Guidance for Industry and FDA Staff

Replacement Reagent and Instrument Family Policy

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This document supersedes "Data for Commercialization of Original Equipment Manufacturers (OEM), Secondary and Generic Reagents for Automated Analyzers," issued June 10, 1996.

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C·D·R·H
Center for Devices and Radiological Health

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of In Vitro Diagnostic Device Evaluation and Safety

Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852.

When submitting comments, please refer to the exact title of this guidance. 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 use the document number (950) to identify the guidance you are requesting.

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Guidance for Industry and FDA Staff

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

1. Introduction

The Replacement Reagent and Instrument Family Policy (RR-Policy) is intended to provide you, the device manufacturer, with information about validating and documenting changes to cleared test systems that do not significantly affect the safety and effectiveness of the device.

This guidance document addresses only previously cleared reagents and instruments. It describes a mechanism for adding either a cleared reagent to a previously cleared instrument, or a new instrument family member to a previously cleared instrument family. OIVD has developed this alternative approach to assist you in meeting the 510(k) requirements for changes that might initially appear significant, but with proper validation it is demonstrated these changes do not significantly affect the safety and effectiveness of cleared devices. FDA believes that, before market introduction, if you evaluate your modified device against predefined acceptance criteria using a proper validation protocol, you establish sufficient control for assuring the safety and effectiveness for minor device modifications.

This guidance document supersedes the guidance entitled, “Data for Commercialization of Original Equipment Manufacturers (OEM), Secondary and Generic Reagents for Automated Analyzers" and reflects existing CDRH practice. This guidance document updates terminology and provides direction based on current FDA policies that incorporate lessons learned and least burdensome principles. This guidance document relies on “Deciding When to Submit a 510(k) for a Change to an Existing Device” and provides recommendations on the types of documentation that should be kept on file at your facility, thus eliminating add-to-files for a change to a device that falls within the scope of this guidance document.[1]

[1] https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080187.htm

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

The Least Burdensome Approach

The issues identified in this guidance document represent those that we believe need to be addressed before your device can be marketed. In developing the guidance, we carefully considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred in your attempt to follow the guidance and address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, you believe that there is a less burdensome way to address the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center web page at: http://www.fda.gov/cdrh/modact/leastburdensome.html.

2. Background

This guidance document seeks to clarify how you can validate device performance and maintain proper documentation at your facility. The policy applies to clinical laboratory testing systems intended for use by clinical laboratory professionals. The RR-Policy does not apply to exempt general purpose reagents or to the following devices or changes that are generally considered significant (21 CFR 807.81); such as:

- systems intended for over-the-counter (OTC) use,
- systems intended for professional home use,
- devices intended for point of care (POC) use,
- class III devices,
- changes in the intended use of a cleared product, or
- devices intended for use in support of blood banking practices.

The following table and regulatory scenarios are designed to help you determine the appropriate regulatory pathway. For help in process flow, see**: "Decision Chart for Cleared Reagents and New Analyzers in Instrument Family."**

Test System Current Regulatory Status		
	Cleared	**New/not cleared**
Reagent	**A**	**B**
Instrument	**C**	**D**

Regulatory status:
A + C = Replacement reagent policy
B + C = new 510(k)
B + D = new 510(k)
A + D = new 510(k) unless the instrument belongs to a cleared family, in which case the replacement reagent policy applies.

3. Definitions

REAGENTS are any of the necessary substances that produce or catalyze reactions that allow an analyte to be detected and measured. FDA-cleared calibrator and quality control material are also considered reagents for RR-policy purposes. Changes to calibrator or quality control material involving the addition of new analytes are significant changes requiring a 510(k) and thus do not fall under this policy and require a new 510(k) (21 CFR 807.81).

Generic Reagents are intended for use manually or with any open system. They offer alternatives for laboratory users who assume responsibility for performance validation.

OEM (original equipment manufacturer) Reagents are dedicated for use with a specific analyzer (closed/partially closed system). They can be produced by the analyzer manufacturer (OEM) or obtained from a supplier.

Replacement Reagents (also known as secondary reagents) are generic reagents produced for use with specified analyzers by suppliers other than an OEM supplier. Replacement reagents may be marketed and labeled for one specific analyzer or may claim multiple analyzers.

ANALYZERS are computer-controlled devices that produce an analytical result from an applied sample by reading a generated signal and modifying or translating the signal into a result.

The **Principle of Analysis** is based on the assay method (e.g., antibody antigenic reaction schemes), assay calibration (e.g., one point versus multiple point), and mode of detection (e.g., photometric or fluorimetric).

An **instrument** refers to the pre-analytic, analytic, and/or post-analytic components including: mechanisms for sampling, processing and measuring human specimens, hardware for detection, and associated controlling software.

Closed systems are analyzers and OEM reagents provided by the same manufacturer and intended by the manufacturer to be used only in combination with each other.

Partially closed systems are analyzers and OEM reagents provided by the same manufacturer that are intended to be used in combination. The analyzers may also be intended to be used with "secondary" reagents for the analysis of analytes for which the manufacturer does or does not provide reagents. In the latter case, the analyzer serves as a general purpose analyzer in an open system.

Open systems are analyzers manufactured with general purpose features for use only with "secondary reagents."

An **instrument family** consists of similar analyzers made by one manufacturer that yield the same analytic result from samples of the same specimen within stated tolerance limits. Different members of the family may have different pre- and post-analytic accessories such as sampling and processing devices or automated data handling and reporting but should fall within the concept of a device family. A device family refers to a group of two or more devices manufactured by or for the same manufacturer and having the same:

1. Basic design and performance characteristics related to device safety and effectiveness that share a common *Design History File (DHF)* (See 21 CFR 820.30(j)),
2. Intended use and function, and
3. Device classification and product code.

A **new instrument family member** is an instrument that has a modification to any instrument family member in either the hardware or software that is beyond a name or cosmetic change, but does not include a change in analytical technology, such as going from photometric to chemiluminescent-based technology. The instrument should fit within the above definition of instrument family.

Representative family member is an instrument family member that best represents the basic design of the family, not necessarily the most recent addition to the family. The representative instrument should not be so far removed from the original so as to become a new instrument (i.e., significant design or software changes).

A **test system** is composed of all test components required to perform an *in vitro* diagnostic test, i.e., clinical laboratory analyzer, reagents calibrators and controls.

LABELING

The **Operator Manual** is labeling that accompanies the instrument. It includes instructions for how to operate the instrument.

The **Package Insert** is reagent labeling that provides instructions for performing the assay.

The **Application Sheet** typically contains analyzer settings, volumes, and parameters to assist laboratories in implementing the use of secondary reagents with open analyzer systems. An application sheet implies adequate performance for the reagent on the analyzer(s).

HIGH RISK DEVICE

IVDs can be high risk to the extent that information from the device generates a misdiagnosis that may result in significant morbidity or mortality.

4. The Use of Validation Protocols

Before you can apply the replacement reagent policy, FDA should have on file an original 510(k) for a new, non-exempt reagent used with a representative instrument family member. Either the instrument or reagent manufacturer can submit the 510(k). In order to claim replacement reagent use on an instrument/analyzer, the analyzer should have the capabilities to run the assay method (e.g., immunoassay) as described in the original 510(k).

First, we recommend that you develop a protocol and acceptance criteria for validating your proposed instrument/reagent combination based on the evaluation protocols used in the original device clearance. Your protocol and predetermined acceptance criteria can then serve to validate the use of different analyzers with the cleared reagents anytime in the future, or can be used to introduce a new family member instrument. We recommend that the criteria for reagents be assay specific and designed to challenge the performance characteristics of the assay. Criteria for the introduction of a new instrument family member should be method specific, but general enough to evaluate all analytes within each method, and designed to challenge the performance characteristics of all assays.

Second, we recommend that your protocol describe the studies that you believe should be completed and stipulate the acceptance criteria for each performance parameter (e.g., method comparison, precision, reference range; see **Study Types table**). You should develop the protocol before you try to validate a reagent on a new instrument platform or a new instrument family member. We recommend that you document why a particular study may not be applicable to your device (if appropriate). An appropriately designated individual(s) should sign and date the protocol, and keep it on file at the site responsible for validation.

Finally, we recommend that you document that the instrument/reagent combination meets the predetermined acceptance criteria that you provided in your validation protocol. You should collect these data prior to marketing each new combination, and maintain appropriate records at the site performing the validation (see also 21 CFR Part 820.180 (Subpart M – Records))

Any modifications to the protocol on file or failure of the test system to meet the acceptance criteria may require a new 510(k). We usually recommend a Special 510(k) in this instance. You may contact OIVD for assistance in determining if you need to file a 510(k).

ELIMINATION OF ADD-TO-FILE

In the past, manufacturers submitted add-to-files containing validation protocol and acceptance criteria before introducing a modified test system. Based on our experience with the RR-Policy, we believe proper validation protocols are sufficient controls for device modifications consistent with the intent of the policy (i.e., modifications that do not affect the safety and effectiveness of the device). As a result, you no longer need to submit an add-to-file prior to marketing different reagent/instrument combinations (including new family members) when both have been previously cleared. As discussed in this document, you

should document and maintain on file your protocols, data analyses, and acceptance criteria (see 21 CFR 820.180).

Clinical Laboratory Improvement Amendments (CLIA) CATEGORIZATION

Under CLIA, tests are categorized according to their complexity (42 CFR 493.5). We recommend that when you request CLIA categorization for a different reagent/instrument combination or new family member additions, you also submit the labeling with sufficient detail for FDA to determine categorization. Replacement reagents should have a package insert and/or application sheet, and each new instrument family member needs instructions for use (e.g., a quick reference guide, the setup section, or operational steps taken from the operators' manual). When requesting CLIA categorization for a test system combination that falls within the scope of this policy, you should clearly designate the request as "For CLIA Categorization Only" (see Draft Guidance for Industry and/or for FDA Reviewers/Staff and/or Compliance - Guidance for Administrative Procedures for CLIA Categorization[2]).

INSTRUMENT CLASSIFICATION

Although most automated clinical analyzers by themselves are class I and exempt from 510(k), reagent/instrument systems are considered ***"combination devices.[3]"*** FDA's Guidance on the CDRH Premarket Notification Review Program provides:

> In its review of the 510(k), the Center will subject the "combination device" to the same sorts of questions and documentation requirements that are applied to a single device. When such a device is found to be SE, 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 that case, the separately regulatable articles will be regulated in separate classes.

A 510(k) may be necessary if the claim associated with the reagent in the system meets the definition for a class I reserved or class II device (21 CFR 860.3; see also the limitations to exemptions under 21 CFR 862.9, 864.9 or 866.9). The analyzer manufacturer can use any cleared non-exempt reagent or can jointly seek clearance for a new reagent along with the instrument. If a 510(k) is necessary, we recommend that you refer to FDA's "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)] - Guidance for Industry and Food and Drug Administration Staff" https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm284443.pdf

SPECIAL 510(k)

A special 510(k) is an alternate means of pre-market notification to a traditional 510(k). The Special 510(k) is a least burdensome mechanism for reporting significant modifications to a previously cleared device (e.g., major design changes; however, modifications to intended use require a traditional 510(k) (21 CFR 807.81)). A special 510(k) may be submitted when the modified test system does not meet acceptance criteria of the validation protocol, but otherwise meets all the RR-Policy requirements. See decision flowchart.

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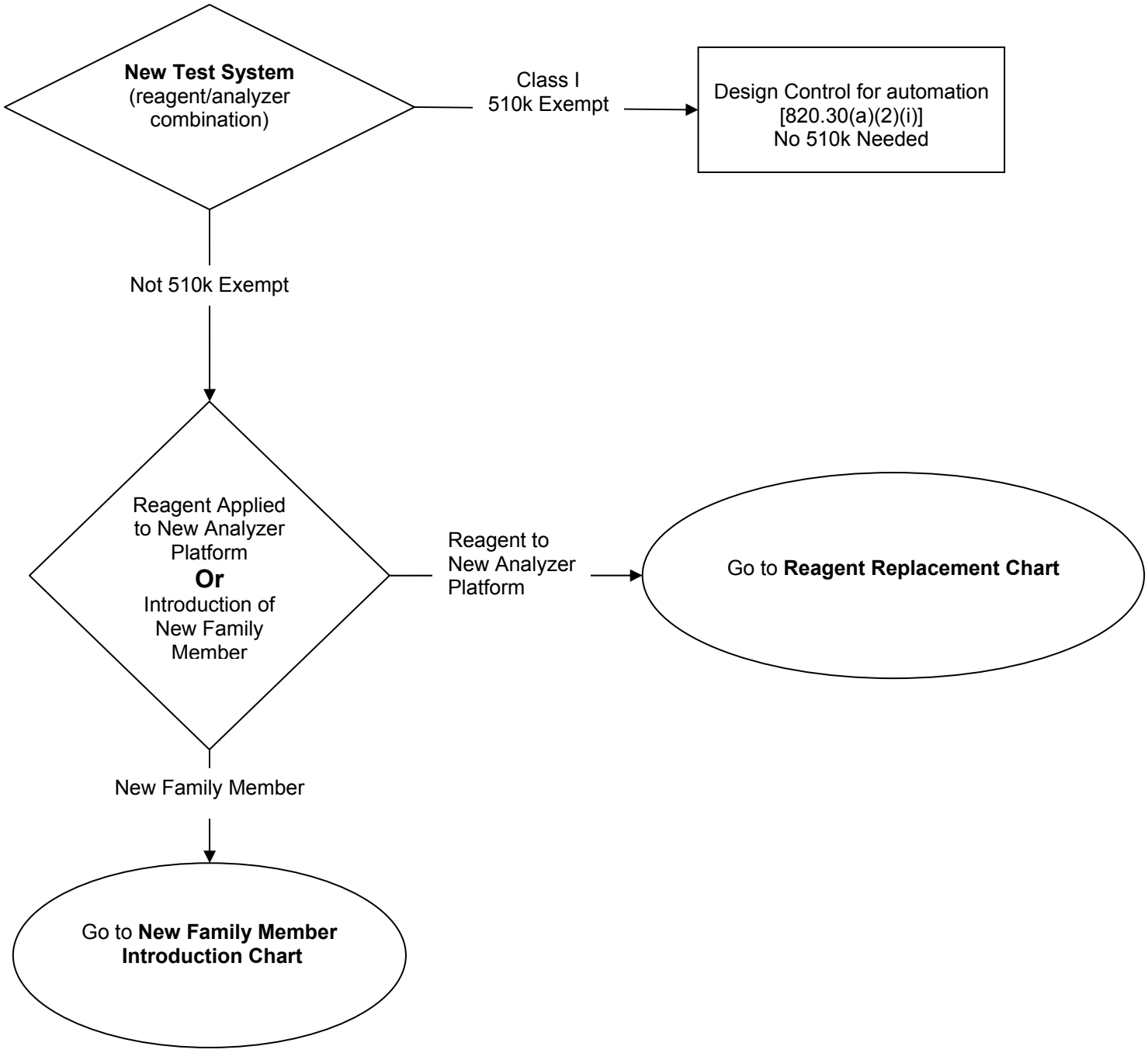
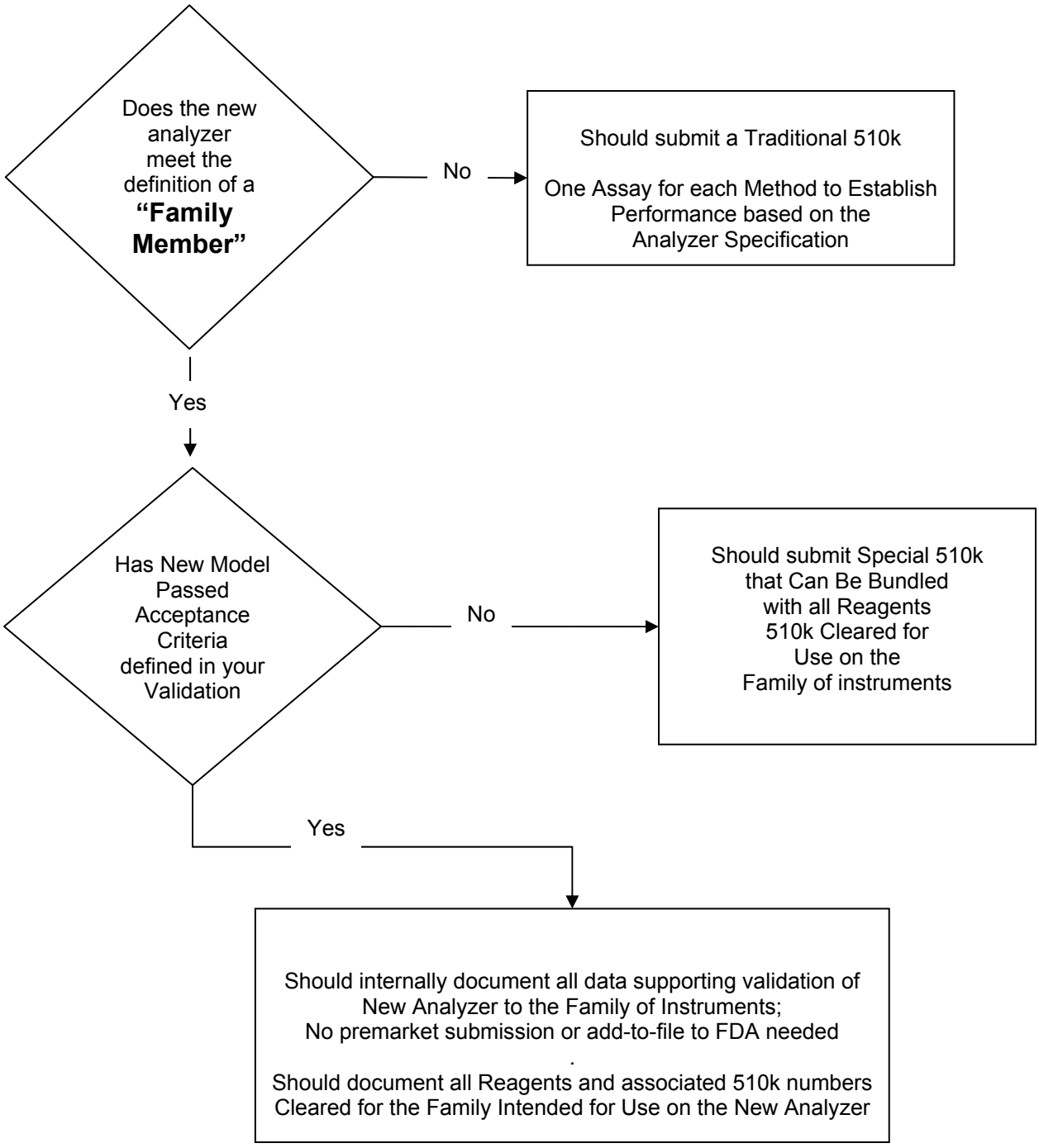
[2] https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm070889.pdf

[3] The combination of a drug and a device is known as a "combination product".

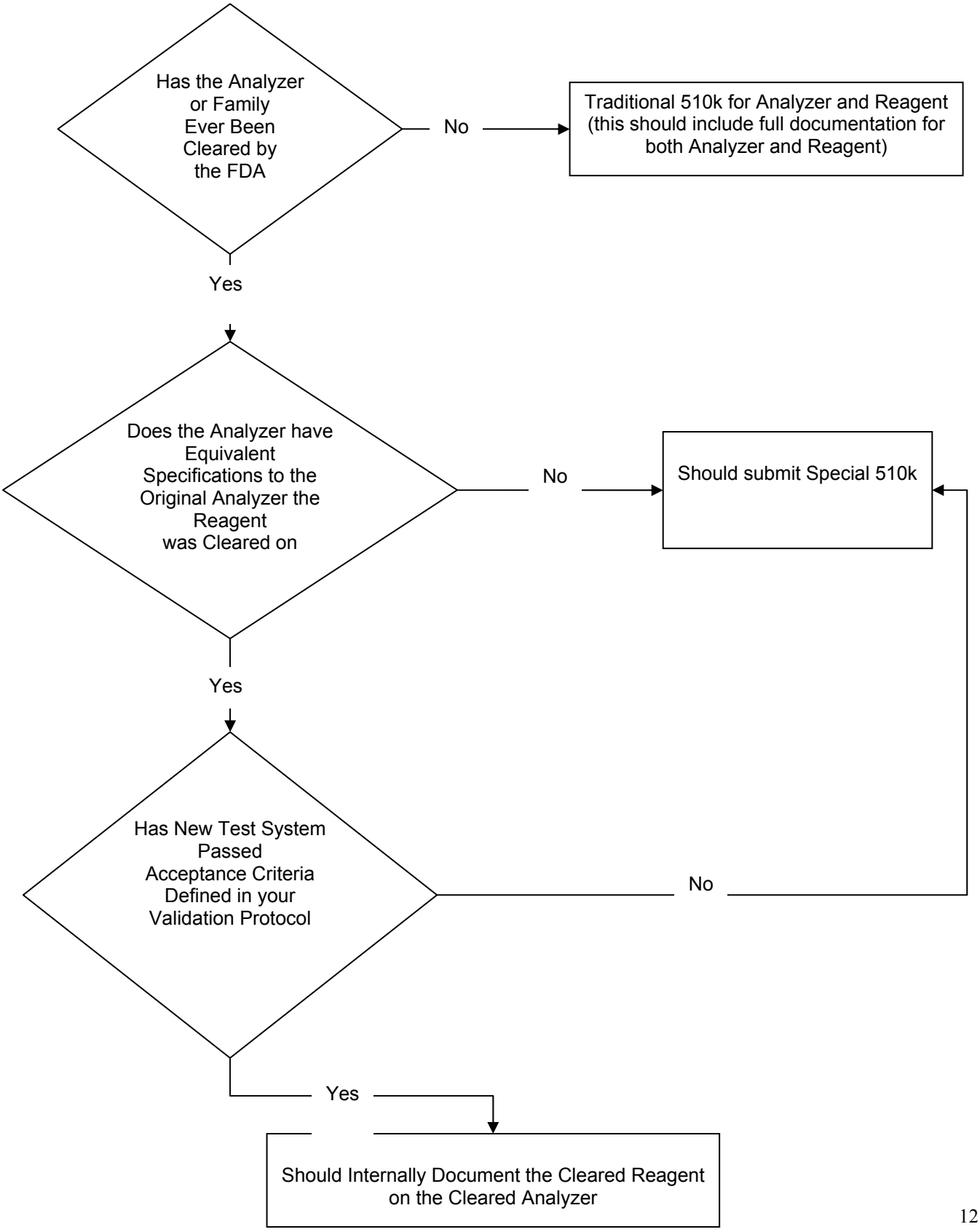
Decision Chart for Cleared Reagents and New Analyzers in Instrument Family



New Family Member Introduction Chart



Reagent Replacement Chart



STUDY TYPES

PARAMETER	ORIGINAL SUBMISSION	ADDITIONAL REAGENTS	ACCEPTANCE CRITERIA
Method comparison	Comparative data based on scientifically valid protocols and statistically sound data assessment, see *NCCLS EP09-A2 Method Comparison and Bias Estimation Using Patient Samples*	Same studies in which N is ≥ the original 510(k).	Statistically Equivalent to Acceptance Criteria in the original 510(k) in order to maintain clearance performance
Precision	Total and within run imprecision data based on scientifically valid protocols and sound data assessment, see *NCCLS EP05-A Evaluation of Precision Performance of Clinical Chemistry Devices*	Same	Same
Sensitivity	Analytical, functional, relative, clinical sensitivity, as appropriate.	Same	Same
Reportable Range	Dynamic range data based on scientifically valid see *NCCLS EP06-A Evaluation of the Linearity of Quantitative Analytical Methods*	Same	Same
Specificity	Clinical and analytical, as appropriate Interference/cross-reactivity study , see *NCCLS EP07-A Interference Testing in Clinical Chemistry*	Same	Same
Reference Ranges	Where appropriate, reference range data based on scientifically valid protocols, see *NCCLS C28-A2 How to Define and Determine Reference Intervals in the Clinical Laboratory*	Where appropriate, reference range data including demographic data based on scientifically valid protocols	