Molecular Diagnostic Instruments with Combined Functions

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

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For questions regarding this document, the CDRH contact is Andrew Grove, PhD, 301-796-6198, Andrew.grove@fda.hhs.gov.
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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 Microbiology Devices

Center for Biologics Evaluation and Research

Preface

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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.

Introduction

This document provides FDA's current thinking on regulation of molecular diagnostic instruments that are intended for use as a device and for other non-device functions. It also provides advice on the type of information that should be provided in a premarket submission for a molecular diagnostic instrument that measures or characterizes nucleic acid analytes and has combined functions. In this document, "combined functions" refer to instruments that serve as a component of an FDA-cleared or approved IVD system but can also be configured by the user for other test purposes, such as basic research.

In this document, for simplicity, "approved/cleared" refers to instruments and functions requiring approval through the PMA process or clearance through the 510(k) process. Similarly, "approval/clearance" refers to both the process for approving instruments through the PMA process and to the process for clearing instruments through the 510(k) process. "Approval/clearance is not required" refers to instruments or functions that do not need to be approved or cleared by FDA, such as those intended solely for use for basic research.

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.

Scope

This document applies to molecular diagnostic instruments that are medical devices[1] used with assays that measure or characterize nucleic acid analytes (human or microbial), and that combine both approved/cleared and functions for which approval/clearance is not required in a single instrument. This document applies to the instrument itself (hardware) as well as to any firmware or other software intended to operate on or to control the instrument. This guidance also addresses software that is distributed as a stand alone device for use with an approved/cleared molecular diagnostic assay.

The document does not apply to instruments approved/cleared for use with assays that are intended to screen donors of blood and blood components and donors of human cells, tissues, and cellular and tissue-based products (HCT/Ps) for communicable diseases.

The recommendations in this document do not apply to assays and reagents. FDA has separately issued draft guidance regarding the marketing of Research Use Only (RUO) and Investigational Use Only (IUO) assays for clinical use, which, when final will address certain uses of reagents and assays that have not received FDA marketing authorization.[2]

Background

Molecular diagnostic instruments, for example, real-time thermocyclers, are critical components of certain *in vitro* diagnostic devices (IVDs). One molecular diagnostic instrument is often used to perform multiple unrelated assays, such as those that detect methicillin resistant *S. aureus* (MRSA), Hepatitis C virus, and genetic markers of cystic fibrosis. These types of instruments are not generally approved/cleared alone, i.e., without an accompanying assay, because their safety and effectiveness or substantial equivalence cannot be evaluated without reference to the assays they run and the assay's defined performance parameters. The same instruments may also be used for additional purposes that do not require FDA approval or clearance, such as for basic scientific research—purposes this document refers to as functions for which approval/clearance is not required. In the past, FDA has provided informal advice in response to individual inquiries regarding the permissibility of having functions for which approval/clearance is not required on an instrument intended to be used with approved/cleared *in vitro* diagnostic assays. This guidance is meant to communicate FDA's policy regarding molecular diagnostic instruments with combined functions.

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[1] Devices are defined in Section 201(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 321(h)).

[2] See Draft Guidance for Industry and Food and Drug Administration Staff Commercially Distributed In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only: Frequently Asked Questions (June 1, 2011), http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM257460.pdf.

Approval of Molecular Diagnostic Instruments

FDA has determined that premarket submissions for molecular diagnostic instruments that have functions for which the sponsor is seeking approval/clearance and additional functions for which the sponsor need not seek approval/clearance, may be considered for regulatory marketing authorization. For FDA to determine that such submissions meet the regulatory criteria for approval or clearance, as applicable, we will assess whether sufficient measures are in place to 1) assure that the functions for which approval/clearance is not required do not interfere with or adversely affect the safety or effectiveness of the approved/cleared functions, and 2) prevent confusion on the part of the end user. These measures may include implementation of the following:

- Instrument and software design controls to assure the safety and effectiveness of the molecular diagnostic instrument with combined functions.
- Validated procedures for users to employ following a use for which approval/clearance is not required to verify that the use will not interfere with subsequent use of the molecular diagnostic instrument as an approved/cleared device, and to document that interference did not occur on subsequent use.
- A risk mitigation plan that provides sufficient information to demonstrate that any risks that could be introduced by having functions for which approval/clearance is not required can be appropriately mitigated.
- Labeling that clearly distinguishes the approved/cleared functions from functions for which approval/clearance is not required (e.g., separate labeling for approved/cleared and functions for which approval approval/clearance is not required).
- Result reports that distinguish between the use of the approved/cleared functions and the use of the same instrument for functions for which approval/clearance is not required.

Upon review of the information supplied in the premarket submission, FDA will determine if such measures described are sufficient to provide a reasonable assurance of safety and effectiveness or substantial equivalence for the approved/cleared functionalities. FDA may request additional information if we determine that it is necessary to assess safety and effectiveness or substantial equivalence of the device.

FDA will review information regarding functions for which approval/clearance is not required only for the purpose of evaluating the risks posed to the approved/cleared functions and adequacy of mitigations. We do not intend to review this information with respect to performance characteristics or suitability for use, and do not intend to provide comment on how instrument functions for which approval/clearance is not required may be marketed, described in labeling, or otherwise made available.

Recommendations for Submissions for Molecular

Diagnostic Instruments with Combined Functions

1. New instruments

For those manufacturers who are developing new molecular diagnostic instruments with functions for which approval/clearance is not required, FDA recommends that the software for such devices clearly separate the approved/cleared functions from any functions for which approval/clearance is not required, so that the user must choose the desired pathway at system start-up. For example, at start-up the instrument gives a choice of either the approved/cleared functions or functions for which approval/clearance is not required, requiring the user to choose one or the other depending on the type of assay to be performed. The user would not be able to switch between functions without first going back to the start-up screen. This approach may serve, for example, to effectively separate the software functions and prevent any confusion on the part of the user as to which function the instrument is performing and to provide a protective mechanism that prevents the user from altering any approved/cleared function parameters.

2. Existing approved/cleared instruments

a. For those manufacturers who already have approved or cleared molecular diagnostic instruments that are also configured to perform functions for which approval/clearance is not required, but have not specifically addressed the issues regarding coexistence of approved/cleared functions and those for which approval/clearance is not required, FDA intends for you to address the recommendations in this document in any new premarket assay submission for which the instrument is intended for use.

b. Alternatively, for manufacturers who would prefer to address these recommendations prior to any new premarket assay submission, you should contact FDA to discuss potential submissions, and the recommendations outlined in this guidance.

3. Submission information, labeling, and marketing

In determining whether to grant approval/clearance for a molecular diagnostic instrument with combined functions for use with an approved/cleared assay, it is FDA's intent to consider the following conditions:

a. Sponsor demonstrates that functions for which approval/clearance is not required do not interfere with approved/cleared functions, by providing sufficient information to establish that the approved/cleared functions are not affected by the functions for which approval/clearance is not required. For example, a sponsor may provide or describe: materials and instructions to verify that the use of functions for which approval/clearance is not required will not interfere with the approved/cleared functions; use of an 'analyte test panel' prior to performing an approved/cleared assay; recalibration procedures; instrument cleaning and maintenance, etc. We

recommend that the sponsor provide documentation on how the separation of approved/cleared functions and those functions for which approval/clearance is not required will be managed through system design measures and labeling, and how it will be applied to avoid or eliminate user confusion about whether a given assay is approved/cleared or not, both during assay operation and reporting of results.

b. Sponsor provides a risk/hazard analysis addressing functions for which approval/clearance is not required in coexistence with approved/cleared functions, and clearly identifies appropriate mitigation measures. Sponsors should consider human factors in the design of the mitigations such as clear menu options, grayed-out software options that are not applicable, etc.

c. Sponsor develops separate labeling (including instrument manuals and other labeling) for the approved/cleared functions. Labeling for the approved/cleared functions is subject to the requirements for in vitro diagnostic products found in 21 CFR 809.10, and should reference only the aspects of the device that were reviewed and approved/cleared by FDA. Additionally, the labeling for the approved/cleared device should indicate that the instrument was approved/cleared to run only the approved/cleared assays. This information should be included in decision summaries, substantial equivalence and approval letters, and instrument manuals.

d. Consistent with the Federal Food, Drug, and Cosmetic Act, the instrument manufacturer or sponsor may not adulterate or misbrand the device by promoting non-approved/non-cleared assays/reagents as approved/cleared for use on the molecular diagnostic instrument, or otherwise imply, directly or indirectly, that FDA has approved/cleared functions for which approval/clearance is not required.[3]

4. *Promotion and labeling issues*

The following provides guidance on labeling and promotion of molecular diagnostic instruments with combined functions. The sponsor of such a product may generally:

- Promote the instrument as approved/cleared for use with assays that are approved/cleared for use on that instrument system.
- Promote the instrument for uses for which approval/clearance is not required (i.e., other than in approved/cleared labeling) without claiming or implying that the uses are approved/cleared.
- Provide information about functions of the molecular diagnostic instrument for which approval/clearance is not required separately from instrument labeling provided for the approved/cleared product.

[3] See Sections 501 and 502 of the FD&C Act (21 U.S.C. 351 and 352).

With regard to these products, a sponsor generally should not:

- Combine approved/cleared and other labeling claims (e.g., "you can use this instrument for detecting MRSA and for basic research").
- Combine labeling describing the approved/cleared functions (i.e., user's manual, brochures, etc.) with information about other functions.
- Claim or imply approved/cleared status for the other functions.
- Imply or claim that the instrument is approved/cleared for any assay other than those the FDA has specifically approved/cleared for use on the instrument.

5. Software/hardware changes

Once a molecular diagnostic instrument with combined functions is approved/cleared, you should notify FDA of changes to the device hardware or software that have the potential to affect the approved/cleared functions of the instrument as required under 21 CFR 807.81(a)(3) and 814.39. This applies to changes to both approved/cleared hardware and software functions and hardware and software functions for which approval/clearance was not required. All changes to both approved/cleared functions and those for which approval/clearance was not required should be included in the manufacturer's IVD change control section in the manufacturer's quality system. Manufacturers should consider the potential impact to both class II and III assays used on their system and perform appropriate risk assessments to determine the need to submit the changes to FDA, based on the recommendations stated in the relevant guidance documents listed below:

- Deciding When to Submit a 510(k) for a Change to an Existing Device http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM080243.pdf

- Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM089360.pdf

6. Third Party assay developers

Assays submitted to FDA by third party assay developers to be run on user-configurable molecular diagnostic instruments, such as those described in this guidance, will be reviewed by FDA on a case-by-case basis to determine whether risks are adequately mitigated, as described above, for use on molecular diagnostic instruments with combined functions. At a minimum, third party assay developers should provide complete instructions for use to allow the end user to perform the assay (including procedures to assure non-interference and proper operation of the instrument and software for approved/cleared functions) on the specified instrument. In addition, the labeling should not rely on or refer to an instrument user manual that is not part of an approved/cleared product's labeling.

MDR Reporting

Manufacturers and user facilities are required to report all device-related adverse events in accordance with the requirements under 21 CFR 803.10. Even though molecular diagnostic instruments covered by this guidance include molecular diagnostic device functions for which approval/clearance is not required, FDA expects malfunctions, injuries, and deaths associated with such functions to be reported as adverse events under 21 CFR Part 803. All instrument device functions, whether approved/cleared or not required to be approved/cleared can have a direct or indirect adverse impact on approved/cleared indications.