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Replacement Reagent and Instrument Family Policy for In Vitro Diagnostic Devices

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Guidance for Industry and Food and Drug Administration Staff

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This document supersedes "Replacement Reagent and Instrument Family Policy; Guidance for Industry and FDA Staff" issued on December 11, 2003.

For questions about this document, contact OHT7: Office of In Vitro Diagnostics at 301-796-7692 and CDRH-OIR-Policy@fda.hhs.gov.

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

Preface

Public Comment

You may submit electronic comments and suggestions at any time for Agency consideration to http://www.regulations.gov. Submit written comments to the Dockets Management Staff, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852. Identify all comments with the docket number FDA-2017-D-6765. Comments may not be acted upon by the Agency until the document is next revised or updated.

Additional Copies

Additional copies are available from the Internet. You may also send an e-mail request to CDRH-Guidance@fda.hhs.gov to receive a copy of the guidance. Please include the document number 950 and complete title of the guidance in the request.

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Guidance for Industry and Food and Drug Administration Staff

This guidance represents 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 an 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 based on performance characteristics when used with a specified instrument to an additional instrument that is either cleared or a member of an instrument family from which another instrument was previously cleared. Through the approach described in the 2003 guidance, manufacturers established sufficient control to maintain the level of safety and effectiveness demonstrated for 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)).

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

FDA believes this guidance is important for public health as FDA continues to promote more timely availability of a wider array of clinical laboratory tests for patient benefit. This guidance is intended to update and provide clarity on the Replacement Reagent and Instrument Family Policy for manufacturers of IVD devices and FDA staff to promote consistent application of the concepts in this guidance. This guidance also incorporates concepts and recommendations from FDA's guidances entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device,"[1] "Deciding When to Submit a 510(k) for a

[1] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-change-existing-device.

Software Change to an Existing Device,"[2] and "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]."[3] and includes recommendations and information specifically regarding:

- Manufacturer's preliminary considerations for determining whether this guidance is applicable (Section II)
- The Replacement Reagent Policy (Section III)
- The Instrument Family Policy (Section IV)
- Examples (Section V)
- Labeling (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)

In addition, the guidance includes two Appendices. Please refer to Appendix 1: Significant Terminology for the meaning of key terms used in this guidance. Please refer to Appendix 2: Flowchart Aids for a series of flowcharts that are intended to supplement this guidance, but are not intended to be used alone. The flowcharts are provided as a visual aid only and are not intended to capture all appropriate considerations in determining whether the policies in this guidance may be applicable for your proposed modifications to certain IVD devices. Refer to the corresponding text of this guidance when using the flowcharts.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, 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 and comprised of a cleared assay that is run on an automated laboratory instrument specified by the assay manufacturer. Specifically, it addresses a manufacturer's application of an assay that was previously cleared for use based on performance characteristics when used 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.

This guidance is not intended to address the following:

- Modifications other than application of a cleared assay to an additional instrument[4]

[2] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-software-change-existing-device.
[3] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/510k-program-evaluating-substantial-equivalence-premarket-notifications-510k.
[4] Additional information related to modifications of devices subject to 510(k) other than application of a cleared assay to an additional instrument is available in the following guidances:

- Class III devices[5]
- Devices indicated for use in support of blood banking practices
- Devices indicated for prescription or over-the-counter (OTC) home use
- CLIA-waived test systems

Section III.B includes discussion of situations in which principles within this guidance may be applicable to systems cleared for point of care (POC) 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. Some current device-specific guidances or Class II Special Controls Documents as discussed on FDA's webpage[6] ("Special Controls Documents") include a broad statement that the Replacement Reagent and Instrument Family Policy is not appropriate for the device type.[7] This guidance modifies such statements so that the Replacement Reagent Policy and Instrument Family Policy described in this guidance may apply to such device types.[8] Based on FDA's current understanding of, and experience with, currently classified device types, FDA believes that the recommendations presented in this guidance could provide alternative mitigation strategies that may allow for equivalent assurances of safety and effectiveness, such that the policy in this guidance could apply for certain IVD devices. This guidance is not intended to supersede any other statements contained in device-specific guidances or Special Controls Documents, but may cover areas not addressed in such device-specific guidances or Special Controls Documents. There may be additional considerations to take into account when determining the applicability of this guidance, and manufacturers should follow the logic scheme and recommendations herein, and must follow any applicable legal requirements, including special controls, to determine if this guidance could be applicable for certain changes to a particular test system.

Recommendations in this guidance are based on FDA experience with previously cleared test systems with established performance. To date, the Replacement Reagent and Instrument Family Policy has largely been utilized for traditional laboratory analyzers. Use of this guidance for other types of test systems or technologies may raise additional considerations. If you have questions regarding how to apply this guidance to a particular technology, we recommend you contact the appropriate review division for your assay and instrument. Manufacturers may use the pre-submission process to obtain feedback either when planning for the initial 510(k) submission (if future modifications to assay-instrument combinations can be anticipated) or after initial clearance. Generally, pre-submissions are most appropriate for Replacement Reagent and Instrument Family Policy discussions of new and evolving technologies. Information on the

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"Deciding When to Submit a 510(k) for a Change to an Existing Device," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-change-existing-device, and "Deciding When to Submit a 510(k) for a Software Change to an Existing Device," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-software-change-existing-device.

[5] 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," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assay-migration-studies-vitro-diagnostic-devices.

[6] https://www.fda.gov/medical-devices/guidance-documents-medical-devices-and-radiation-emitting-products/class-ii-special-controls-documents.

[7] For example, the Special Controls Document entitled "Instrumentation for Clinical Multiplex Test Systems," available at https://www.fda.gov/medical-devices/guidance-documents-medical-devices-and-radiation-emitting-products/instrumentation-clinical-multiplex-test-systems-class-ii-special-controls-guidance-industry-and-fda, states that the Replacement Reagent and Instrument Family Policy guidance document "does not apply to instrumentation for clinical multiplex test systems."

[8] Such modifications are made effective under this guidance document, even if the documents being so modified are not specifically updated to reflect the changes.

pre-submission process can be found in FDA's guidance document entitled "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program."[9]

This guidance applies to a large spectrum of marketed class I "reserved" or class II-510(k) IVD test systems intended for use in CLIA-regulated laboratories performing testing with nonwaived tests.[10] While most automated clinical instruments by themselves are classified as class I and exempt from submission of a 510(k), assay/instrument systems are considered "combination devices." A 510(k) submission is required if the test system includes a claim 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) submission, CDRH subjects a "combination device" to the same procedure, 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, in which case the separately regulatable articles may be regulated in accordance with their separate classes. Indications of an assay for use with an additional instrument is a change of the type that indicates compatibility with a different type of device, component, or accessory that was not indicated as compatible previously and thus that change would likely be considered a change that could significantly affect the safety or effectiveness of the device and likely require submission of a new 510(k) under 21 CFR 807.81(a)(3)(i).[11]

This guidance addresses a manufacturer's application of an assay that was previously cleared for use based on performance characteristics when used 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. The following tables illustrate regulatory scenarios and corresponding applicable sections of the guidance. In the tables below, Assay A and Instrument C were both reviewed within previous 510(k)s and are part of separate previously cleared test systems, whereas neither Assay B nor Instrument D were previously cleared.

Test System Current Regulatory Status		
	Cleared	**Not previously cleared**
Assay	A	B
Instrument	C	D

Assay and Instrument combinations	**Applicable Regulatory Policy in this Guidance**
A+C	*See* Section III (Replacement Reagent Policy)

[9] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program.
[10] *See* 42 CFR 493.2.
[11] For additional information about when to submit a new 510(k), see the guidance "Deciding When to Submit a 510(k) for a Change to an Existing Device," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-change-existing-device.

A+D	*See* Section IV (Instrument Family Policy) to help determine if D is an instrument family member of C. Note: A+D is outside the scope of this guidance if D is not an instrument family member as described in Section IV.
B+C or B+D	None (outside the scope of this guidance); 510(k) required (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 previously cleared test systems. 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 combination of assay and instrument 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 an additional instrument should determine whether a new 510(k) is needed, by completing the following steps: (i) the manufacturer should confirm that the assay was previously cleared and the instrument was either previously cleared or is an instrument family member of an instrument that was previously cleared as described in Section IV (*see* Tables in Section II) and (ii) apply the considerations described within Sections III and IV of this guidance. Should a manufacturer determine, after applying the logic scheme and considering the issues described below (i.e., test system operating principles and changes to the indications for use, risk-based assessment, and verification and/or validation activities), that a new 510(k) is not needed and proceed with marketing the modified test system, the manufacturer must document, as part of the device master record, the design, production, or process changes made,[12] and should document the manufacturer's assessment of whether a new 510(k) is required ("510(k) assessment") (*see* Section III.D).

If the manufacturer determines that a new 510(k) is required, the manufacturer may also consider whether a Special or Abbreviated 510(k) may be appropriate. (*See* FDA's guidance documents entitled "The Abbreviated 510(k) Program"[13] and "The Special 510(k) Program."[14])

[12] *See* 21 CFR 820.30(i), 21 CFR 820.70(b), and 21 CFR 820.181. For additional information about documenting design, production, or process changes, see Appendix B of the guidance "Deciding When to Submit a 510(k) for a Change to an Existing Device," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-change-existing-device.

[13] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/abbreviated-510k-program.

[14] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/special-510k-program.

A. Assessment for changes to test system operating principles and changes to the indications for use

A1. Assay key components and fundamental test principles

As noted, the first step in a manufacturer determining whether the Replacement Reagent Policy may be applicable in their specific situation is to confirm that the assay was previously cleared and the instrument was either previously cleared or is an instrument family member of an instrument that was previously cleared, as described in Section IV (*see* Tables in Section II). Further, the assay manufacturer should determine whether the use of the cleared assay on the additional instrument would require changes that alter assay key components or fundamental test principles. 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 new 510(k) is likely required because such alterations could result in changes to test system performance or interpretation of patient results that could significantly affect safety and effectiveness. A new 510(k) is also likely required for changes to assay value assignment methods or calibration schemes if they could significantly affect test system performance or interpretation of patient results, and thus would be likely to affect the safety and effectiveness of the device.

Examples of changes that are less likely to affect performance or operating principles include modifications to outer cartridges or reagent preservatives. However, the manufacturer should also conduct a risk-based assessment and design verification and/or validation activities to confirm (refer to Sections III.B and III.C for additional details).

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

A2. Instrument and software 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 those of 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 additional instrument relevant to the assay were demonstrated in a cleared 510(k) (*see* Example 2 in Section V). If these conditions do not apply, a new 510(k) is likely required.

The Replacement Reagent Policy applies only to open systems. For purposes of this guidance, an open system instrument has general purpose features intended for use with a wide array of assay types that share a similar methodology (e.g., similar detection methods, similar processing and interpretive software). An open system generally does not impose constraints (e.g., through software or labeling) for use with only specific types of reagents (e.g., those produced by or for the instrument manufacturer), or for detection of only certain types of analytes. If the same manufacturer has responsibility for the quality systems for both the assay

and the instrument, in many cases the system can be considered open for that manufacturer, even if the system is not open for other manufacturers.

If software, such as for system integration, system constraints (noted above), signal processing, data acquisition, interpretation, or other calculations needed to produce clinical results, are modified in order to run the assay on the additional instrument, a new 510(k) is likely required because it is likely that such alterations could result in changes to test system performance that could significantly affect the safety or effectiveness of the test system.

If application of a cleared assay to an additional instrument does not alter the instrument principles or software (including assay-specific software), proceed to Section III.A3 below.

A3. Changes to the Indications for Use

Examples of changes to the indications for use that would likely require a new 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, addition of a "high sensitivity" performance claim, or addition of POC use to a test system not previously cleared for such use. For general information regarding when a change to indications would likely require the submission of a new 510(k), see Section V.A. of FDA's guidance entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device."[15]

B. Risk-based assessment

The assay manufacturer should conduct a risk-based assessment for any modified test system.[16] 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. When the risk-based assessment indicates that the performance[17] of the modified test system could significantly change relative to the performance characteristics of the cleared test system, including performance claims in the labeling, a new 510(k) is likely required. A manufacturer's risk-based assessment should identify any new or significantly modified existing risks, as applicable. For additional information concerning risk-based assessment, see FDA's guidance entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device."[18] For IVD-specific discussion, see Section V.D3. of that guidance.

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[15] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-change-existing-device.

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

[17] For IVDs, performance generally refers to the analytical and clinical specifications established as part of the most recent 510(k) clearance. Analytical performance refers to the documented ability of an IVD test or test system to measure or detect a target analyte or substance that the IVD is represented or purported to identify or measure. Clinical performance refers to the documented ability of an IVD to identify, measure, monitor, or predict the presence or absence of, or the future development of, a clinical condition or predisposition, for which the device is intended. *See* FDA's guidance entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-change-existing-device.

[18] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-change-existing-device.

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 could have the potential to be significant and change the clinical performance of the device. In general, significant changes include those that could affect clinical interpretation or decision making. For example, if reference ranges or claimed cutoff concentrations for the intended use population(s) are expected to be altered as a result of the change in performance associated with the modified test system, this is considered a change to clinical performance, and a new 510(k) is likely required.

Within each risk-based assessment, manufacturers should take into account the cleared indications for use and the various clinical and performance needs associated with such use(s). In addition, manufacturers should also consider susceptibility to change of the specific assay technology. For example, careful attention should be paid when a new combination of an instrument and assay includes modifications to reaction conditions, especially for technologies that include complex interactions of components (e.g., multiplex), 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. Changes that are significant for clinical decision making are likely to require a 510(k) since such changes could significantly affect the safety and effectiveness of the test system.

In performing the risk-based assessment of the changed test system, manufacturers should consider whether a modification could cause possible effects that would lead a risk-based assessment to identify new risks or significantly modified existing risks that could significantly affect the safety or effectiveness of the device and thus a submission of a new 510(k) would likely be required.[19]

In summary, if the 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 (i.e., verification and validation activities) to verify this initial assessment. Section III.C further discusses this testing and its role in evaluating whether a change could significantly affect safety and effectiveness.

B1. Additional Considerations for POC Test Systems

Unlike many central laboratory test systems, many current POC test systems are designed for use with a manufacturer's specified instrument(s), and are not designed for use with additional instruments (i.e., they are not open systems as described in Section A.2). As noted, the Replacement Reagent Policy applies only for open test systems. However, in certain cases, particularly when the assay and instrument manufacturer are the same and the original and additional instrument(s) are closely related family members (*see* Section IV), the manufacturer could apply policies discussed in this guidance in combination with the recommendations in the guidance "Deciding When to Submit a 510(k) for a Change to an Existing Device"[20] to determine whether a 510(k) may be required prior to marketing. Please note these guidances are not intended to address all risk assessment (or testing) considerations for modifications of POC test systems. Therefore, we recommend that, after considering the policies described in these guidances, you contact the appropriate review division(s) if you need further clarity.

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[19] *See also* example 32 of Appendix A in the guidance "Deciding When to Submit a 510(k) for a Change to an Existing Device," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-change-existing-device, for an example of a manufacturer performing a risk assessment for a material change to an assay's reagent to identify any new risks or significantly modified existing risks and determining that it should submit a new 510(k).

[20] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-change-existing-device.

An example of a change to an instrument used with an assay that likely does not constitute a significant change or modification to require a new 510(k) would be a change to the exterior of the instrument that does not affect reaction conditions or usability. By contrast, some changes to an assay's instrument could affect reaction conditions, processes followed by POC users (e.g., error reporting, calibration, sample or control handling), or susceptibility to environmental changes in POC use conditions, even when such changes do not alter the operating principles, and therefore may require submission of a new 510(k).

POC test systems may present a higher likelihood of preanalytical and use error than non-POC test systems, challenges related to the types of multi-tasking common to the POC environment, and challenges due to varying environmental conditions (e.g., temperature, movement, or vibrations). Therefore, a manufacturer's risk assessment for a POC test system generally should include the risk impact of changes in user workflow. Examples may include providing new information to the user or modifying the manner in which information is presented. Changes to the layout of device controls may impact device use differently in different use scenarios and should be considered as part of the risk assessment for POC test systems.

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, accepted methods and performance criteria for evaluation of the specific device (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 generally be used to verify and validate the modification. 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 combination of instrument and assay (relative 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 combination of instrument and assay:

- 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 measuring interval in accordance with CLSI guidelines EP-06, or, if

appropriate, recovery to standard materials or methods.

- Method comparison studies in accordance with CLSI guidelines EP-09. Generally, this is a comparison of results obtained with the additional instrument to those obtained with the instrument in the cleared 510(k) (or the instrument or method used as comparator in that 510(k)).[21] Sample types (e.g., matrix), measurand value range, and comparator methods should be consistent with the original 510(k). If comparison to a well-known reference method(s) or material(s) was needed to support the original 510(k) (e.g., because of known lack of standardization among cleared assays), we recommend incorporating the same material(s) or method(s) to ensure similar performance for the new combination of assay and instrument.

Similarly, where relevant, manufacturers should include the following within verification and validation activities for the new combination of assay and instrument:

- Interference studies in accordance with CLSI guidelines EP-07, as needed for the particular reagents, or detection methods.
- Carry-over or cross-contamination studies.
- Matrix equivalence studies in accordance with CLSI guidelines EP-35.
- On-board stability for reagent, calibrator, and sample.
- 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, FDA recommends that the manufacturer follow this; however, using the same standard or guideline that was followed to support the cleared 510(k) may also be appropriate.

In some cases, the manufacturer might determine, based on the change to the specific combination of assay and instrument, that some of the study types included in the original 510(k) are not needed. In such cases, the manufacturer should clearly document the risk-based 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 that manufacturer's new or additional 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 sample 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

[21] In cases where a direct method comparison is not feasible, such as when the original, cleared instrument (Analyzer A) is no longer available, other approaches may sometimes be appropriate. For example, in some cases it may be acceptable to compare results obtained with the additional instrument (Analyzer C) to those of another legally marketed instrument (Analyzer B). Using the results of comparison studies of B vs. A and C vs. B and the precision of A, B, and C, the differences between C and A can be evaluated. Alternatively, in some cases, a recognized reference method (R) might be used. In this case, using the results of comparison studies of A vs. R and C vs. R and the precision of A, R, and C, it may be possible to evaluate the differences between C and A.

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 new 510(k) is likely required.

For most IVD assays, analytical validation, including method comparison, may be sufficient to validate that performance does not change when the assay is applied to an additional similar instrument. However, in some cases, analytical validation alone may not be 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 study is necessary to answer safety and effectiveness questions relating to a particular modification to a test system, a new 510(k) is likely required. In contrast, use of de-identified clinical samples for standard testing to verify analytical performance may not in itself normally necessitate a new 510(k).

C2. Manufacturer's Assessment 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 application of the assay to the additional instrument could significantly affect safety or effectiveness, and a new 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 new 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., changes to test system operating principles and to the indications for use, risk-based assessment, and design verification and/or validation activities), that a new 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 510(k) assessment (*see* Section III.D).

D. Documentation

Among other requirements, FDA's quality system regulation (QS regulation) requires manufacturers of finished 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 risk-based rationale should be included within the documentation.

IV. Instrument Family Policy

The Instrument Family Policy specifically addresses modifications made 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. 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. A manufacturer may choose to use separate design history files (DHF) (*see* 21 CFR 820.30(j)) for individual instrument family members (and cross-reference the other DHFs as needed) or use a single DHF for both the original instrument as well as a modified instrument. In either case, the design information within the DHF for each instrument should demonstrate that each instrument can be considered an instrument family member (as defined above), rather than an instrument that is not an instrument family member.

The instrument manufacturer should perform testing to confirm that instrument features, including software, are within the claimed tolerance limits or specifications (*see also* FDA's guidance entitled "General Principles of Software Validation").[22] The manufacturer should also maintain documentation of the relationship between the proposed instrument family member and an instrument 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 an additional instrument family member should follow the logic scheme and consider the issues in Section III to determine if a new 510(k) is needed. Similar to any instruments to which the Replacement Reagent Policy is applied, the new instrument family member should yield no significant difference in results for a given sample, using the same assay.

The manufacturer might determine that application of an assay to a new instrument family member does not call for the entire range of testing that was performed to support the 510(k) for the initial assay clearance. 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. Knowledge of differences between family member instruments is important for this type of determination based on risk assessment. Therefore, a determination regarding reduced testing can most easily be made when the assay and instrument manufacturer are the same. A manufacturer should fully document the risk-based rationale for this type of determination. It would not be sufficient to meet the recommendations in this guidance, for example, for an assay manufacturer to simply document that testing was not performed because the instrument is an instrument family member. If there are multiple instruments within an instrument family, manufacturers should assess assay performance with the new instrument family members relative to an instrument whose performance was demonstrated in a cleared 510(k) in order to ensure comparability for successive changes to instruments within the instrument family. (Also see discussion of method comparison studies in particular, including footnote 19 in Section III.C.1.)

[22] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-principles-software-validation.

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.

Rheumatoid factor immunological test systems (RF assays) are Class II devices, regulated under 21 CFR 866.5775, and subject to 510(k). The First RF Immunoassay manufactured by manufacturer 1 was previously cleared for use with the ABC Immunofluorescence Instrument. The manufacturer of the Second RF Immunoassay, manufacturer 2, now plans to apply its assay to the cleared ABC Immunofluorescence Instrument.

Scenario A – The Second RF Immunoassay was cleared based on performance with the cleared XYZ Immunofluorescence Instrument, which has similar capabilities as the ABC Immunofluorescence Instrument. Manufacturer 2 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 RF Immunoassay performance was the same on the ABC Immunofluorescence Instrument as on the XYZ Immunofluorescence Instrument. Therefore, manufacturer 2 determined that a new 510(k) was not needed to market the Second RF Immunoassay for use with the ABC Immunofluorescence Instrument, and documented the change and 510(k) assessment to the file.

Scenario B – There is no previously cleared 510(k) for the Second RF Immunoassay. Although other assays for RF have been cleared for use on the ABC Immunofluorescence Instrument, manufacturer 2 is required to submit a 510(k) and obtain clearance before marketing the Second RF Immunoassay (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

Enzyme immunoassays to quantitatively measure multiple endogenous clinical chemistry analytes were cleared based on performance using the Open System Instrument. For this cleared test system, 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 Open System 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 assay manufacturer submits a new 510(k) for use of its assay with the Open System Instrument.

3 – Test system operating principles: Optics and software changes

Assay A was cleared for use on Instrument A', which contains assay-specific software. The manufacturer now plans to also market its assay on the previously cleared Instrument B'. 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).

4 – Risk-based assessment and change to indication[23]

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 cleared instruments, similar in methodology to the one used to support initial CVD 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. In addition, the same type of testing conducted to support the 510(k) verified there was no change to performance caused by the additional instruments. Based on this, the manufacturer determined that a new 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 POC instrument for fingerstick samples. The modified test system uses a sample size of 10 uL. This modification represents a change to the sample type (venous to fingerstick) and volume which could significantly change the clinical performance claims and reference range relative to the claims in the labeling of the cleared test system. In addition, this modification represents a change in the intended user and use environment (from central laboratory to POC), as well as in operating principles (e.g., miniaturizing the instrument changed the basic capabilities and specifications of the instrument) relative to the cleared test system. For each of the reasons above, the manufacturer submits a new 510(k) for use of the assay on the miniaturized POC instrument.

[23] 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 new 510(k) depends on whether the change could significantly affect the safety or effectiveness of the cleared test system.

5 – Design verification and/or validation activities

The EZPZ troponin assay was cleared for use at central (core) laboratories with the SAFT clinical chemistry instrument. Clinical 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 using the manufacturer's established analytical and clinical protocols demonstrated unexpected assay performance that does not meet the acceptance criteria established at the time of the initial 510(k) clearance. These differences raise questions about whether the change in analytical performance may affect clinical performance. The manufacturer plans to address these issues using different protocols and/or acceptance criteria from those used in the initial 510(k) and thus submits a new 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 of the SAFT instrument. The changes to the system (relative to the one using SAFT) include a small change in the shape of the outer instrument 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 and indicates that no other features of the SAFT instrument are affected by these changes. Testing using the manufacturer's established protocols demonstrates assay performance is not affected by the change. 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[24]). 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.[25] Some manufacturers choose to include settings for new combinations of an assay and an instrument 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 combination of assay and instrument within the scope of this guidance should not significantly affect assay labeling, including performance claims.

[24] FDA has the authority to issue a "substantially equivalent (SE) with limitations" letter under section 513(i)(1)(E) of the FD&C Act if FDA determines and states in writing that "there is a reasonable likelihood that the device will be used for an intended use not identified in the proposed labeling for the device" and such use "could cause harm."

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

VII. Clinical Laboratory Improvement Amendments (CLIA) Categorization

FDA categorizes IVD test systems according to their CLIA complexity (42 CFR 493.17) and enters the categorizations in the CLIA database following clearance or approval. *See* the FDA's guidance document entitled "Administrative Procedures for CLIA Categorization."[26] 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 we recommend 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 assay and instrument 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. Inclusion of the 510(k)-cleared package insert is also recommended to help streamline the categorization process.

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).[27]

[26] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/administrative-procedures-clia-categorization.

[27] If there is sufficient scientific rationale, method comparison studies can utilize devices other than the predicate as a comparator within a method comparison study to support a new 510(k).

Appendix 1: Significant Terminology

The following significant terminology is provided in this appendix to clarify the meaning of terms used in this guidance for purposes of this guidance only. In some instances, existing definitions or descriptors from the medical device regulations have been used or referenced.

Instrument	A device that produces an analytical result from an applied clinical 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)	DHF means a compilation of records which describes the design history of a finished device. The DHF shall contain or reference 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	Labeling accompanying an in vitro diagnostic product with instructions for performing and interpreting the assay and any other required information. *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, instruments, software, assay reagents, calibrators, and controls.

Appendix 2 – Flowchart aids for determinations regarding the Replacement Reagent and Instrument Family Policy

The flowcharts in this Appendix are intended to supplement the guidance. For ease of use, the logic flow has been broken down into smaller sections that include:

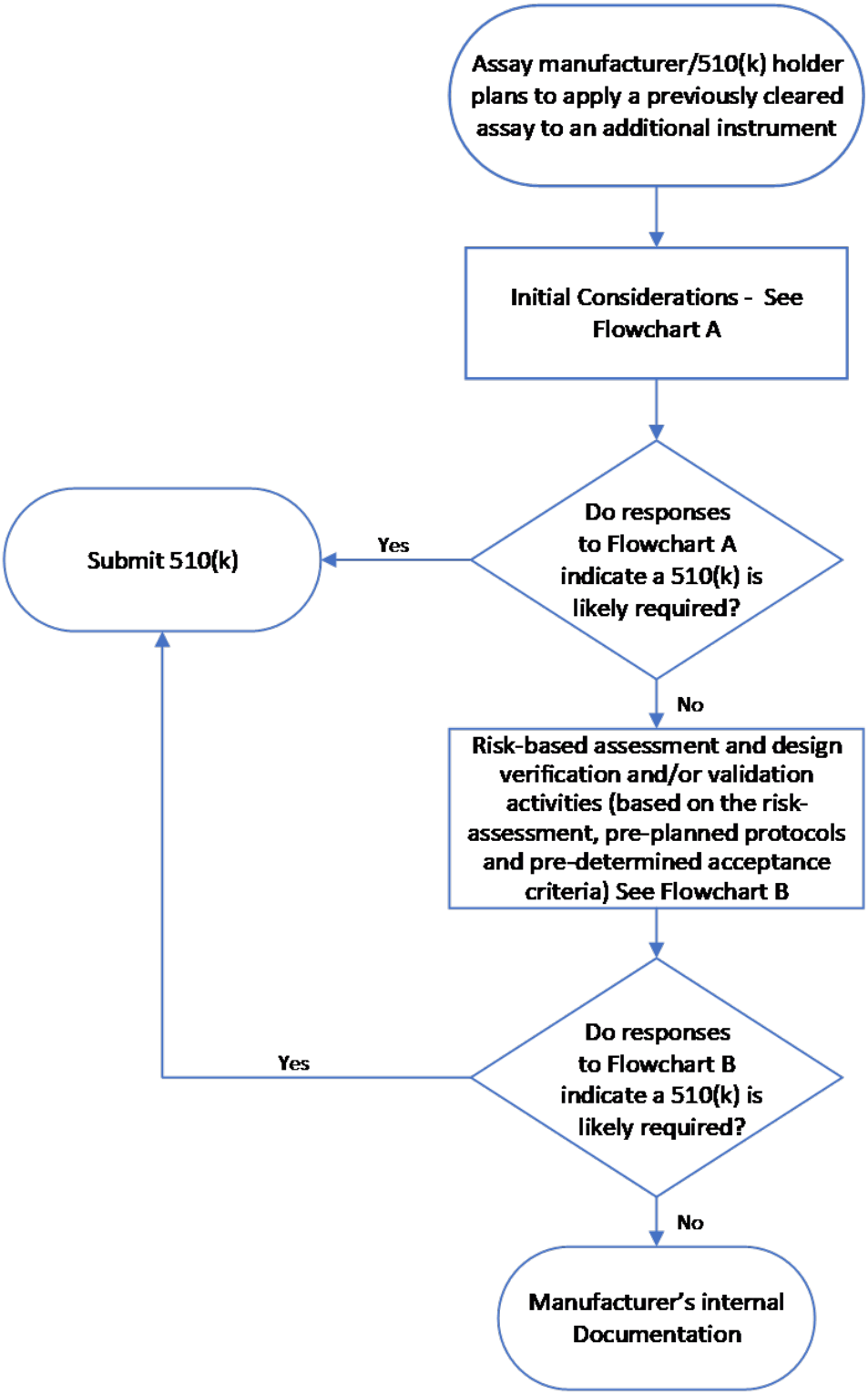
- Overall Flowchart, which identifies the overall steps for consideration in the manufacturer's determination to apply a previously cleared assay to an additional instrument (Figure 1).
- Flowchart A, which focuses on the initial considerations the manufacturer should address (Figure 2).
- Flowchart B, which focuses on the risk-based assessment and design verification and/or validation activities (Figure 3).

Sections within Figures 2 and 3 refer to corresponding sections within this guidance. Manufacturers should not use the flowcharts alone in making determinations regarding the need for a new 510(k). In addition, when using the flowcharts, the reader should interpret "Submit 510(k)" to mean a new 510(k) is likely required. "Manufacturer's internal documentation" means a new 510(k) is not likely to be required, and that the manufacturer must document, as part of the device master record, the design, production, or process changes made,[28] and should document the manufacturer's 510(k) assessment with appropriate documentation.

As previously stated, if you have questions regarding how to apply this guidance to a particular technology, we recommend you contact the appropriate review division for your assay and instrument.

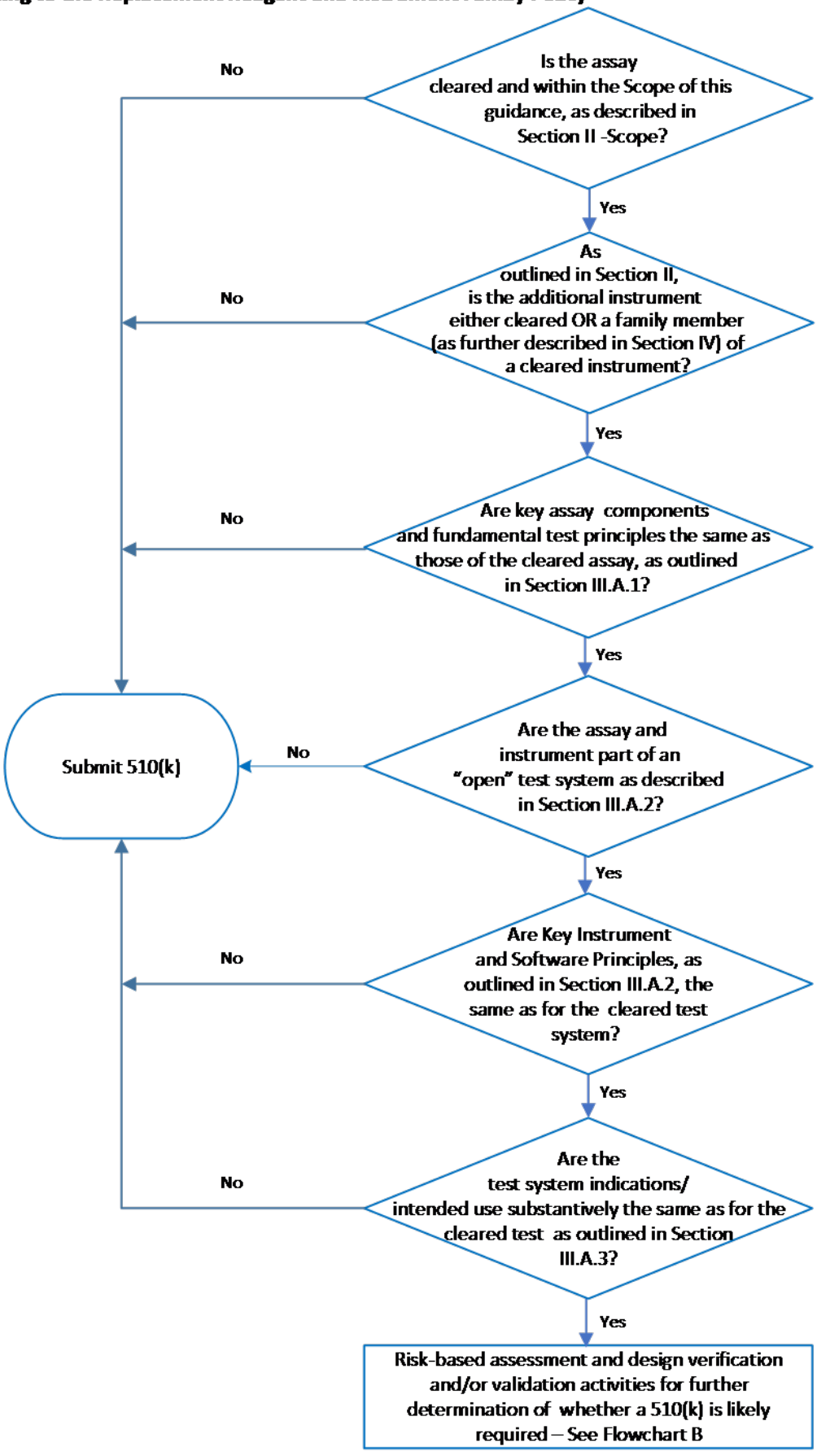
[28] *See* 21 CFR 820.30(i), 21 CFR 820.70(b), and 21 CFR 820.181.

Figure 1. - Overall Flowchart - Manufacturer's determination of whether a 510(k) is likely required according to the Replacement Reagent and Instrument Family Policy



Reminder: Flowcharts are provided as a visual aid, but do not capture all appropriate considerations. Refer to accompanying text in the guidance when using this flowchart.

Figure 2. Flowchart A – Initial Considerations for determining whether a 510(k) is likely required according to the Replacement Reagent and Instrument Family Policy



Reminder: Flowcharts are provided as a visual aid, but do not capture all appropriate considerations. Refer to accompanying text in the guidance when using this flowchart.

Figure 3. Flowchart B – Risk-based assessment and design verification and/or validation activities to determine whether a 510(k) is likely required according to the Replacement Reagent and Instrument Family Policy