (strong negative, weak positive, strong positive or other control values). (This does not include QC material for pharmacogenetic tests, or tests for heritable markers. These types of QC materials are addressed in the guidance document, "Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: Quality Control Material for Cystic Fibrosis Nucleic Acid Assays", http://www.fda.gov/cdrh/oivd/guidance/1614.pdf)

IV. Information to Include in a 510(k) for Assayed QC Materials

A. Device Description

Your device description in the 510(k) should include the following types of information, as applicable:

- Intended use (including the types of assays and analyzers the material is intended to be used with).
- Information concerning the composition of the QC material, including:
  - Concentrations of each analyte in each level of QC material.
  - The relevance of the concentrations chosen (e.g., concentrations represent common medical decision points, concentrations are chosen to incorporate the range of the assay and to challenge the cut-off or decision point of clinical importance).
  - Base matrix (e.g., serum, blood, urine, buffer), and any known matrix effects that affect assay performance (see definitions in Section IV.B.1 below).
  - Added components such as stabilizers, preservatives, clarifiers, conjugated materials etc., and any known matrix effects of these added components that affect assay performance.
  - Any other information pertinent to users concerning how the QC material is prepared. If you market calibrators and control material for a single assay, we recommend that

you clarify what steps were taken to ensure that these materials will provide assessments independent of each other. For example, the controls and calibrators could be prepared from separate lots of serum pools (or other materials).

- Analyte source, e.g., human or animal species, synthetic or recombinant. For recombinant nucleic acid material, you should include the vector, the source of the cloned nucleic acid region or gene, and specific nucleic acid sequence. For a microorganism, you should include the strain, and portion of the microorganism, the media or cell line used for culture.
- Safety information, including methods you used to test for infectious agents. When blood products are used, you should include a certification statement that the animal/human source components used in the control are safe and that any blood product derived material has been tested by FDA approved (or equivalently recognized) assays and found to be negative for the communicable disease agents, as stated in 21 CFR Part 610. If inactivation methods have been used for infectious agents, you should describe the methods and the results demonstrating non-infectivity.

B. Performance Evaluation and Results

1. Matrix Effects

The matrix refers to all components of a material system, except for the analyte[2]. For QC materials this generally refers to the base material (e.g., serum, buffer) and added components such as stabilizers or preservatives. The matrix effect refers to the influence of a property of the sample, other than the analyte, on the measured value of the analyte. Viscosity, surface tension, turbidity, ionic strength, and pH are among causes of matrix effects.

Ideally, QC materials simulate the composition of patient samples as closely as possible in order to minimize matrix effects and correctly reflect the expected performance with patient samples. Use of matrices such as human serum, urine, or whole blood-derived samples may help accomplish this. However, in efforts to reduce cost or increase convenience or safety, modifications might be made to the matrices. For example, animal and synthetic matrices are used to protect laboratory personnel from exposure to human infectious agents. Preservatives, stabilizing agents, antimicrobials, and clarifying agents may also be added to enhance the ease of use and stability of a QC material. Manufacturing processes, (e.g., lyophilization or inactivation) may significantly alter the physical, chemical, or biological properties of the QC material. Although these various matrices and additives at times have benefits, these deviations from human samples may compromise the QC material's ability to sufficiently reflect performance of the assay for "natural" human samples. We consider this a potential risk to health since QC material is the best source of ongoing "feedback" a laboratory has to monitor whether results reported to physicians are sufficiently accurate. Therefore, we recommend that you evaluate matrix effects of your QC material relative to the intended use human samples and describe relevant findings in the package insert.

[2] See ISO (International Standards Organization) harmonized terminology database.

Another related issue is that as a result of differences in matrices, QC materials might differ from patient samples in terms of preparatory steps required for the assay (e.g., dilution, extraction, centrifugation or other pre-treatment). We recommend that, whenever feasible, you design the QC material so that it may monitor performance of preparatory steps as well as the operational steps of the assay itself. If this is not the case, you should indicate to users in the package insert which operational steps of the assay the QC material might not be able to monitor.

The degree of evaluation that is appropriate depends on the amount of information generally known about the specific matrix and how well its biochemical properties are understood. In some cases the evaluation can be accomplished by spiking the analyte(s) into the QC material matrix and in parallel into the intended use patient samples across the range of the assay. You should compare results to determine (1) bias of the QC material matrix relative to the natural sample (2) differences in precision between the QC material and the sample and (3) differences in tolerance to factors that could affect assay performance (e.g., stability, reagent deterioration). When relevant for your QC material, you should include results of such testing in your package insert.

In some cases you may find it helpful to refer to the Clinical and Laboratory Standards Institute (CLSI) guideline, EP-14-A2, "Evaluation of Matrix Effects" for further guidelines, especially if your QC material is intended for a specific test system.

2. Analyte Value Assignment

You should describe the materials and protocols you used to determine the analyte value and range you specify in the package insert. You should include the following:

- Specific system(s) with which testing was performed (assay and instrument).
- The number of replicates, runs and instruments, and time frame of the evaluation.
- The statistical analyses used to establish the range.
- Results for each analyte level, including coefficients of variation and standard deviations, with confidence intervals.

You should indicate your acceptance criteria for difference between the nominal (target) value and the mean values and ranges you determine.

3. Stability

You should describe the process by which you determined stability, in both "opened" and "closed" forms, of the QC material. The term "closed" refers to closed shelf life stability; "opened" refers to the opened conditions, including reconstituted or on-board conditions. You should describe the studies performed to determine stability, including:

- The conditions, (e.g., temperature, reconstitution conditions) under which the QC material was stored during the stability evaluation.

- The methods for measuring stability, including the type of instrument and/or assay used, the parameters measured (e.g., recovery of concentration or activity).
- The manufacturer's criteria for stability (e.g., 5% recovery based on a specific method at the expiration date).
- Results demonstrating that the manufacturer's criteria for stability were met.

You should evaluate QC material stability separately from assay reagent stability, so that reagent instability will not confound the evaluation.

Manufacturers should conduct real-time stability testing on an ongoing basis. Accelerated stability testing can sometimes be used in a 510(k) to supplement real-time stability testing, if real-time testing to support the expiration date is not yet complete. If accelerated stability testing is used in this way, you should outline your testing conditions in the 510(k). You should also provide information (e.g., literature) to support that the model you used to evaluate the accelerated stability results is appropriate for your particular analyte.

4. "Surrogate" QC material

When a QC material is different in composition from the analyte it is intended to monitor (e.g., a plasmid containing DNA versus infectious organism), there may be differences between results obtained with the QC material and those obtained with intended use samples (as there may be for matrix effects discussed above). In such cases, you should perform testing on actual clinical samples run in parallel with the QC material to verify that the QC material is as sensitive as actual patient samples to anticipated analytical variables. These may include variables such as temperature variations, reagent deterioration, or pipetting or sample transfer errors. Analogous to evaluation of matrix effects, this testing helps assure that the same factors that affect a patient diagnostic test result would have a similar effect on the result obtained with QC material, and could, thereby, alert the user to analytical error.

V. Labeling

You should refer to 21 CFR 809.10 for labeling requirements. The following recommendations are meant to help you apply these requirements to QC materials. Many of the items described in this section are applicable for both assayed and unassayed QC materials. Items relating to analyte levels, or specific assays or systems, for which QC materials are intended, are applicable only for assayed QC materials.

Intended Use

The intended use section should define the QC material and its use. For both assayed and unassayed QC material, you should include the following:

- The analyte(s).
- Whether the material is assayed or unassayed.
- Whether the material is intended for quantitative or for qualitative systems or assays.

For assayed material you should also include:

- The analyte levels the material is intended to monitor (e.g., assay cutoff, decision points, limits of assay range, as appropriate).
- The system, instrument, or type of test the QC material is intended to be used with.

If the QC material monitors specific aspects of the assay, but not the entire process (e.g., all steps after pre-treatment, instrument linearity), you should clarify this in the intended use.

Reagents

For assayed QC materials you should include all analytes and levels (if not already included in the intended use). Inclusion of analyte levels is important even for qualitative assays since it is important for users to know if the QC material will challenge the cutoff of their particular assay. You should express analyte concentrations using whichever parameter is most relevant for the analyte and test system (e.g., weight, activity).

For both assayed and unassayed material you should describe the analyte source (e.g., from human or animal species, synthetic, or purified chemicals). For recombinant nucleic acid material, you should include the vector, the source of the cloned nucleic acid region or gene and specific nucleic acid sequence. For a microorganism, you should include the strain, and if applicable, the portion of the microorganism (gene, antigen, etc.). You should describe the media or cell line used for culture.

When applicable for your QC material, you should include donor characterization for the source material to the extent that it is relevant for clinical use of the QC material.

You should describe the matrix, including the base material (serum, buffer, etc.), stabilizers, preservatives, or clarifiers added. If any preservatives or other materials require special handling by the laboratory, you should indicate this to the user.

You should describe inactivation methods used for potentially infectious material in your QC material. When blood products are used, you should include a certification statement that the animal/human source components used in the control are safe and that any blood product derived material has been tested by FDA approved (or equivalently recognized) assays and found to be negative for the communicable disease agents as stated in 21 CFR Part 610.

Other than the analyte levels, all items above should typically be included in the labeling for both assayed and unassayed QC material. Labeling for unassayed materials should not include analyte values since description of values is likely to be interpreted by the user to mean that these values have been assigned and validated by the manufacturer. For unassayed materials, we also discourage description of the analyte in relation to reference materials such as WHO, since this is likely to be interpreted by the user to mean that the QC material is traceable to the reference material and that the manufacturer has assigned the analyte value.

Operating Instructions

For both assayed and unassayed QC materials, you should include handling and storage instructions. You should describe stability (expiration dating) under the opened and closed storage conditions you recommend to users. We recommend that you include a description of

acceptance criteria for determining stability (e.g., +/- x% recovery using a given assay).

Warnings
For both assayed and unassayed QC materials, you should include applicable warnings concerning handling (e.g., warnings concerning handling of communicable disease agents, or chemical components that require special handling).

Assigned target values and ranges
For assayed QC materials only, you should describe how target values and ranges were established, including instruments or methodologies used for testing, the number of observations, instruments, laboratories, and any other relevant conditions of testing. For each analyte at each level, you should include results of the statistical evaluation including the mean(s) and standards deviation(s), with confidence intervals.

Frequency for QC
You should include a statement that QC materials should be used in accordance with local, state, and/or federal regulations or accreditation requirements.

Performance characteristics
Where appropriate you should include results of testing for matrix effects and/or effects of "surrogate QC material". You should describe:

- Any significant matrix bias along with a brief description of how the bias was determined.
- Any significant difference between the QC material and typical patient samples in terms of conditions known to cause analytical error.

Limitations
For assayed QC material you should state that the ranges given are intended only as guidelines and that laboratories should determine the ranges based on their own test system and tolerance limits.

For unassayed materials you should indicate that values are not assigned by the manufacturer and that each laboratory should establish its own analyte values and ranges.

You should include a description of any assay conditions that the QC material may not monitor because of matrix effects or surrogate QC material (e.g., pre-treatment steps, instability under certain conditions) if these have not already been described in the intended use.