Contains Nonbinding Recommendations

Draft – Not for Implementation

Replacement Reagent and Instrument Family Policy for In Vitro Diagnostic Devices

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Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance is being distributed for comments purposes only

Document issued on December 18, 2017

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For questions about this document regarding CDRH-regulated devices, contact Avis Danishefsky at 1-301-796-6142 or Avis.Danishefsky@fda.hhs.gov.

When finalized this document will supersede "Replacement Reagent and Instrument Family Policy," issued on December 11, 2003

U.S. FOOD & DRUG ADMINISTRATION

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

Preface

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Replacement Reagent and Instrument Family Policy for In Vitro Diagnostic Devices

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Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction

In 2003, FDA issued updated guidance on the "Replacement Reagent and Instrument Family Policy" for in vitro diagnostic (IVD) devices. The 2003 guidance described a mechanism for manufacturers to follow when applying an assay that was previously cleared for use based on performance characteristics with a specified instrument, to an additional instrument that was previously cleared or that is a member of an instrument family from which another member has been previously cleared. Through the approach described in the 2003 guidance, manufacturers establish sufficient control to maintain the level of safety and effectiveness demonstrated in the cleared device for these types of modified devices, when evaluated against predefined acceptance criteria using a proper validation protocol, without submission of a premarket notification (510(k)).

FDA believes this guidance is important for public health as it promotes more timely availability of a wider array of clinical laboratory tests for patient benefit. To ensure that its full benefits are realized, FDA is providing additional clarity to help manufacturers and FDA better apply the concepts in this guidance.

For consistency of terminology with previous guidances and FDA-manufacturer communications, this draft guidance continues to use the terms "Replacement Reagent" and "Instrument Family Policy." Within discussions in this draft guidance, the term "assay" is used instead of the term "reagent" to better represent typical scenarios because most assays in test systems are currently comprised of multiple reagents. *See* Appendix for definitions of the terms used in this guidance.

This draft guidance, when finalized, is intended to update and provide clarity on the Replacement Reagent and Instrument Family Policy for manufacturers of IVD devices and FDA staff. It incorporates concepts and recommendations from FDA's guidance entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device"

(https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm514771.pdf), and includes recommendations and information specifically regarding:

- Manufacturer's initial considerations for determining whether the Replacement Reagent Policy or Instrument Family Policy are applicable (Sections II)
- The Replacement Reagent Policy (Section III)
- The Instrument Family Policy (Section IV)
- Illustrative scenarios and examples (Section V)
- Labeling considerations (Section VI)
- Clinical Laboratory Improvement Amendments (CLIA) categorization when the manufacturer determines, taking into account the considerations described in this guidance, that a 510(k) is not needed (Section VII).

FDA's guidance documents, including this draft 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 guidance means that something is suggested or recommended, but not required.

II. Scope

This guidance pertains to IVD test systems regulated by CDRH comprised of an assay subject to 510(k) that is run on an automated laboratory instrument specified by the assay manufacturer. Specifically, it addresses a manufacturer's application of a previously cleared assay to an additional instrument that was previously cleared or that is a member of an instrument family for which another member has been cleared.

This guidance is not intended to address the following:

- Modifications other than application of a cleared assay to a new instrument[1]
- Class III devices[2]
- Devices indicated for use in support of blood banking practices
- Devices indicated for use in point of care settings
- Devices indicated for over-the-counter (OTC) use
- Devices indicated for prescription home use

Special cases also exist where FDA has established final guidance for modifications to specific devices and/or specific requirements (e.g., special controls) that are identified in the classification regulation.[3] Some

[1] Additional information related to modifications of devices subject to 510(k) other than application of a cleared assay to a new instrument is available in the following guidances:
"Deciding When to Submit a 510(k) for a Change to an Existing Device"
(https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM514771.pdf) and
"Deciding When to Submit a 510(k) for a Software Change to an Existing Device"
(https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM514737.pdf).

[2] For modifications to test systems with assays classified as Class III, *see* the FDA's guidance document entitled "Assay Migration Studies for In Vitro Diagnostic Devices"
(https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm092752.pdf).

[3] OIR final guidance documents can be accessed here.

current final device-specific guidances or special controls state that the Replacement Reagent and Instrument Family Policy is not appropriate for the device type (e.g., Class II Special Controls Guidance Document: Instrumentation for Clinical Multiplex Test Systems (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077819.htm). This guidance, when finalized, will modify such statements so that the Replacement Reagent Policy and Instrument Family Policy described in this guidance may apply to such device types. Based on FDA's current understanding of and experience with currently classified device types, FDA believes that the recommendations provided in this guidance could provide for alternative mitigations that provide equivalent assurances of safety and effectiveness, but there may be additional considerations to take into account. This guidance, when finalized, is not intended to supersede anything else contained in such final device-specific guidances or special controls but may cover areas not addressed in such device-specific guidances or special controls.

Recommendations in this guidance are based on FDA experience with previously cleared test systems with established performance. To date, the Replacement Reagent Policy has largely been utilized for traditional laboratory automated chemistry and immunoassays. Use of this guidance for other types of test systems may raise additional considerations. Manufacturers may use the pre-submission process to obtain feedback on the appropriate application of this policy to their assay(s) either during their initial 510(k) planning (i.e., if future modifications to assay-instrument combinations can be anticipated) and/or at any time after the initial clearance of the assay. Information on the pre-submission process can be found in FDA's guidance document entitled "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff" (https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf).

This guidance, when finalized, applies to a large spectrum of marketed Class I "reserved" or Class II-510(k) IVD test systems intended for use in moderate or high complexity CLIA-regulated laboratories. While most automated clinical instruments by themselves are classified as class I and exempt from 510(k), reagent/instrument systems are considered "combination devices." A 510(k) is required if there are claims regarding a reagent in the system that meets the definition for a class I reserved or class II device (*see* sections 510(k), 510(l) and 513(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR 807.81 and 860.3; *see also* the limitations to the exemption from premarket notification requirements found in 21 CFR 862.9, 21 CFR 864.9, or 21 CFR 866.9 depending on the part in which the device is classified). In its review of the 510(k), CDRH subjects a "combination device" to the same sorts of questions and requirements, including documentation requirements, that are applied to a single device. When such a device is found to be substantially equivalent, it combines devices from different classes and is classified in the highest of the predicate device classifications unless the combined devices are regulatable as separate articles (e.g., they are detachable). In the latter case, the separately regulatable articles will be regulated in separate classes.

The following tables are designed to help illustrate regulatory scenarios for which different sections of this guidance should be considered. In these examples:

- Assay A was previously cleared to be run on Instrument A' based on performance demonstrated with Instrument A'.
- Assay B was previously cleared to be run on Instrument B' based on performance demonstrated with Instrument B'.
- Neither Assay C nor Instrument C' is part of a cleared test system.

	Cleared test systems comprised of			Not part of a previously cleared test system
Assay	A	or	B	C
Instrument	A'		B'	C'

Assay and Instrument combinations	Applicable Regulatory Policy in this Guidance
A+B' or B+A'	*See* Section III (Replacement Reagent Policy)
A+C' or B+C'	*See* Sections III and IV (Instrument Family Policy)
C+C', C+B', or C+A'	None (outside scope); Submit 510(k) (21 CFR 807.81(a)(2))

III. Replacement Reagent Policy

Generally, 510(k) clearance for test systems is based on assay performance characteristics demonstrated with an instrument (or instruments) specified by the assay manufacturer. Once an assay has been cleared based on performance with a specified instrument, assay manufacturers may choose to modify the test system by applying the same cleared assay to additional laboratory instruments evaluated as part of a previously cleared test system. Such assays are referred to as replacement reagents. One common scenario is when the assay and instrument are both manufactured by the same manufacturer. However, the Replacement Reagent Policy may also apply when the assay and instrument are each produced by separate manufacturers. The assay manufacturer should assess capabilities and performance of the new assay and instrument combination under the quality system requirements for the assay to ensure acceptable performance of the test system. Additionally, the assay manufacturer is responsible for ensuring that the modified test system continues to meet design specifications. FDA encourages communication between assay manufacturers and instrument manufacturers to ensure that any changes to the instrument do not impact the performance of the test system.

Manufacturers planning to modify their test systems by applying a cleared assay to a new instrument should determine whether a 510(k) is needed after taking into account the considerations described below. Should a manufacturer determine, after applying the logic scheme and considering the issues described below (i.e., test system operating principles, risk-based assessment, and verification and/or validation activities), that a new 510(k) is not needed and proceed with the modified test system, the manufacturer should make sure to document, as part of the device master record, the change and its assessment of whether a new 510(k) is required to be submitted (*see* Section III.D).

A. Test system operating principles

To date, the Replacement Reagent Policy has largely been utilized for traditional laboratory automated chemistry and immunoassays. If you have questions concerning how to apply this guidance to an evolving technology, we recommend you contact the appropriate review division in FDA. This could be done using the pre-submission process or during premarket review of the initial test system if future modifications can be anticipated.

A1. Assay key components and fundamental test principles

The manufacturer should first use the Tables in Section II above to determine whether the Replacement Reagent Policy applies to the new test system. The assay manufacturer should then determine whether the use of the cleared assay on the additional instrument requires changes that alter assay key components or fundamental test principles for which a new 510(k) is required. A modification to a test system that alters key components or such operating principles of the test system could significantly affect safety and effectiveness, in which case a new 510(k) is required (21 CFR 807.81(a)(3)(i)). Assay key components may include specific antigen-antibody or enzyme-substrate components, conjugates or signaling components, reaction surfaces, or components used in separation methods. Fundamental test principles may include detection modes (e.g., ion selective electrode, colorimetric absorbance, fluorescence detection, turbidimetry, nephelometry), measurement methods (e.g., endpoints or rate measurements; quantitative, semi-quantitative, or qualitative), methods for signal processing, data acquisition and interpretation, or assay-specific pre-analytical steps. If assay key components or fundamental test principles need to be modified in order to apply the assay to the additional instrument(s), a 510(k) is likely required. A 510(k) is also likely required for significant changes to assay value assignment methods or calibration schemes, as such changes are likely to be critical to overall test performance and result in modified reporting of performance in labeling.

Examples of changes to the test system that are less likely to affect assay performance or test system operating principles include modifications to outer cartridges or reagent preservatives; however, the manufacturer should conduct a risk-based assessment and design verification and/or validation activities to confirm.

If application of a cleared assay to an additional instrument does not alter the assay key components or fundamental test principles, proceed to section A2 below.

A2. Instrument principles

The assay manufacturer should confirm that the principles of analysis of the instrument with which the assay will be intended for use are comparable to the instrument with which assay performance was demonstrated in a cleared 510(k). For example, the two instruments should have common detection and measurement methods, control of reaction conditions, and signal processing. The assay manufacturer should confirm that basic capabilities of the new instrument relevant to the assay were demonstrated in a cleared 510(k) (*see* Example 2 in Section V below). If these conditions do not apply, a 510(k) is likely required.

The Replacement Reagent Policy applies to open systems. For purposes of this guidance, an open system has general purpose features intended for use with a wide array of assay types, including those that share a similar methodology (e.g., similar detection methods, similar processing and interpretive software). An open system generally does not impose restrictions (e.g., through software) for use with only certain types of reagents or for detection of only certain types of analytes.

The Replacement Reagent Policy does not apply to closed systems. For purposes of this guidance, a closed system includes an instrument intended for use with specific reagents or reagent types and specific reaction schemes.

If software, such as for system integration, system restrictions (noted above), signal processing, data acquisition, interpretation, or other calculations needed to produce clinical results, needs to be modified in

order to run the assay on the instrument, then a new 510(k) is likely required.

If application of a cleared assay to an additional instrument does not alter the instrument principles or software, proceed to Section III.B below.

B. Risk-based assessment

The assay manufacturer should conduct a risk-based assessment for any modified test system.[4] The risk-based assessment should address analytical and clinical performance, indications for use, and any other factors that could affect the risk profile of the IVD. For additional information concerning an initial risk-based assessment, *see* FDA's guidance entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device" (https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm514771.pdf).

B1. Performance

When the risk-based assessment indicates that the performance of the modified test system could significantly change (e.g., statistically or clinically significant changes) relative to performance claims in the labeling for the cleared test system, a 510(k) is likely required. A manufacturer's risk-based assessment should identify new risks or significantly modified existing risks when applicable. For additional information, *see* section 5.D.3 of FDA's guidance entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device" (https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm514771.pdf). Changes to test system performance characteristics (e.g., precision, linearity or recovery, interference, assay traceability, detection limits, bias or scatter observed in method comparison) from those indicated in the labeling for the cleared test system have the potential to affect clinical decisions. For example, if reference ranges (or claimed cutoff concentrations) for the intended use population(s) are expected to change as a result of the change in instrument, this is considered a change to clinical performance, and a 510(k) is likely required.

B2. Changes to Labeling Affecting the Indications for Use

Within each risk-based assessment, manufacturers should take into account the cleared indications for use and clinical needs and performance associated with such use. For additional information regarding when a change to indications for use would likely require the submission of a 510(k), *see* section 5.A. of FDA's guidance entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device" (https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm514771.pdf). Examples of changes to labeling affecting the indications for use that would likely require a 510(k) include (but are not limited to) change in output between qualitative, semi-quantitative, and quantitative results, change in clinical sample type (such as serum to cerebrospinal fluid (CSF), urine, or whole blood) or significant change in performance claims, such as a change in cut-off value, or addition of a "high sensitivity" performance claim to the assay.

In addition to specifically considering performance and changes to the labeling which affect the indications

[4] Manufacturers should note that a risk analysis may be required as part of design validation (*see* 21 CFR 820.30(g)).

for use, manufacturers should also consider susceptibility to change of the specific assay technology. For example, careful attention should be paid when a new instrument-assay combination includes modifications to reaction conditions, especially for technologies that are sensitive to small variations in assay parameters (e.g., temperature changes within antibody-antigen reactions) or where small differences in results have the potential to affect clinical decisions (e.g., small changes to the analytical sensitivity of troponin assays may significantly affect clinical assay performance). Changes that are clinically significant in terms of clinical decision making are likely to require a 510(k).

In summary, if the initial risk-based assessment does not raise any of the issues noted above or otherwise identify new risks or significantly modified existing risks, the manufacturer should perform testing to verify this initial assessment. Section III.C below discusses this testing.

C. Design verification and/or validation activities

The assay manufacturer is responsible for verifying and/or validating the modified test system as part of design controls (*see* 21 CFR 820.30). Verification and validation activities should be based upon the manufacturer's quality processes, including its risk-based assessment for the specific device and changes involved.

C1. Consideration of Protocols and Acceptance Criteria

For IVDs, standard methods and performance criteria that have been established for evaluation of the specific device, as appropriate (e.g., protocols and criteria used to support the original 510(k), or a protocol and criteria established in the original 510(k) that described how anticipated changes would be evaluated) should be used to verify and validate the modification, as applicable. The assay manufacturer should develop a testing protocol and pre-specified acceptance criteria for each assay prior to testing. Protocols should be sufficiently robust and challenging to ensure that any significant changes to the performance of the new instrument-assay combination (compared to the performance of the cleared instrument-assay system) will be identified. The acceptance criteria should be clinically justified and ensure that all performance claims in the labeling for the cleared test system will continue to be met. If verification or validation test methods or acceptance criteria other than those discussed above are necessary to evaluate the change, it is likely that the change could significantly affect safety or effectiveness and that submission of a new 510(k) is required.

For example, if the following types of protocols were included in the cleared 510(k) for the assay, the manufacturer should consider them for inclusion in testing protocols for the new assay-instrument combination:

- Testing in accordance with CLSI (Clinical and Laboratory Standards Institute) guidelines EP-17 to support a specified Limit of Blank, Limit of Detection, and Limit of Quantitation.
- Testing in accordance with CLSI guidelines EP-05 to support precision at limits of the claimed measuring range, and at medical decision points.
- Linearity across the assay range, or, if appropriate, recovery to standard materials or methods.
- Method comparison studies in accordance with CLSI guidelines EP-09. Sample types (e.g., matrix), range and comparator methods should be consistent with the original 510(k). If comparison to a well-known reference method(s) or material(s) or clinical endpoint(s) were needed to support the original 510(k) (e.g., because of known lack of standardization among

cleared assays), we recommend you incorporate the same material(s), method(s), or clinical endpoint(s) to ensure similar performance for the new assay-instrument combination.

- Interference studies as appropriate for the particular reagents and instrument detection methods in accordance with CLSI guidelines EP-07.

Similarly, where relevant for the additional instrument, manufacturers should consider including the following within verification and validation activities for the new assay-instrument combination:

- Carry-over or cross-contamination studies
- Matrix equivalence studies
- On-board reagent, calibrator and sample stability
- Hook-effect studies

The bullets above are examples of common types of testing, and are not meant as a comprehensive list. The assay manufacturer should determine appropriate testing based on a risk-based assessment for the specific device and changes involved. If an updated, FDA-recognized standard or guideline has been published since the time of assay clearance, it is preferable that the manufacturer follow this; however, it is also acceptable to use the same standard or guideline that was followed to support the cleared 510(k).

In some cases the manufacturer might determine, based on the change to the specific assay-instrument combination, that some of the study types included in the original 510(k) are not needed. In such cases, the manufacturer should clearly document the justification for this (*see* Section III.D). These types of determinations may be more common when the assay manufacturer is the same as the instrument manufacturer, and the assay is being applied to a new instrument family member.

In general, FDA anticipates that in order to demonstrate that assay performance characteristics are the same as those represented in the assay labeling, test protocol samples sizes should be similar. However, a manufacturer could determine that performance characteristics in the assay labeling can be statistically supported based on testing with a smaller sample size. In such cases, the manufacturer should document the statistical rationale.

If a manufacturer determines that the new test system necessitates a different verification and/or validation scheme (e.g., new types of studies not included in the cleared 510(k) are needed to demonstrate performance, or non-standard verification or validation test methods are necessary to produce the expected results), a 510(k) is likely required.

For most IVD assays, analytical validation, including method comparison, is sufficient to validate that performance does not change when the assay is applied to a new, similar instrument. However, in some cases, analytical validation alone is not adequate to assess the impact of the change and assessment of critical clinical performance parameters, such as clinical sensitivity and specificity, may be needed (*see* Section V, example 6). If a clinical investigation is necessary to answer safety and effectiveness questions relating to a particular modification to a test system, a 510(k) is likely required. In contrast, use of de-identified clinical samples for standard testing to verify analytical performance does not normally necessitate a 510(k).

C2. Consideration of Results

Should the results of verification and validation using standard methods and performance criteria established

for the evaluation of the specific device indicate that (a) the performance of the modified test system is within the criteria, (b) the performance of the modified test system has not significantly changed relative to claims in the labeling for the cleared test system, and (c) otherwise, no new risks or significantly modified existing risks are noted, then it is unlikely that the replacement reagent could significantly affect safety or effectiveness, and a 510(k) is likely not required.

If the results of routine verification and validation produce any unexpected issues or otherwise prove inadequate to verify and/or validate the modified test system, it is likely that the modification could significantly affect the test system's safety and effectiveness, and a 510(k) is likely required. This might be the case, for example, when pre-specified acceptance criteria are not met (e.g., when changes are made to widen pre-specified acceptance criteria).

Should a manufacturer determine, after applying the logic scheme and considering the issues described above (i.e., test system operating principles, risk-based assessment, and design verification and/or validation activities), that a 510(k) is not needed, and proceed with the change to the test system, the manufacturer should make sure to document the changes to the test system and the manufacturer's assessment of whether a new 510(k) is required (*see* Section III.D).

D. Documentation

Among other requirements, FDA's quality systems regulation (QS regulation) requires manufacturers of finished medical devices to review and approve changes to device design and production (21 CFR 820.30 and 820.70) and to document changes and approvals in the device master record (21 CFR 820.181). An appropriately designated individual (or individuals) should sign and date documentation for internal analyses and activities. The manufacturer must keep records, and these records must be made available to an FDA investigator (*see* section 704(e) of the FD&C Act; *see also* 21 CFR part 820 subpart M ("Records")). Documentation should include comparison between the old and new assay-instrument combination, risk-based assessment, detailed protocols, acceptance criteria, and results. If the manufacturer determined that some of the types of testing included in the initial 510(k) were not needed, the specific rationale should be included within the documentation.

IV. Instrument Family Policy

The Instrument Family Policy specifically addresses modifications to an instrument by its original manufacturer, to produce a new version of the instrument (i.e., a new instrument family member). Instruments within a family are the same in terms of the hardware and software components related to the test reaction and interpretation. Further, the term instrument family, as used in this guidance, means a group of one or more instruments produced by, or for, the same manufacturer, having the same general architecture, design, tolerance limits, and capabilities, such as detection methods, signal range and intensity, and reaction conditions. Test systems that include instruments within a family have 21 CFR 820.30(j) compliant design history files that demonstrate that one instrument can be considered a modification of the other, rather than a new instrument. Examples of the types of differences between instrument family members include improvements to some features of the user interface, ability for higher sample throughput due to pre-analytical features, or increased data storage. Instruments within a family share a common device classification regulation and product code.

The instrument manufacturer should perform testing to confirm that instrument features, including software, are within the claimed tolerance limits or criteria. *See also* FDA's guidance entitled "General Principles of Software Validation" (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085371.pdf). The manufacturer should also maintain documentation of the relationship between the proposed family member and a family member (or members) cleared by FDA, including a description of the technological similarities and differences between the instruments, including software differences.

An assay manufacturer planning to apply its assay to a new instrument family member should follow the logic scheme and consider the issues in Section III to determine if a 510(k) is needed. Similar to any instruments to which the Replacement Reagent Policy is applied, the new instrument family member should yield the same result (i.e., no statistical difference in results) for the same samples using the same assay.

If there are multiple instruments within a family, performance of assays with new family members should be compared to an instrument whose performance was demonstrated in a cleared 510(k) in order to ensure comparability for successive changes to instruments within the family. If the assay manufacturer and instrument manufacturer are the same, that manufacturer might determine that application of an assay to a new family member does not call for the entire range of testing performed to support the 510(k) for the same assay. For example, if the change to an instrument is known to involve only post-analytic data storage, it is unlikely that interference characteristics would be affected, and the manufacturer might determine that interference testing is not needed. Manufacturers should fully document the rationale for this type of decision. It is not sufficient, for example, for an assay manufacturer to simply document that testing was not performed because the instrument is a family member.

If the new instrument does not fall within the "instrument family" definition, and was not reviewed within a previously cleared 510(k), in general, the application of the new instrument to the test system could significantly affect the safety or effectiveness of the test system, and a new 510(k) is likely required.

V. Examples

1 – Scope; Replacement Reagent Policy applies to cleared assays only

ANA (antinuclear antibody) assays are Class II devices, regulated under 21 CFR 866.5100, and subject to 510(k). The First Inc. ANA Immunoassay was previously cleared for use with the ABC Fluorescence Instrument. The Second Inc. ANA Immunoassay manufacturer now plans to apply its assay to the ABC Fluorescence Instrument.

Scenario A – The Second ANA Immunoassay was cleared based on performance with the XYZ Fluorescence Instrument, which has similar capabilities as the ABC Fluorescence Instrument. The Second ANA Immunoassay manufacturer assessed the considerations described in Section III above, and performed a risk-based assessment and design verification and validation activities. The risk-based assessment did not identify any new risks or significantly modified existing risks, the design verification and validation activities did not produce any unexpected issues of safety or effectiveness, and the Second ANA Immunoassay performance was the same on the ABC Fluorescence Instrument as on the XYZ Fluorescence Instrument. Therefore, the manufacturer determined that a 510(k) was not needed to market the Second ANA Immunoassay for use with the ABC Fluorescence Instrument and documented the

change and 510(k) assessment to the file.

Scenario B - There is no previously cleared 510(k) for the Second ANA Immunoassay. Although other assays for ANA have been cleared for use on the ABC Fluorescence Instrument, the Second ANA Immunoassay manufacturer is required to submit a 510(k) and obtain clearance before marketing this specific assay (sections 510(k) and 513(f)(1) of the FD&C Act; 21 CFR 807.81(a)(2)).

2 – Test system operating principles; Demonstrated instrument capabilities (e.g., detection method)

Enzyme immunoassays to quantitatively measure multiple endogenous clinical chemistry analytes in serum and plasma were cleared based on performance using the Open System Instrument. Results are based on absorbance measurements.

Scenario A – A therapeutic drug monitoring (TDM) Assay cleared to quantitatively measure a therapeutic drug in serum and plasma is based on absorbance measurements with a manufacturer-specified instrument. The TDM Assay manufacturer investigated the Open System Instrument, and determined it has capabilities needed to accurately measure results with its assay. These capabilities were demonstrated during clearance of the multiple endogenous chemistry analytes assays. No changes need to be made to the TDM Assay or to the Open System Instrument in order to use this assay with this instrument. Furthermore, based on the risk-based assessment, the TDM Assay manufacturer determined that using the TDM Assay with the Open System Instrument does not significantly modify existing risks or create risks that were not previously identified for this assay, and performance is expected to be the same. The manufacturer performed testing which verified this expectation. Based on this, the manufacturer determined that a new 510(k) was not needed to market the TDM Assay to run on the Open System Instrument and documented the change and 510(k) assessment to the file.

Scenario B –A qualitative urine assay to detect multiple clinical chemistry analytes was previously cleared for use with an instrument specified by the assay manufacturer. The qualitative urine assay manufacturer now plans to market its assay for use with the Open System Instrument. However, to date, assays cleared for use with the Open System Instrument have all been quantitative. Use of the Instrument for qualitative assays calls for alternative instrument calibration schemes and software, and performance of the Instrument with qualitative assays has not yet been demonstrated. Therefore, the qualitative urine assay manufacturer submits a 510(k) for use of its assay with the Open System Instrument.

Scenario C – A fluorescence-based TDM Assay to quantitatively measure a specified therapeutic drug in serum and plasma was cleared to run on a manufacturer-specified instrument. The Assay manufacturer plans to market the fluorescence-based TDM Assay for use with the Open System Instrument. However, on searching FDA's public 510(k) and CLIA databases, the TDM Assay manufacturer notes that there are no fluorescence-based assays cleared for use on the Open System Instrument. Therefore, the manufacturer determines that changes to the operating principles of the Open System Instrument (e.g., absorbance to fluorescence detection method) are needed to use its assay with this instrument, and submits a 510(k) for use of the assay in combination with the Open System Instrument.

3- Test system operating principles

The CD-I panel assay was cleared for use with flow cytometer A, which has three lasers and ten channels. The CD-II panel assay was cleared for detection of similar biomarkers as the CD-I panel assay and uses

different fluorescent markers. It was cleared for use with flow cytometer B which has two lasers and six channels. The manufacturer now plans to market the CD-II panel assay on flow cytometer A. Because the changes in test system operating principles and components (e.g., addition of laser, change in interpretive software (template)) are likely to result in changes to performance, the manufacturer submits a 510(k) prior to marketing the new assay-instrument combination.

4 – Test system operating principles

Assay A was cleared for use on Instrument A', which contains assay-specific software. The manufacturer now plans to market the assay on Instrument B' as well. However, there are differences in signal processing between these instruments due to differences in light source and other optics components. It is expected that these changes to test system operating principles are likely to affect assay performance. In order to run the assay on Instrument B', the manufacturer needs to significantly modify its software to address the differences. The manufacturer submits a new 510(k).

5 – Risk-based assessment; Change to indication[5]

The CVD cholesterol assay was cleared for quantitative measurements of high-density lipoprotein (HDL) and low-density lipoprotein (LDL) in venous blood samples based on performance with a laboratory instrument specified by the manufacturer. The instrument is intended for use in centralized laboratories. The test uses a sample volume of 65 uL.

Scenario A – The manufacturer plans to apply the assay to additional instruments similar in methodology to the one used to support initial clearance. The reagent volumes used by the additional instruments vary from 50 to 75 uL. The reagents to sample ratio is unchanged. The manufacturer's risk-based assessment did not identify any new risks or significantly modified existing risks and indicated that the performance is expected to remain the same, and the same testing conducted for the 510(k) verified there was no change to performance. Based on this, the manufacturer determined that a 510(k) was not needed, and documented the change and 510(k) assessment to the file.

Scenario B - The assay manufacturer plans to market the assay with a miniaturized point of care instrument for fingerstick samples. The modified test system uses a sample size of 10 uL. This modification represents a change to a sample type (venous to fingerstick) and size which could significantly change the clinical performance claims and reference range relative to the claims in the labeling of the cleared test system. Separately, this change also affects the intended user and use environment (central laboratory to point of care) and represents a change to test system operating principles (e.g., miniaturizing the instrument changed the basic capabilities and specifications of the instrument). For each of the reasons above, the manufacturer submits a 510(k) for use of the assay on the miniaturized point of care instrument.

6 – Design verification and/or validation activities; Assay application to a new instrument calls for clinical data for adequate validation of the modification

The EZPZ troponin assay was cleared for use with the SAFT clinical chemistry instrument. Clinical

[5] Note that a change in the instrument for use with an assay, as described in the scenarios above, may also constitute a change in indication, but as discussed in this guidance, whether such change requires a 510(k) depends on whether the change could significantly affect the safety or effectiveness of the cleared test system.

performance of the assay from the prospective clinical study performed using the EZPZ assay-SAFT instrument combination (sensitivity, specificity, positive predictive value, and negative predictive value) is described in the labeling.

Scenario A - The assay manufacturer plans to apply the assay to the SAFR instrument, which is similar in technology to the SAFT instrument, but is designed and manufactured differently (e.g., different sample processing internal layout, different sample workflow, etc.). The assay manufacturer performs a risk-based assessment, which does not identify any new risks or significantly modified existing risks, but design validation and verification activities demonstrate slightly different assay performance near the clinical decision point of the assay (at the low end of the measuring range). This analytical data raises new questions about whether analytical data are sufficient to demonstrate that clinical performance of the assay has not changed such that the change necessitates a different verification and/or validation scheme. The manufacturer submits a 510(k) for the combination of the EZPZ troponin assay with the SAFR instrument.

Scenario B - The assay manufacturer plans to apply the assay to the SAFTS instrument, an instrument family member which is identical to the SAFT instrument except for the size and color of the outer box and minor differences in the user interface. The assay manufacturer performs a risk-based assessment, which does not identify any new risks or significantly modified existing risks. In addition, because the analytical features of the instrument are identical to the SAFT instrument, the manufacturer determines that no new testing is needed to assess the application of the assay to the instrument family member. Based on this, the manufacturer determines that a new 510(k) is not needed to market the EZPZ troponin assay to run on the SAFTS instrument, and the manufacturer documents the change and 510(k) assessment to the file.

VI. Labeling

Labeling for IVDs must comply with 21 CFR Parts 801 and 809 and any applicable device-specific requirements (e.g., special controls, restrictions, or limitations found in a clearance with limitations). Package inserts for a new assay-instrument combination within the scope of the Replacement Reagent Policy or Instrument Family Policy, should include any new procedural steps relevant for use of the assay with the additional instrument.[6] Some manufacturers choose to include settings for new assay-instrument combinations in an application sheet. In these cases, FDA recommends that the package insert refer to the application sheet, and vice versa to ensure users are aware of all relevant information. Assay package inserts or accompanying application sheets should clearly state which instruments have been tested for use with the assays. For instrument modifications, operator manuals should include any updated specifications and instructions. The addition of a new assay-instrument combination within the scope of this guidance should not significantly affect assay labeling including performance claims.

VII. Clinical Laboratory Improvement Amendments (CLIA) Categorization

FDA categorizes IVD test systems according to their CLIA complexity (42 CFR 493.5) and enters the categorizations in the CLIA database following clearance or approval. *See* the FDA's guidance entitled

[6] This refers only to small changes in procedural steps. Significant changes may require a 510(k).

"Administrative Procedures for CLIA Categorization" (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070889.pdf). For modifications relating to application of cleared assays to additional instruments, assay manufacturers should submit CLIA categorization requests to FDA in order for the test system to be incorporated in the CLIA database. A CLIA categorization request for application of an assay to an additional instrument using the Replacement Reagent Policy or Instrument Family Policy should include:

- a signed cover page, with contact information, clearly designating the request "For CLIA Categorization Only" and including a statement that the manufacturer has followed the logic scheme and considered the issues in this guidance.
- specification of which instruments (cleared or family member) and cleared assays are being combined, including reference to all related 510(k) numbers. This information can be most clearly represented in table format, especially if multiple assays or instruments are involved.
- the package insert (and application sheet, if applicable), for the new test system specifying the additional instruments.

Additionally, for systems with new instrument family members (i.e., instruments that are not part of a previously cleared 510(k) and were not previously categorized), the manufacturer should include the Operator Manual (or excerpts including the instrument name, intended use, manufacturer or distributor, changes to the cleared instrument and any procedural changes).

In addition, if the assay manufacturer is different from the instrument manufacturer and is applying its assay to a new instrument family member (i.e., that was not part of a test system reviewed within a cleared 510(k)), the assay manufacturer should also include information (e.g., confirmation from the instrument manufacturer) to support that the instrument is an instrument family member as defined in this guidance.

FDA will assign a discrete CLIA Record ("CR") number to this submission, notify the sponsor of the tracking number, and attempt to notify the sponsor of the categorization within 30 days of the request. Following notification to the sponsor, FDA posts the categorization(s) in the public CLIA database. Categorization in response to a CLIA categorization request is not a substantial equivalence determination, and is not meant to indicate FDA review of the manufacturer's internal assessments and testing. A modified instrument (including family member) or new assay-instrument combination categorized in response to a CLIA categorization request based on the Replacement Reagent Policy or Instrument Family Policy, and without a 510(k) clearance for the modification, should not be used as a predicate device for a new 510(k).

Appendix: Definitions

The definitions provided in this appendix are for purposes of this guidance only.

Instrument	A device that produces an analytical result from an applied sample by reading a generated signal and modifying or translating the signal into a result. The instrument may also control pre-analytic, and/or post-analytic components including: mechanisms for sampling and processing specimens, and software for interpretation and storage.
Assay	A set of all reagents and instructions needed for measurement or detection of the analyte.
Design history file (DHF)	The DHF is defined in 21 CFR 820.3(e). The DHF contains or references the records necessary to demonstrate that the design was developed in accordance with the approved design plan and the requirements of 21 CFR part 820.
Instrument family	A group of two or more instruments produced by (or for) the same manufacturer, having the same general architecture, design, tolerance limits, and capabilities, such as detection methods, signal range and intensity, and reaction conditions. Instruments within a family are the same in terms of the hardware and software components related to the test reaction and interpretation, and share a common device classification regulation and product code. Examples of the types of differences between instrument family members include improvements to some features of the user interface, ability for higher sample throughput due to pre-analytical features, or increased data storage.
Package insert	Assay labeling with instructions for performing and interpreting the assay. *See* 21 CFR parts 801 and 809, as applicable (e.g., 21 CFR 809.10(b)) and any applicable device-specific requirements (e.g., special controls, restrictions, or limitations found in a clearance with limitations). Other forms of labeling noted in this guidance include: Operator manual which accompanies the instrument and contains its description, claimed specifications, and instructions. Application sheet which contains settings for applying the manufacturer's assay to a specified instrument. Note: When an assay manufacturer makes available an application sheet for a specific instrument(s), this implies adequate performance for the assay on the instrument(s).
Reagent	A substance or component of an assay that allows a target analyte to be detected or measured. An assay typically includes multiple reagents.
Replacement Reagent	Replacement reagent refers to a previously cleared reagent that is being applied to an additional instrument. IVD manufacturers should refer to the considerations described in Section III of this guidance, including test system operating principles, risk-based assessment, and design verification and/or validation activities, to help determine whether reagent application to the additional instrument calls for a new 510(k).
Test system	All test components required to perform an in vitro diagnostic test, including but not limited to, clinical laboratory instruments, software, assay reagents, calibrators, and controls.