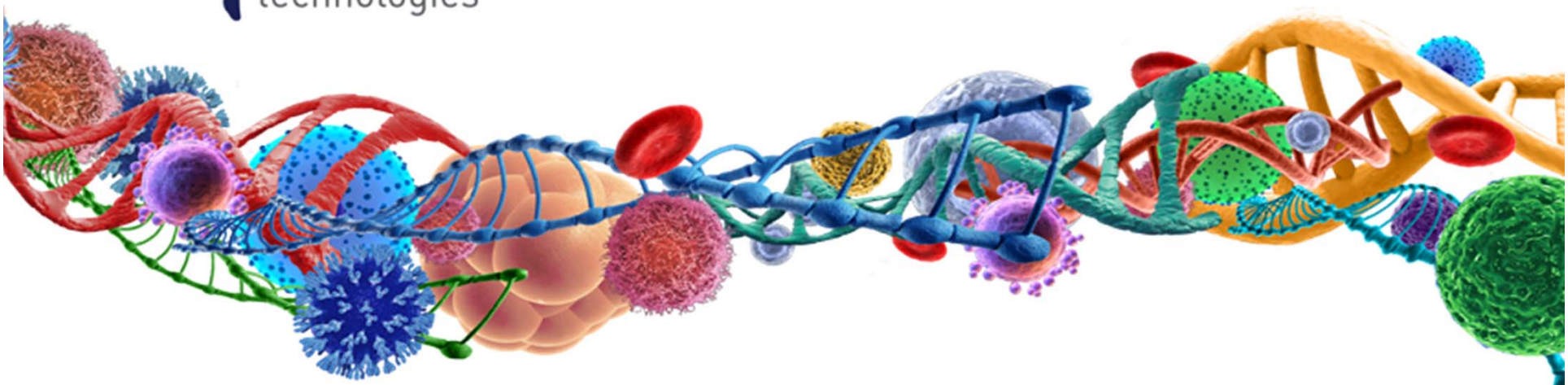

Draft Guidance: Molecular Diagnostic Instruments with Combined Functions - April 9, 2013

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Introduction

This guidance 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.

- Example Devices- PCR, Sequencing
- IVD and RUO utility on the same box

It also provides context concerning 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.

Background

- Approved/ cleared instruments may be used for additional purposes that do not require FDA approval or clearance, such as for basic scientific research (RUO).

- In the past, FDA has provided informal advice in response to Q&A 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.

- Industry experiences associated with this guidance
  - Anyone?

What is meant by purposes/ functions that do not require FDA approval or clearance?

Common terminology associated with these functions:

- RUO functionality
- Open Utility
- Test Development
- User-Configurable
- User- Defined

Scope

In Scope:

- This document applies to molecular diagnostic instruments that are used with assays that measure or characterize nucleic acid analytes (human or microbial), and that combine both approved/cleared functions and RUO functions.

- 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.

Out of Scope:

- 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.

FDAs input concerning SW Design/ Implementation

New Instruments under development:

- When 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.

FDAs input concerning SW Design/ Implementation

Existing instrument considerations:

- 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 manufacturers to address the recommendations in this document in any new premarket assay submission for which the instrument is intended for use.**

OR

- For manufacturers who 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.

What is FDA looking for within the submission?

FDA is looking to assess whether:

1) **Boundaries** exist between the IVD and RUO functionality.

- Separation - A clear separation of the approved/cleared functions from any functions for which approval/clearance is not required.
- Non Interference - Provide sufficient information to establish that the that RUO functionality does not interfere with or adversely affect the safety or effectiveness of the approved/cleared functions.

2) **Labeling** is in place to prevent confusion on the part of the end user.

- Labeling/Instructions - 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 /clearance is not required).
- Patient/results reports - 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.

Submission information – *con't*

3) **Design, mechanisms and procedures** exist to ensure interference does not exist.

- Design Controls - Ensure that Instrument and software design controls exist to assure the safety and effectiveness of the molecular diagnostic instrument with combined functions.
  - 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.
  - Describe how the design/ labeling 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. Such as; notation on screens, results reports, printouts, etc.
- Mechanisms/procedures - Materials and instructions provided that will verify that the use of functions for which approval/clearance is not required will not interfere with the approved/ cleared functions such as:
  - 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.
    - ✓ Use of an "analyte test panel" is required prior to performing an approved/cleared assay;
    - ✓ Recalibration may be required when switching modes, choose one function or another at start up, return to start screen in order to enter new mode/ function, etc
    - ✓ General instrument cleaning and maintenance, procedures/ frequency, etc.

Submission information – con't

4) Risk Mitigation plans that provide 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.

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

Review process

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 (beyond what has been described) if they 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. They 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.
  - For example; RUO manual or other RUO labeling may be requested

Labeling and Promotion concerns

- Ensure that separate labeling exists (including instrument manuals and other labeling) for the approved/cleared functions.
- Device labeling should reference only the aspects of the device that were reviewed and approved/cleared by FDA.
- The labeling for the approved/cleared device should indicate that the instrument was approved/cleared to run only the approved/cleared assays. This information will be included in decision summaries, substantial equivalence and approval letters, and instrument manuals.
- For example:

The QuantStudio™ Dx Real-Time PCR Instrument with QuantStudio™ Dx Software is intended to perform fluorescence-based PCR to provide detection **of FDA cleared and approved nucleic acid sequences** in human-derived specimens. The QuantStudio™ Dx Real-Time PCR Instrument with QuantStudio™ Dx Software is intended for in vitro diagnostic use by trained laboratory technologists **in combination with nucleic acid reagent kits/tests manufactured and labeled for diagnostic purposes on this instrument.**

- Do not promote/ imply that FDA has approved/cleared functions for which approval/clearance is not required.

Labeling and Promotion concerns– con't

OK to -

- 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.

NOT ok to-

- 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.

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.
- 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 your change control system.**
- Consider the potential impact to both class II and III assays used on the system and perform appropriate risk assessments to determine the need to submit the changes to FDA using the following guidance documents:
  - Deciding When to Submit a 510(k) for a Change to an Existing Device
  - Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process

Third Party Assay Developers

- Assays submitted to FDA by third party assay developers to be run on user-configurable molecular diagnostic instruments will be reviewed by FDA on a case-by-case basis to determine whether risks are adequately mitigated, as described, 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.

- The labeling should not rely on or refer to an instrument user manual that is not part of an approved/cleared product's labeling. (cannot refer to RUO manual for instructions)

Note on MDR reporting

- Even though molecular diagnostic instruments covered by this guidance include molecular diagnostic device functions for which approval/clearance is not required (RUO), FDA expects malfunctions, injuries, and deaths associated with such functions to be reported as adverse events under 21 CFR Part 803.