Guidance for Industry and FDA Staff

Class II Special Controls Guidance Document: Quality Control Material for Cystic Fibrosis Nucleic Acid Assays

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Food and Drug Administration
Center for Devices and Radiological Health

Office of In Vitro Diagnostic Device Evaluation and Safety
Division of Immunology and Hematology Devices

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 you submit comments, please refer to the docket number 2006D-0515. Comments may not be acted upon by the Agency until the document is next revised or updated.

Additional Copies

Additional copies are available from the Internet at: http://www.fda.gov/cdrh/oivd/guidance/1614.pdf. You may also send an e-mail request to dsmica@fda.hhs.gov to receive an electronic copy of the guidance or send a fax request to 240-276-3151 to receive a hard copy. Please use the document number 1614 to identify the guidance you are requesting.

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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 quality control material for cystic fibrosis nucleic acid assays into class II (special controls). A quality control material for cystic fibrosis nucleic acid assays is a device intended to help monitor reliability of a test system by detecting analytical deviations such as those that may arise from reagent or instrument variation in genetic testing. This type of device includes recombinant, synthetic, and cell line-based DNA controls.

This guidance provides recommendations to manufacturers regarding preparation of premarket notifications and labeling for DNA quality control (QC) material used in genetic testing for cystic fibrosis. These QC materials can be used to monitor the pre-analytical and/or analytical performance (e.g., extraction, amplification, and detection steps) of nucleic acid-based in vitro diagnostic assays (IVDs) that are used for this testing. The recommendations in this document are applicable to controls used in either genetic variation[1] detection assays or assays for determination of specific genotypes.

This guidance addresses external QC material used in qualitative testing. It does not generally 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 is issued in conjunction with a *Federal Register* notice announcing the

[1] In this guidance document we use the term genetic variation to encompass wild-type sequences, mutations, or polymorphisms.

classification of quality control material for cystic fibrosis nucleic acid assays. Any firm submitting a premarket notification (510(k)) for quality control material for cystic fibrosis nucleic acid assays will need to address the issues covered in this special controls guidance document. However, the sponsor 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, guidance documents 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 guidance documents 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 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

QC materials are used with a test system to help monitor the analytical performance of that test system. A particular QC material may monitor the entire test system or only one aspect of it. QC materials are typically used to assess the performance of potential sources of variability of an assay or system, such as reagents, operator procedures, and/or instrumentation, including software malfunctions.

FDA believes that special controls, when combined with the general controls, will be sufficient to provide reasonable assurance of the safety and effectiveness of a quality control material for cystic fibrosis nucleic acid assays. 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 the device identified in this guidance, and (3) obtain a substantial equivalence determination from FDA before marketing the device.

This guidance document identifies the classification regulation and product code for quality control material for cystic fibrosis nucleic acid assays (refer to Section 4 – **Scope**). In addition, other sections of this guidance document identify the risks to health and describe measures that, if followed by manufacturers and combined with the general controls, will generally address the risks associated with quality control material for cystic fibrosis nucleic acid 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 those available at http://www.fda.gov/cdrh/devadvice/314.html

3. Abbreviated 510(k) Submissions

As explained in **"The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications; Final Guidance,"** 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.pdf

4. Scope

The scope of this document is limited to the following devices as described in 21 CFR §866.5910 (product code NZB):

21 CFR § 866.5910 Quality control material for cystic fibrosis nucleic acid assays. A quality control material for cystic fibrosis nucleic acid assays is a device intended to help monitor reliability of a test system by detecting analytical deviations such as those that may arise from reagent or instrument variation in genetic testing. This type of device includes recombinant, synthetic, and cell line-based DNA controls.

The recommendations in this guidance document may also apply to other types of QC materials used in genetic and pharmacogenetic tests. However, the recommendations do not fully address issues related to QC materials used in tests for infectious agents. Nor do they fully address RNA QC materials.

5. Risks to Health

QC material is intended to help monitor reliability of a test system. Therefore, failure of the QC material for cystic fibrosis nucleic acid assays to perform as indicated may lead to error in assessment of test results, and reporting of inaccurate results. This could potentially lead to patient mismanagement. For example, if the controls fail even though the test system was accurate, this may lead to unnecessary retesting, and delay in reporting results. In cases of patient samples that are difficult to obtain, this may cause additional risk to the patient. Conversely, if the QC material does not accurately reflect when the test system has failed, this may lead to false assurance of test operability, and reporting of inaccurate patient results. The inability to accurately reflect test system failure with patient samples may be due to the material not monitoring all errors or variabilities in a system or sample. In some cases, controls may be intended to monitor only some types of system or sample errors or variabilities. Therefore, it is

important for the manufacturer to clarify to users which aspects of test performance the controls are intended to monitor.

In the table below, FDA has identified the risks to health generally associated with the use of a quality control material for cystic fibrosis nucleic acid assays addressed in this document. The measures recommended to mitigate the identified risk are described in this guidance document, as shown in the table below. You should conduct a risk analysis, prior to submitting your premarket notification, to identify any other risks specific to your device. Risks may vary depending on the type of QC material used in genetic testing, the intended use of the genetic test, the sample type, and how the QC material is used. For example, there might be different potential errors associated with external controls when they are spiked into the specimen that is assayed. The premarket notification should describe the risk analysis method. If you elect to use an alternative approach to address the 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
Control failure, including inability to reflect test system failures, which could potentially lead to:	Sections 7-8
Delay in diagnosis Need for patient specimen recollection Improper patient management	

6. Device Description

You should include the following types of information in your 510(k), as applicable:

Intended Use

You should specify the following:

- The genetic assay or type of assay for which the QC material is intended. This includes the analyte, methodology and technological characteristics (including analyzer, if applicable), and matrix.
- The analytical procedure(s) or portion(s) of the assay (e.g. extraction, amplification, and/or detection) that the QC material is intended to monitor.

Description of the materials

You should include the following information concerning the composition of the QC material in your 510(k):

- The specific gene and gene sequences. You should describe the specific wild type and mutant alleles or polymorphisms included in the QC material. This should include the exons and introns represented and location of specific mutations or polymorphisms present, or the specific nucleic acid sequence. It may be helpful to reference recognized standards and guidelines for testing specific variations. We recommend that your controls include wild type DNA in addition to the gene variations your device contains. In this way your device will contain both positive controls (e.g., mutations, variants) and negative controls (wild type).
- Information on the source of the DNA, e.g., human or animal species, synthetic or recombinant. For cell line-based controls, you should include information about the cell line source, the media used for culture, and (if the information is available to you) how the cell lines are generated.
- Concentrations and/or volumes of each analyte and the relevance of the concentrations chosen. The concentration of the QC material used in the assay(s) should be representative of the typical concentration of the samples tested.
- A description of dilution or other pre-analytical steps that a user would perform on the QC material.
- A description of the base matrix from which the QC material DNA is to be extracted and any known matrix effects that affect assay performance. The matrix refers to all components of the material system other than the analyte. You should list all added components, stabilizers, clarifiers, conjugated materials, preservatives, etc., and describe whether these added components affect assay performance.
- If the particular genetic assay that your controls will be used with commonly includes reflex testing, and your QC material includes those variants that are tested as a reflex, you should provide clear instructions for the use of your controls in the reflex tests.
- A description of relevant characteristics of the donor material, when applicable.
- A brief description of the methods you used to test for infectious agents, and methods you used to inactivate these reagents. When blood products are used, you should include a certification statement that the animal/human source components or any blood product derived material used in the QC material have 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.

7. Performance Characteristics

In your 510(k), you should detail the study design you used to evaluate each of the performance characteristics outlined below. You should provide a description of the acceptance criteria and original, unresolved results for your performance testing. You should evaluate all genetic variations, including each allelic variant, present in your device. These studies should be performed using FDA-cleared or approved assays or an accepted reference method (i.e., bidirectional sequencing). The issues described below

are broadly applicable, regardless of the specific technology or instrumentation used by the genetic assay.

Pre-analytical factors

Matrix effects

A matrix effect refers to the influence of a property of the sample, other than the analyte, on the measured value of the analyte. Ideally, QC materials simulate the composition of patient samples as closely as possible in order to minimize matrix effects and reflect the expected performance with patient samples. However, matrix modifications such as preservatives, stabilizing agents, antimicrobials, and clarifying agents are often added to enhance the ease of use and stability of a QC material. Some manufacturing processes, e.g., lyophilization or inactivation, may significantly alter the physical, chemical, or biological properties of the QC material. These deviations from human samples may compromise the QC material's ability to sufficiently reflect performance of the assay for "natural" human samples. Therefore, we recommend that you evaluate matrix effects of your QC material and determine if there are bias differences in the results of the QC material relative to the patient sample. Matrix effects can be evaluated by spiking the QC material matrix and the intended-use, patient samples with analyte concentrations that represent the range of the assay and comparing the results. We recommend that within this testing you include the effects of anticipated analytical variables on your QC material such as temperature variations, reagent deterioration, or pipetting or sample transfer errors. This testing helps assure that the same factors which affect a patient diagnostic test result would have a similar effect on the results obtained with the QC material, and thereby alert the user to analytical error. When relevant for your QC material, you should include the results of such testing in your package insert.

Extraction method evaluation

Due to different matrices, QC materials might also differ from patient samples in terms of response to pre-analytical steps required for an assay (e.g., dilution, extraction, centrifugation or other pre-treatment). Typically, you should evaluate your QC materials using the same procedural steps that would be used to prepare a patient specimen. This includes steps such as dilution, extraction, centrifugation, or other pre-analytical steps. You should determine any effects of these steps on reproducibility, expected results, and stability of your QC material. Ideally, QC materials are processed along with patient specimens, so that procedural mishaps that are likely to introduce errors (e.g., sample carryover or contamination) are likely to occur in the controls as well. In some cases, however, QC material is only intended to monitor some of the analytical steps. If this is the case, you should clarify this in the labeling.

We recommend that you evaluate the ability of common extraction techniques to extract your DNA QC material. In your 510(k), you should include specific information about the extraction procedures you evaluated and the results obtained. You should also specify any additional methods you tested for purification and/or quantification of your QC materials, if applicable.

External sites that evaluate your QC material performance should also include evaluation of the extraction and purification steps. We recommend that you allow external sites to use whatever extraction and purification procedures they would normally use, so that you may evaluate effects of variations in the pre-analytical process on the performance of your controls.

Analytical Performance

Concentration Limits

We recommend that you test concentrations of your QC material that span the likely input range of clinical samples, and determine both the upper and lower limits, in terms of concentration and sample volume, for which the assay reproducibly yields correct results.

Traceability, Expected Results

You should provide a description of the methods you used to validate the presence and quantity of the wild type materials and the various mutations or polymorphisms contained in your QC material. Methods to do this may include bidirectional sequencing or traceability to a standard. You should provide results of this testing for each genetic variation included in the QC material.

When possible, you should describe the traceability of your QC material, including the procedures you use for value assignment and your results and acceptance criteria for this testing.

Analytical Evaluations at External Clinical Laboratories

Studies to evaluate the performance characteristics of the genetic QC material should be performed at external sites. This provides an independent evaluation of consistency and performance of the QC material by the intended user in situations where it will most likely be used. We recommend that you evaluate reproducibility at 3 or more sites. At least two of these sites should be external sites. Each site should evaluate multiple replicates of three QC material lots on different days by different operators. You should summarize the within-run, between-run, and between-operator results obtained for each site, as well as across the sites. We recommend that you test your QC materials on a variety of representative FDA-cleared/approved assays and instruments with which your QC materials are likely to be used. Since controls are valuable because they represent known results whose predictable performance may be influenced by an unpredictable environment, it may be desirable for you to perform testing that would mimic system failure. We suggest you evaluate conditions that are likely to cause failure to interpretation of assay results (e.g., reagent deterioration) for their influence on your QC materials. One example is to evaluate the effect of decreasing concentrations of primer extension reagents to mimic reagent deterioration.

In your 510(k) you should summarize performance characteristics for each test system, including:

- A description of the test systems or assays used; the number of testing replications, test runs and instruments, lots tested, and the results obtained.
- Results demonstrating that the expected genetic variations are present and that the assay does not produce unexpected results.
- A description of the study design you used to test whether your QC material can detect known analytical problems of the system.

Stability Studies

You should describe your study design for determining stability in both “opened” and “closed” forms of the QC material. The term "closed" means prior to opening; the term "opened" refers to materials that have been opened, including reconstituted or on-board conditions. You should provide the acceptance criteria for each study and the results obtained. We recommend that you use FDA-cleared assays or an accepted reference method to assess that your criteria were met within your claimed stability time period. You should evaluate stability for all the genetic variations in your QC materials. You should assess the following types of stability:

Real-time stability (shelf-life)
You should conduct real-time stability testing at temperatures at which the QC materials will be used and stored. 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.

Stress testing (shipment):
You should perform studies to evaluate QC material performance with corresponding assay(s) after exposure to stress conditions such as elevated temperatures and multiple freeze/thaw cycles since these types of temperature fluctuations could occur during shipping. We recommend that you perform these evaluations with multiple lots.

8. 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. Final labeling for an in vitro diagnostic device must comply with the requirements of 21 CFR 809.10 before it is introduced into interstate commerce.

Intended Use

In the intended use section you should define the QC material and its use. You should specify the genetic assay (and analyzer, if applicable), analyte and matrix, and analytical procedure or portion of the assay (i.e., extraction, amplification, and/or detection) that the QC material is intended to monitor. 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.

Product description

You should provide a description of the following aspects of your device:

- DNA source, concentration, and composition of the product.
- Specific genetic variations (e.g., mutations, polymorphisms, alleles) present in your QC material.

- 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.
- When applicable, donor characterization for the source material to the extent that it is relevant for clinical use of the QC material.
- 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 or any blood product derived material used in the control have 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.

Directions for Use

You should include handling and storage instructions. You should describe stability (expiration dating) under the opened and closed storage conditions that you recommend to users.

You should provide instructions for use in sufficient detail to explain how the controls are meant to be implemented in a test system. You should include all procedures that end users should perform with the QC materials (e.g., dilution steps, temperature requirements, quantifying methods, extraction methods) and specify any procedures or conditions to which the QC materials should not be exposed.

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

Warnings

You should include warnings concerning handling, as applicable (e.g., handling of communicable disease agents or chemical components that require special handling).

Performance characteristics and Expected Results

You should include study descriptions and results of your performance studies, including expected results, reproducibility, stress testing, and stability studies. You should list FDA-cleared or approved assays that were used to assess the performance of your QC material.

You should describe the protocols you used to establish expected results, including analytical methods, instruments or methodologies used for testing, the number of observations, test runs and instruments, laboratories, and any other relevant conditions of testing.

In summarizing the reproducibility studies, you should list all genetic variations present in your QC material and the result obtained using each of the FDA-cleared assays tested. We recommend that you list this in tabular form. The intended user can then determine whether or not a particular genetic assay can detect all variations covered by the QC material.

You should state any matrix effects, and any significant differences between the QC material and typical patient samples in terms of conditions known to cause analytical error.

Limitations

We recommend you include any limitations of your QC material that may confound test results. Variables such as probe and primer design may affect the ability to accurately identify some DNA variations. Conditions such as nonspecific amplification due to mis-priming, probe cross-reactions, and near neighbor interferences, or conditions affecting primer and probe binding, can contribute to false results. Additional limitations that might be applicable, depending on the QC material and the assay(s) it is intended to monitor, may be summarized as follows:

- In some test systems, neighboring mutations and polymorphisms may interfere with expected test results.
- Interferences and cross-reactions may occur in some detection methods.
- Recoveries may vary depending on extraction method, instrumentation, cycle time, temperature, reagents, method variation, and systematic or random errors.
- Rare mutations not present in the QC materials or detectable by the assay may be present in the specimen.
- External controls are intended to verify that a system is working properly, but all system variances cannot always be accounted for and therefore controls do not provide complete assurance that the test system has performed reliably.

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.