Class II Special Controls Guidance Document: Instrumentation for Clinical Multiplex Test Systems - Guidance for Industry and FDA Staff

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

Office of In Vitro Diagnostic Device Evaluation and Safety
Division of Chemistry and Toxicology 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 **Regulations.gov (http://www.regulations.gov)** . When submitting comments, please refer to Docket No . 2005D-0069. Comments may not be acted upon by the Agency until the document is next revised or updated.

Additional Copies

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Guidance for Industry and FDA Staff

Class II Special Controls Guidance Document: Instrumentation for Clinical Multiplex Test Systems

1. Introduction

This guidance document was developed as a special controls guidance to support the classification of instrumentation for clinical multiplex test systems into class II (special controls). This type of device is intended to measure and sort multiple signals generated by an assay from a clinical sample. This instrumentation is used with a specific assay to measure multiple similar analytes that establish a single indicator to aid in diagnosis. Such instrumentation may be compatible with more than one specific assay. The device includes a signal reader unit, and may also integrate reagent handling, hybridization, washing, dedicated instrument control, and other hardware components, as well as raw data storage mechanisms, data acquisition software, and software to process detected signals.

This guidance is relevant to instrumentation for use with the subset of multiplex tests that measure multiple similar analytes that establish a single indicator to aid in diagnosis. Examples of such tests include an assay that analyzes multiple single nucleotide polymorphisms (SNPs) to determine a patient's genotype, or an assay that analyzes multiple alleles to determine a patient's genotype. Depending on the nature of the multiplex test for use with the instrumentation, the instrumentation could aid in clinical applications, such as screening or diagnosis of disease, drug selection and dosing, patient management, and the assessment of disease progression and regression.

A specific multiplex assay or test that is intended to be run on instrumentation for clinical multiplex test systems is considered a separate device, and does not fall under the scope of 21 CFR 862.2570. Such specific assays often include software that is used to process the particular signal measurements that result from the specific assay, as well as reagents for carrying out the test. Such software is regulated as part of the specific assay to which it pertains. However, as noted above, instrumentation for clinical multiplex test systems does include its own software, including data acquisition software and software to process detected signal, which are used with any assay run on that instrumentation.

Manufacturers of instrumentation for clinical multiplex test systems should only claim diagnostic applications for their device that are associated with legally marketed multiplex assays.

This guidance is issued in conjunction with a Federal Register notice announcing the classification of instrumentation for clinical multiplex test systems. Any firm submitting a premarket notification (510(k)) for a device of this type will need to address the issues covered in this special controls guidance document. The firm must show that its device addresses the issues of safety and effectiveness identified in this guidance, either by meeting the recommendations of this guidance or by some other means that provides equivalent assurances of safety and effectiveness.

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 (/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceProvisionsofFDAModernizationAct/ucm136685.htm)**."

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2. Background

FDA believes that special controls, when combined with the general controls, provide reasonable assurance of the safety and effectiveness of instrumentation for clinical multiplex test systems. 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 instrumentation for clinical multiplex test systems. (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 these devices 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 **Premarket Notification 510(k) (/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm)**.

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).

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

An Abbreviated 510(k) submission must include the required elements identified in 21 CFR 807.87, including the proposed labeling for the device sufficient to describe the device, its intended use, and the directions for its use. In an Abbreviated 510(k), FDA may consider the contents of a summary report to be appropriate supporting data within the meaning of 21 CFR 807.87(f) or (g); therefore, we recommend that you include a summary report. The report should describe how this guidance document was used during the device development and testing and the methods or tests used. The report should also include a summary of the test data or description of the acceptance criteria applied to address the risks identified in this document, as well as any additional risks specific to your device. This section suggests information to fulfill some of the requirements of 21 CFR 807.87 as well as some other items that we recommend you 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 9 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 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 6 and 7 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) briefly present the data resulting from the test in clear and concise form, such as a table, **or** (2) describe the acceptance criteria that you will apply to your test results.[3] (See also 21 CFR 820.30, Subpart C - Design Controls for the Quality System Regulation.)
- If you choose to rely on a recognized standard for any part of the device design or testing, you may include either: (1) a statement that testing will be conducted and meet specified acceptance criteria before the product is marketed, or (2) a declaration of conformity to the standard.[4] Because a declaration of conformity is based on results from testing, we believe you cannot properly submit a declaration of conformity until you have completed the testing the standard describes. For more information, please refer to section 514(c)(1)(B) of the Act and the FDA

guidance, **Use of Standards in Substantial Equivalence Determinations; Final Guidance for Industry and FDA (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073752.htm)**.

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 instrumentation for clinical multiplex test systems.

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4. Scope

The scope of this document is limited to the following devices as described in 21 CFR 862.2570 (product codeNSU):

21 CFR 862.2570 Instrumentation for clinical multiplex test systems.

Instrumentation for clinical multiplex test systems is a device intended to measure and sort multiple signals generated by an assay from a clinical sample. This instrumentation is used with a specific assay to measure multiple similar analytes that establish a single indicator to aid in diagnosis. Such instrumentation may be compatible with more than one specific assay. The device includes a signal reader unit, and may also integrate reagent handling, hybridization, washing, dedicated instrument control, and other hardware components, as well as raw data storage mechanisms, data acquisition software, and software to process detected signals.

A specific multiplex assay or test that is intended to be run on instrumentation for clinical multiplex test systems is considered a separate device. This guidance document does not address performance characteristics for such assays. The guidance document, ***Replacement Reagent***

and Instrument Family Policy **(/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM071465.pdf)**, does not apply to instrumentation for clinical multiplex test systems.

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5. Risks to Health

FDA has identified the risks to health associated with this type of device as potentially inaccurate results, or inaccurate reports, which may lead to incorrect diagnoses or patient evaluation that could result in inappropriate and possibly dangerous patient management. Specifically, failure of instrument components, including reagent introduction and hybridization systems, signal detection mechanisms, instrument control and data acquisition software, and raw data storage mechanisms could lead to inaccurate results. Likewise, failure of data management and database software could result in the compromise of patient identification or mis-matched results. Furthermore, failure of the instrumentation to generate any results at all can deny or delay beneficial, appropriate therapies.

In the table below, FDA has identified the risks to health generally associated with the use of instrumentation for clinical multiplex test systems, as 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, before 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
Inaccurate or absent results due to failure of instrumentation components	Sections **7** and **9**
Inaccurate or absent results or reports due to failure of data management and database software	Section **8**

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6. Device Description

In your 510(k), you should identify the regulation, the product code, and a legally marketed predicate device. In order to help FDA efficiently review all the aspects of your device compared with the predicate, you should include a table that outlines the similarities and differences between the predicate and your device.

Key issues in the review of a new device are the specific intended use, the type of specimens tested, and the technology utilized. You may submit appropriate peer-reviewed literature references relevant to the technology of the device in addition to the descriptive information to adequately describe the new instrumentation. You should include the following descriptive information to adequately characterize the new instrumentation for clinical multiplex test systems.

Intended Use

You should clearly describe the intended use of the device. Some instrumentation may have multiple intended uses. For example, the instrumentation may be able to measure more than one type of molecule (e.g., DNA or RNA). We recommend a separate application for each intended use that requires unique and separate supporting studies. You should consult the appropriate review divisions in the Office of In Vitro Diagnostic Device Evaluation and Safety for advice on submitting instrumentation with multiple intended uses.

Device description

You should identify the legally marketed assay or assays to be used with the instrumentation. The multiplex assay for use on the instrument may be submitted in the same 510(k) as the instrument, or in a separate 510(k).

We recommend that you provide a thorough explanation of all aspects of the device methodology. This could include, but is not limited to, the following:

- How the instrument is designed to carry out its functions related to amplification, hybridization, or signal detection.
- Additional instrument components that you provided, or recommend for use, and their function in the system.
- The sample type(s) that may be run on the instrumentation.
- Types of output generated by the instrumentation and system parameters (e.g., reading ranges).
- Related peer-reviewed literature references, if applicable.

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7. Performance Characteristics

Precision/Reproducibility

We recommend that you characterize the reproducibility of the instrumentation for clinical multiplex test systems using a well-characterized sample with positive and negative control assays. We recommend that you design the study to assess overall instrumentation performance, e.g., sample processing consistency, scanner drift. You should justify statistically the sample size for the reproducibility study. You should include two or more operators and three or more instruments in the study, and ensure that samples are masked and expected results are unknown to operators. For instrumentation that can be used to run more than one type of assay (e.g., genotyping and expression arrays), you should demonstrate reproducible performance for each type of assay. You should provide the protocol (including statistical methods), results and analysis for between-assay, between-scan, between-instrument, between-operator, or other evaluations, as appropriate. If applicable, we recommend that you report the following types of information.

- Coefficients of variation (CV) with confidence intervals, for between- instruments, operators, device lots, and intra- and inter-assay, as appropriate. If the device is used with a micro-array type of assay, intra- and inter-assay evaluations are especially important to establish reliability of the device.
- Pairwise correlation coefficients, scatter plots, and ANOVA analysis of data from all relevant elements of the reproducibility study. You should also report any additional metrics, as appropriate.
- Any bias that you observe during your reproducibility studies, and an explanation to account for the bias.

You should select materials and design your reproducibility evaluation in a way that will produce sufficient reproducibility data across all aspects of the instrumentation and across all dimensions (including time). Depending on the design of the assays intended to be run on the instrumentation, this may include attention to features such as probes, substrates, and samples. To fully investigate signal detection uniformity and stability, you should use assays with signal features that show minimal change with exposure to signal detection (e.g., signal deterioration) and time. For platforms that contain sample preparation steps such as amplification, hybridization, or washing, you should design a reproducibility protocol that will stress the instrumentation to an appropriate degree, i.e., you should not use an assay system that is so robust as to obscure changes in sample integrity that may occur during preparation or assay steps.

Method Comparison

If appropriate, you may evaluate the performance of your instrumentation against your predicate device. The results are usually reported as percent agreement. In cases where you cannot directly compare performance characteristics of your device to those of your predicate, FDA believes that

the best way to test performance is to compare to a gold standard method, when available.

Calibration

You should develop and recommend a calibration program and maintenance schedule for each portion of the instrumentation.

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8. Software

You should submit software documentation for the data acquisition software or other software component of your instrumentation that is detailed in accordance with the level of concern (See: ***Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices*** **(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089543.htm)**. 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 (through the action or inaction of a health care provider).

We consider the following points to be important elements in preparing software documentation for FDA review:

- You should fully describe the software design. You should not include software utilities that are specifically designed to support uses beyond those of the legally marketed assays identified in your 510(k). You should also consider privacy and security issues in your design. Information on some of these issues may be found at the following website regarding the **Health Insurance Portability and Accountability Act (HIPAA) (http://www.hhs.gov/ocr/privacy/hipaa/understanding/index.html)**.

- You should submit a 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.

- You should complete verification and validation (V&V) activities for the version of software that will be utilized for the submission in demonstrating substantial equivalence.

- If the information you include in the 510(k) is based on a version other than the release version, you should identify all differences 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 (/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM085371.pdf)**.
- **Guidance for Off-the-Shelf Software Use in Medical Devices; Final Guidance for Industry, FDA Reviewers and Compliance (ssLINK/ucm073778.htm)**.
- **21 CFR 820.30 (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=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.

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9. 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 proposed labeling that satisfies the requirements of 21 CFR 807.87(e). Although final labeling is not required for 510(k) clearance, final labeling must comply with the requirements of 21 CFR 809.10 before an in vitro diagnostic device is introduced into interstate commerce.

Performance Characteristics

When describing performance characteristics of the device, we recommend that you describe all relevant aspects of your protocol, including materials used and results. We also recommend that you provide graphic representations of the results.

User Manual

We recommend that you provide a user manual that addresses all components of the instrumentation for clinical multiplex test systems. Your user manual should provide an adequate description of the role of the software, the user interface with the software, as well as results of performance testing to demonstrate that the software functions as designed. We recommend pictorial representations of computer screens, graphical user interfaces (GUIs), and other elements that aid the user in correctly using the software.

The user manual, where possible, should also include descriptions of how the user can recognize incorrect operation or failure of the instrumentation, and a troubleshooting guide.

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[1] **The New 510(k) Paradigm (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080187.htm)**

[2] Refer to **Indications for Use Form (http://www.fda.gov/downloads/aboutfda/reportsmanualsforms/forms/ucm360431.pdf)** (PDF File Size: 1.03MB) for the recommended format.

[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 (/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm142706.htm)** (Screening Checklist for All Premarket Notification [510(K)] Submissions).

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More in Guidance Documents (Medical Devices and Radiation-Emitting Products) (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm)

Cross-Center Final Guidance (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081752.htm)

Office of Compliance Final Guidance (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070269.htm)

Office of the Center Director Final Guidance (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm110228.htm)

Office of Communication and Education Final Guidance (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070271.htm)

Office of Device Evaluation Final Guidance 2010 - 2016
(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm198577.htm)

Office of Device Evaluation Final Guidance 1998 - 2009
(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070272.htm)

Office of Device Evaluation Final Guidance 1976 - 1997
(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080283.htm)

Office of In Vitro Diagnostics and Radiological Health Final Guidance
(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070274.htm)

Office of Surveillance and Biometrics Final Guidance
(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070275.htm)

Office of Science and Engineering Laboratories Final Guidance
(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070277.htm)

Draft Guidance
(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm407274.htm)

Radiation-Emitting Products Guidance
(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm283507.htm)

Withdrawn Guidance
(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm425025.htm)