Asian Harmonization Working Party
WORKING TOWARDS MEDICAL DEVICE HARMONIZATION IN ASIA

PROPOSED FINAL DOCUMENT

Title:	Replacement Reagent and Instrument Family Policy
Authoring Group:	Work Group 2, Pre-market: IVDD
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Preface

The Asian Harmonization Working Party established this document based on Replacement Reagent and Instrument Family Policy guidelines worldwide. The document is intended to provide non-binding guidance for use in the regulatory system of in vitro diagnostic (IVD) medical devices, and has been subject to consultation throughout its development.

1.0 Introduction

The objective of the Asian Harmonization Working Party (AHWP) is to encourage convergence at the worldwide level in the evolution of regulatory systems of medical devices, including in vitro diagnostic (IVD) medical devices and software as a medical device (SaMD) in order to protect the public health by those regulatory means considered the most suitable.

This document has been developed to encourage and support global convergence of regulatory systems. It is intended for use by Regulatory Authorities (RAs), Conformity Assessment Bodies (CABs) and industry, and will provide benefits in establishing, in a consistent way, an economic and effective approach to the control of medical devices in the interest of public health. It seeks to strike a balance between the responsibilities of RAs to safeguard the health of their citizens and their obligations to avoid placing unnecessary burdens upon the industry.

One such opportunity is the implementation of a Replacement Reagent and Instrument Family Policy. Requiring a new registration to apply each already approved test kit/assay to an already approved instrument that is a member of the same instrument family creates unnecessary burden for both the manufacturer and regulator. A Reagent Replacement Policy is a risk-based approach that relies on the manufacturer's Quality Management System (QMS), including risk-based assessments, and criteria, testing, and internal documentation for each reagent application, to allow a portfolio or "menu" of low or medium risk reagents to be moved to a previously approved instrument or an instrument in the instrument family. This innovative approach maintains patient safety, makes wise use of valuable regulatory resources, and ensures uninterrupted access to the most innovative products.

A second important opportunity is the Instrument Family Policy whereby an instrument can be added to an already existing Instrument Family. In turn, the Instrument Family allows the Replacement Reagent Policy to take effect.

AHWP believes this guidance will ease the burden for In vitro diagnostic manufacturers and regulators while providing an important health benefit to patients as it promotes faster availability of In vitro diagnostics for patients.

Work Group 2 of the AHWP has prepared this guidance document. Comments or questions should be directed to the Chair of AHWP Work Group 2 whose contact details may be found on the AHWP web page (http://www.ahwp.info/).

Note: The term "Registered medical device/IVD medical device" refers to a medical device that can be legally marketed in relevant jurisdictions.

2.0 Rationale, Purpose and Scope

2.1 Rationale

Establishing consistent worldwide requirements to implement Replacement Reagent and Instrument Family Policies for in vitro diagnostic (IVD) medical devices offers significant benefits to the manufacturer, user, patient and regulator. These innovative approaches maintain patient safety, make wise use of valuable regulatory resources, and ensure uninterrupted access to the most innovative products. .

2.2 Purpose

The Replacement Reagent and Instrument Family Policy describes a mechanism for adding either an approved test kit/assay to a previously approved instrument (Replacement Reagent Policy), or a new instrument family member to a previously approved instrument family (Instrument Family Policy).

The document provides guidance on registration requirements, e.g. conformity assessment and submission dossier for Manufacturers, Regulatory Authorities (RAs) and Conformity Assessment Bodies (CABs) on test system or/and instrument modifications that do not significantly affect the safety and effectiveness of the in vitro diagnostic (IVD) medical device.

Note:
Moving an already approved reagent to a new already-approved instrument is as a general rule not considered a significant change provided key criterion are met, and the manufacturer has verified that performance on the new instrument or platform does not impact key safety and performance characteristics. For significant changes, please refer to AHWP/WG2-WG1-WG3/F001:2019 Categorization of Changes to a registered Medical Device. For non-significant changes, please refer to AHWP/WG1/F002:2016 Guidance for Minor Change Reporting, whereby the reporting depends on jurisdiction.

2.3 Scope

This guideline addresses the mechanism for adding

- a previously approved IVD Test kit/Assay (to be used in a specified instrument) to an additional or alternative previously-approved instrument to expand the Test System.
- a new instrument to an instrument family

This guidance is not intended to address the following:

- Modifications other than application of an approved IVD Test kit/Assay to a new instrument
- Significant change to the instrument
- High risk IVD MDs
- IVD MDs intended for use in support of blood banking practices
- IVD MDs intended for use in point of care settings
- IVD MDs for self-testing

3.0 References

AHWP/WG2-WG1/F001:2016 *Definition of the Terms 'Medical Device' and 'In Vitro Diagnostic (IVD) Medical Device'.*

AHWP/WG1a/F002:2013 (now restructured to WG2) *Essential Principles of Safety and Performance of IVD Medical Devices.*

AHWP/WG2-WG1-WG3/F001:2019 *Categorisation of Changes to a registered Medical Device.*

AHWP/WG1/F002:2016 *Guidance for Minor Change Reporting*

US FDA Draft Guidance for Industry and FDA Staff: Replacement Reagent and Instrument Family Policy for In Vitro Diagnostic Devices 2017

US Guidance for Industry and FDA Staff; Assay Migration Studies for In Vitro Diagnostic Devices 2013

Korea MFDS guideline "Guideline for Approval and Evaluation of Reagent of the Family In Vitro Diagnostic Devices" (2015/BI-2015-08)

GHTF/SG1/N70:2011 *Label and Instructions for Us for Medical Devices.*

4.0 Terminology and Definitions

Medical Device - The term is as defined in AHWP/WG2-WG1/F001:2016 "Definition of the Terms 'Medical Device' and 'In Vitro Diagnostic (IVD) Medical Device'

IVD Medical Device - The term is as defined in AHWP/WG2-WG1/F001:2016 "Definition of the Terms 'Medical Device' and 'In Vitro Diagnostic (IVD) Medical Device'"

Manufacturer - For the purpose of this document, the term "manufacturer" includes the manufacturer, its authorized representative or any other person who is responsible for placing the device on the market.

Regulatory Authority - It is a government agency or other entity that exercises a legal right to control the use or sale of medical devices within its jurisdiction, and may take enforcement action to ensure that medical products marketed within its jurisdiction comply with legal requirements. (AHWP/WG1a-WG7/PD007)

Risk Management - A systematic application of management policies, procedures and practices to the tasks of analyzing, evaluating, controlling and monitoring risk (e.g., ISO 14971:2019 Medical devices -Application of risk management to medical devices)

Significant change[1]- Means a change that could reasonably be expected to affect the safety and/or performance of a medical device.

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.

Master Instrument - Represents the reference instrument type within an instrument family.

[1] The term significant change and major change are used in different jurisdiction but generally they can be used interchangeably

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 GMDN (Global Medical Device Nomenclature) code or other similar nomenclature designation. 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.

Instrument Family Policy - Describes a mechanism for adding a new instrument family member to a previously approved instrument family

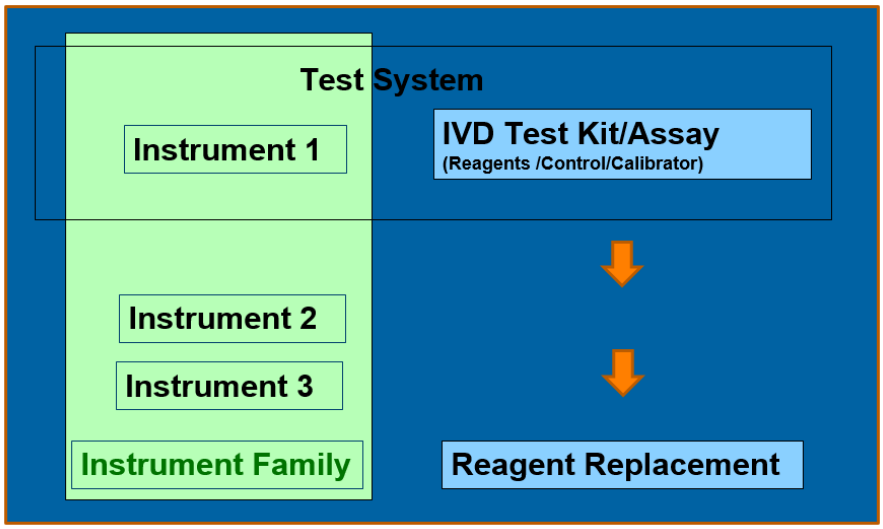
Reagent - A substance or component of an IVD Test kit/Assay that allows a target analyte to be detected or measured. An IVD Test kit/Assay typically includes multiple reagents.

IVD Test kit / Assay - A set of all reagents, calibrators and controls and instructions needed for measurement or detection of the analyte.

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.

Replacement Reagent Policy - Describes a mechanism for adding an approved test kit/assay to a previously approved instrument.

Figure 1- Visualization of the terminology and definition



Label - Is written, printed, or graphic information either appearing on the medical device itself, or on the packaging of each unit, or on the packaging of multiple devices.

Instructions for Use - Refers to general and technical information provided by the manufacturer to inform the device user of the medical device or IVD medical device's intended purpose and proper use and of any contraindications, warnings, or precautions to be taken. It is provided by the manufacturer to support and assist the device users in its safe and appropriate use.

Note : Instructions for use (IFU) can also be referred to as “package insert” or “directions for use” and may also include “User Manual” or “Technical Manual.”

Self-testing IVD Medical Device - An IVD medical device intended for use by a lay user who is responsible for collecting the data or specimen, by themselves and on themselves, relying solely on the instructions provided by the manufacturer. This use can also include performing the test and interpreting the results by themselves and on themselves. (Modified from IMDRF/GRRP WG/N47FINAL:2018)

Lay person - Individual that does not have formal training in a relevant field or discipline. [SOURCE: ISO 18113-1:2009]

Note : Includes the directions supplied by the manufacturer for the use, maintenance, troubleshooting and disposal of an IVD medical device, as well as warnings and precautions.

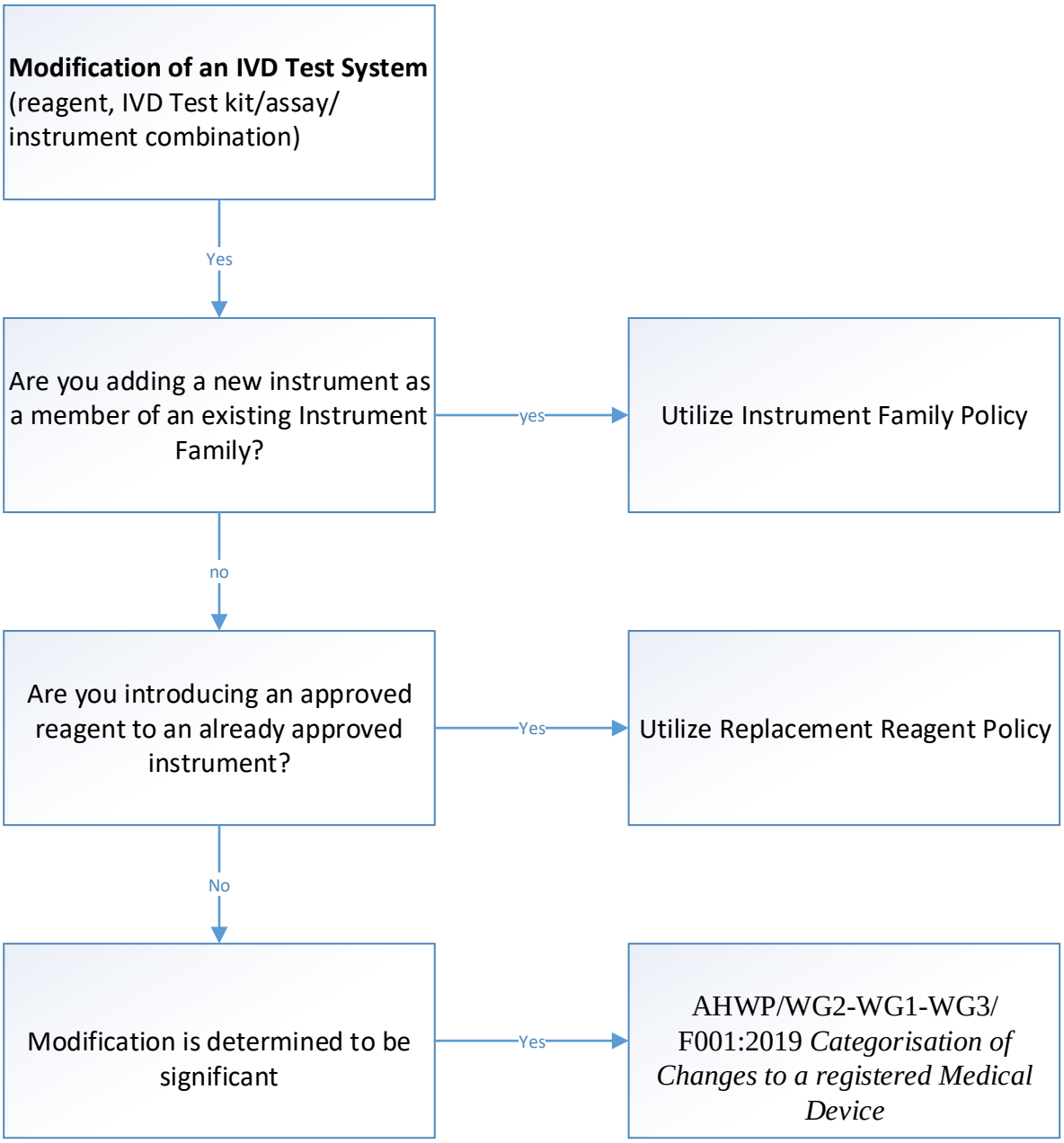
5.0 General Principles

Before applying the Replacement Reagent or Instrument Family Policy, the registration requirements for the IVD test kit/Assay used with an approved/registered instrument family member should be met, as required by a Regulatory Authority (RA) or Conformity Assessment Body (CAB).

The following scenarios should be considered to determine the appropriate regulatory pathway, if an IVD test kit/Assay manufacturer modifies the test system, e.g. adding a new version of the instrument to the same approved reagent or IVD test kit/Assay evaluated as part of a previously approved test system.

Flowchart 1

Decision Chart for an Approved IVD Test Kit/Assay adding a New Instrument to an already Approved Test System



5.1 Determination of Which Policy Applies

The following tables help to illustrate regulatory scenarios to determine if the Replacement Reagent or Instrument Family Policy Applies.

Table 1 and Table 2: Determination of Which Policy Applies (adapted from *US FDA Draft Guidance for Industry and FDA Staff: Replacement Reagent and Instrument Family Policy for In Vitro Diagnostic Devices 2017*)

	Approved Test System comprised of		**Not part of the approved Test System**
IVD Test kit/Assay	A	B	C
Instrument	A’	B’	C’

IVD Test kit/Assay and Instrument combinations	**Applicable Regulatory Policy in this Guideline**
A+B’ or B+A’	Replacement Reagent Policy
A+C’ or B+C’	Instrument Family Policy
C+C’, C+B’, C+A’	Out of scope, significant change

Note:
IVD Test kit/Assay A was previously approved to be run on Instrument A’ based on performance demonstrated with Instrument A’.
IVD Test kit/Assay B was previously approved to be run on Instrument B’ based on performance demonstrated with Instrument B’.
Neither IVD Test kit/Assay C nor Instrument C’ is part of an approved test system.

5.2 Instrument Family Policy Requirements – Process and Requirements

Instrument Family Policy specifically addresses modifications to an instrument by its original manufacturer, to produce a new version of the instrument. 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 have the same classification.

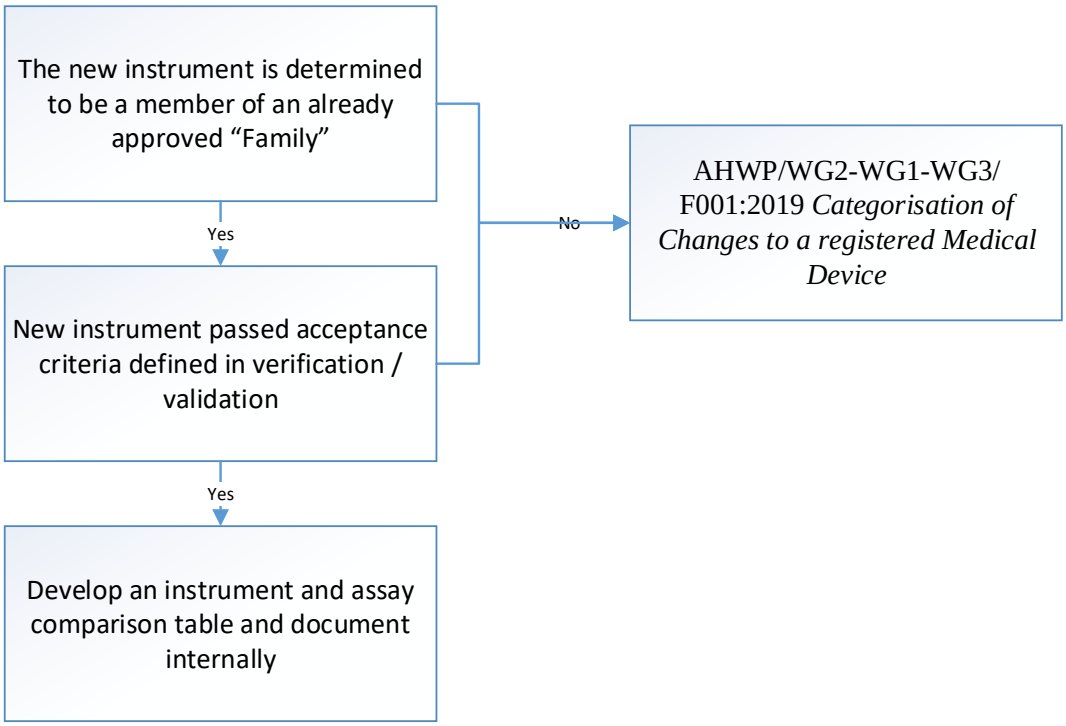
In order to determine if an instrument could be a member of an instrument family, the IVD Test kit/Assay manufacturer should make assessments regarding:

- Instrument features (hardware and software components related to test reaction and interpretation), including software risk,
- Verification and/or validation activities
- Design history files demonstrate that one instrument can be considered a modification of the other

0 Scheme to Follow

The following flowchart describes how to perform the assessment.

Flowchart 2
Logic Scheme of the Instrument Family Policy



5.2.2 Verification and/or Validation Activities

The instrument manufacturer should perform testing to confirm that instrument features (the same general architecture, design, tolerance limits, and capabilities, such as detection methods, sample volume, signal range and intensity, and reaction conditions, including software), are within the claimed tolerance limits or criteria.
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.

5.2.3 Documentation

The following table depicts an example of the comparison of the instrument features.

Table 3: **Instrument Comparison**

No.	Item of comparison	Instrument A	Instrument B
1	Model Name		
2	Manufacturer		
3	General Architecture		
4	Design		
5	Tolerance Limit		
6	Detection Method		
7	Sample Volume		
8	Signal Range and Intensity		
9	Reaction Conditions		

5.3 Replacement Reagent Policy – Process and Requirements

Generally, approval of test systems is based on Test kit/Assay performance characteristics demonstrated with an instrument (or instruments) specified by the Test kit/Assay manufacturer. The Test kit/Assay and instrument within the same Test system could be manufactured by the same manufacturer or by separate manufacturers.

Replacement Reagent Policy can be used to:

(1) Apply Test kit/Assay to additional instrument or a newly approved instrument family members

(2) Basic premise: New combination of previously approved assay and previously approved instrument based on demonstrated equivalent performance.

Once the Test kit/Assay manufacturer modifies the test system by applying the same approved Test kit/Assay to additional instruments evaluated as part of a previously approved test system, the manufacturer should:

- Assess performance of the new combination under the quality system requirements to ensure acceptable performance of the modified test system, and
- Ensure that the modified test system continues to meet design specifications by which the original test kit/Assay was approved.

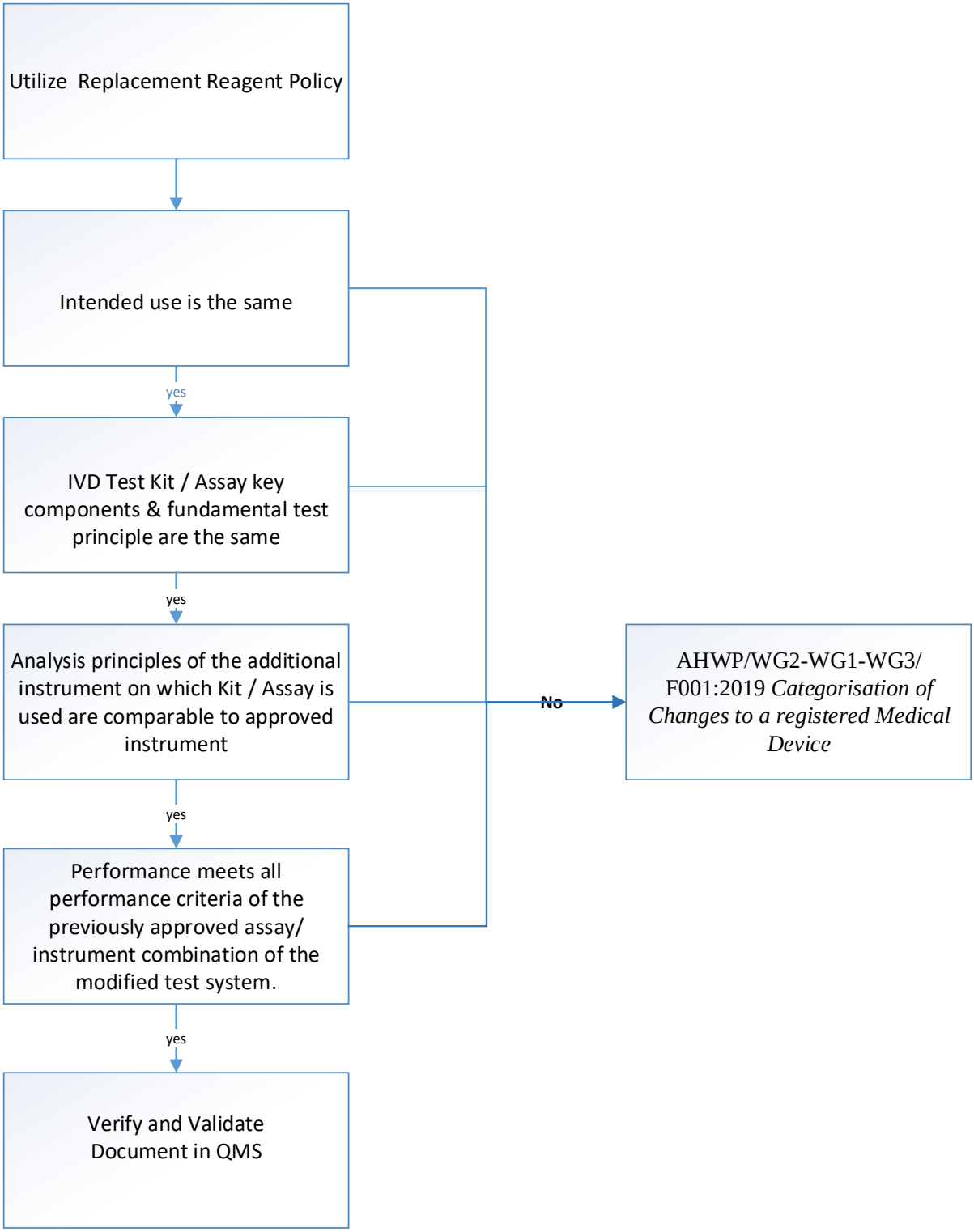
In order to determine whether to proceed with the modified test system without a new submission for every test kit/Assay, the IVD Test kit/Assay manufacturer should make assessments regarding:

- Test System operating principles,
- Risk, and
- Verification and/or validation activities subject to inspection

0 Scheme to Follow

The following flowchart describes how to perform the assessment.

Flowchart 3
Logic Scheme of the Replacement Reagent Policy



Error! Reference source not found. **Verification and/or Validation Activities**

The IVD Test kit/Assay manufacturer should perform a risk analysis and verify and/or validate the modified test system as part of the Quality Management System under the design control. 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.

The IVD Test kit/Assay manufacturer should:

- perform a risk-based protocol with acceptance criteria based on the specifications of the originally approved test kit/assay being applied;
- develop a protocol and acceptance criteria for validating the proposed instrument/reagent combination based on the evaluation protocols used in the original device approval;
- challenge the performance characteristics of the IVD Test System;
- consider standard methods and performance criteria that have been established for evaluation of the specific Test System;
- describe the studies to be completed and stipulate the acceptance criteria for each performance parameter (e.g., method comparison, precision, accuracy around decision points, reference range; see example below).
- include a statistically valid number of test samples and validated specimen types as appropriate.

5.3.3 Documentation

The following tables depict examples of the comparison and acceptance criteria for each performance parameter of the approved and modified instrument IVD Test kit/Assay.

Table 3: **Instrument IVD Test kit/Assay Comparison** (Replacement Reagent Policy applies, but can be adopted for Instrument Family Policy, where either A' or B' can serve the Master Instrument)

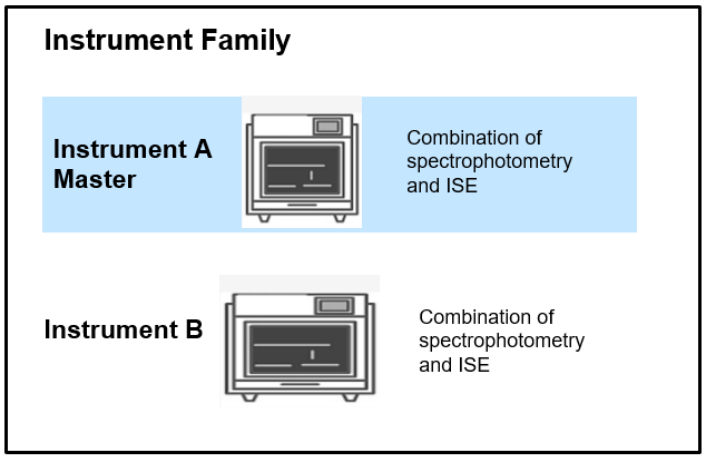
No.	Item of comparison	Approved Instrument (refer to A' in Table 1)	Approved Instrument (refer to B' in Table 1)
1	Model Name		
2	Manufacturer		
3	Intended Use		
4	Principle of Measurement		
5	Type of Specimen		
6	Test Kit / Assay		
7	Specification		
8	Calibration Method		
9	Embedded Software		

Table 4: **Acceptance Criteria for Each Performance Parameter Comparison (**Replacement Reagent Policy applies**)**

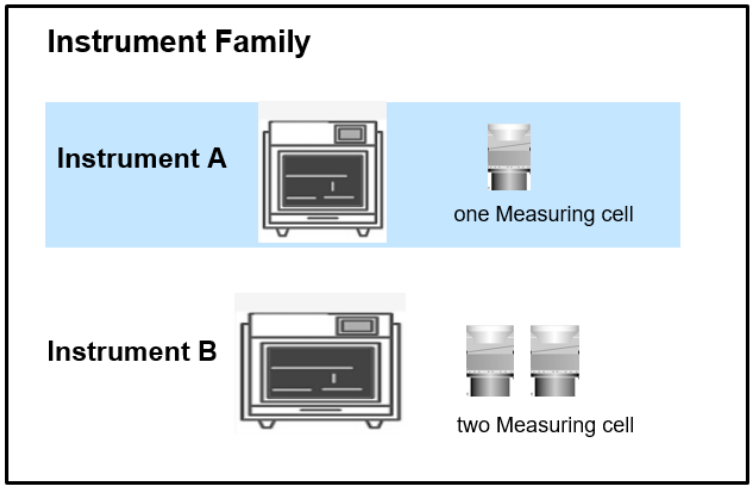
No.	**Performance Parameter**	**Test Method by Each Test Item**		Identical /non identical
		Performance of approved Test System (refer to A+A' or B+B' in Table 2)	Performance of approved IVD Test Kit applied to previously approved instrument (refer to A+B' or B+A' in Table 2)	
Test System & Model Name				
1	Correlation			
	Acceptance Criteria			
2	Precision			
	Acceptance Criteria			
3	Sensitivity – Analytical vs Clinical			
	Acceptance Criteria			
4	Accuracy			
	Acceptance Criteria			
5	Specificity – Analytical vs Clinical			
	Acceptance Criteria			
6	Range of reference			
7	Method Comparison			
8	Linearity/Recovery			
9	Cut-off concentration (for qualitative assays)			
10	LoB/LoD/LoQ			
11	Onboard stability (including internal environmental conditions such as IVD Test Kit/Assay primary reagent container or vessel size, shape, construction)			
12	Carry over testing (depending on instrument design)			
13	Hook effect			

6.0 Case Studies

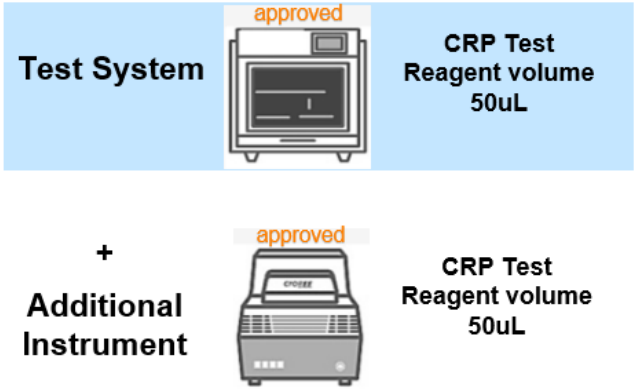
6.1 Examples Instrument Family Policy

Example 1 **Instrument Family Policy applies**	**Assessment** **Validation/Verification** **Documentation**
A new instrument maintains the same measurement technology as the master instrument of the instrument family, e.g. Combination of spectrophotometry and ISE, therefore the manufacturer would like to add it to the approved instrument family.  	**Assessment** Analysis principles of the additional instrument on which Test Kit / Assay is used are comparable to approved instrument Design history files demonstrate that one instrument can be considered a modification of the other **Validation/Verification Documentation** Operator manual Comparisons table of original instrument and new instrument. Internal Validation Documentation **Decision** Instrument Family Policy applies

Example 2 **Instrument Family Policy applies**	**Assessment** **Validation/Verification** **Documentation**
The manufacturer develops an instrument with double throughput by duplicating the measuring cell. All instrument components and design specification remain the same. Internal validation protocol defines appropriate performance testing for applying the approved assay menu from the original instrument to the high throughput instrument.	**Assessment** Analysis principles of the additional instrument on which Test Kit / Assay is used are the same to approved instrument Design history files demonstrate that one instrument can be considered a modification of the other **Validation/Verification Documentation** Operator manual

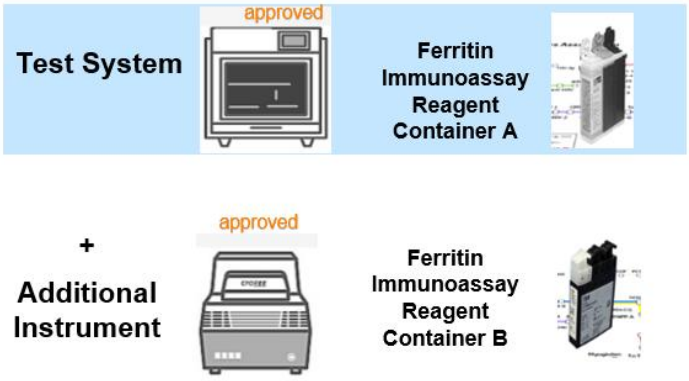
	Comparison table of original instrument and additional instrument. Internal Validation Documentation **Decision** Instrument Family Policy applies

6.2 Examples - Replacement Reagent Policy

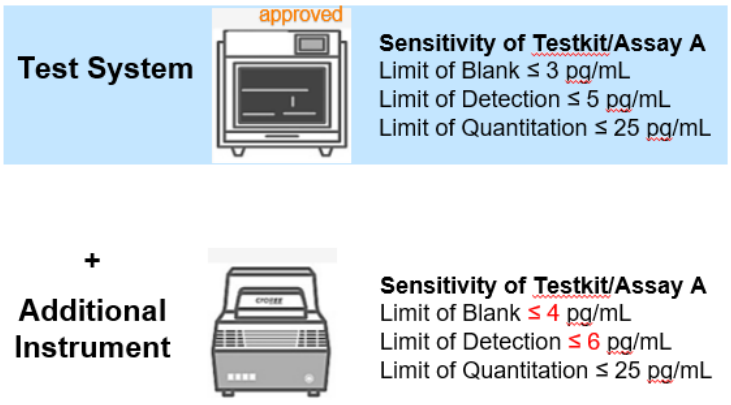
Example 3 **Replacement Reagent Policy applies**	**Assessment** **Validation/Verification Documentation**
A manufacturer (and owner of the assay) has approved a new IVD test kit/assay for high sensitive CRP (C-reactive protein) on an automatic IVD instrument. The manufacturer wants to apply "a new IVD test kit/assay" with the "approved IVD test kit/assay for CRP to the additional approved members of the instrument family. The reagent volumes of the new IVD test kit/assay used by the additional instruments is the same (50 ul). The reagents to sample ratio is unchanged. The validation on the additional instruments shows equivalent performance meeting all previously determined specification of the approved test kit/assay.  This example can also be applied to multiple assays that fit the same criteria if desired.	**Assessment** Performance of the modified test system does not significantly change the analytical / clinical validity of the approved test system **Validation/Verification Documentation** Risk assessment Validation and Verification Protocol Comparison table of the two instruments Acceptance criteria for each performance parameter comparison **Decision** Replacement Reagent Policy applies

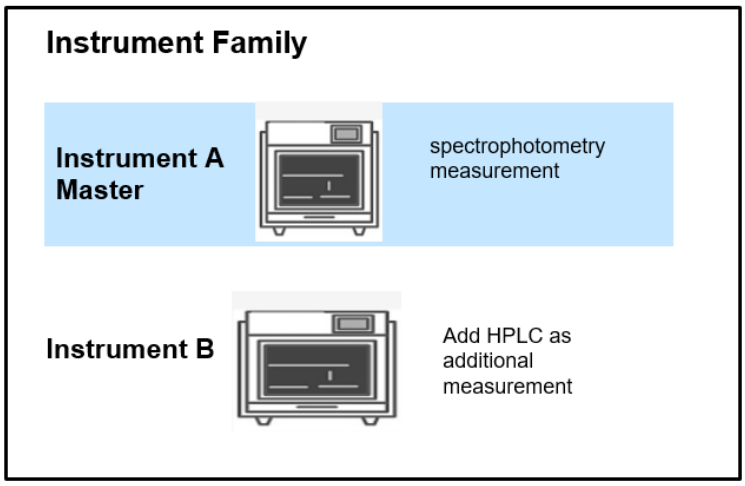
Example 4 **Replacement Reagent Policy applies**	**Assessment** **Validation/Verification** **Documentation**
A manufacturer (and owner of the assay) has approved a new IVD test kit/assay for high sensitive CRP (C-reactive protein) on an automatic IVD instrument. The manufacturer wants to apply "a new IVD test kit/assay" with the "approved IVD test kit/assay for CRP to the additional approved members of the instrument family. The reagent volumes of the new IVD test kit/assay used by the additional instruments vary from 50 to 75 uL. The reagents to sample ratio is unchanged. The validation on the additional instruments shows equivalent performance meeting all previously determined specification of the approved test kit/assay. **Test System** approved  **CRP Test Reagent volume 50uL** **+** **Additional Instrument** approved  **CRP Test Reagent volume 50-75uL**	**Assessment** Performance of the modified test system does not significantly change the analytical / clinical validity of the approved test system as it is the same reagent with different volume and unchanged sample ratio. **Validation/Verification Documentation** Risk assessment Validation and Verification Protocol Comparison table of the two instruments Acceptance criteria for each performance parameter comparison **Decision** Replacement Reagent Policy applies

Example 5 **Replacement Reagent Policy applies**	**Assessment** **Validation/Verification** **Documentation**
A manufacturer wants to move the approved assay for Ferritin immunoassay with a new reagent container to a new member(s) of an instrument family. The change to a new container with the same material is validated. The composition of the reagents used are the same, and new reagent containers meet all shelf life and open onboard stability claims. All performance claims of the assays applied to the new instrument (member of an	**Assessment** IVD Test Kit / Assay key components & fundamental test principle are the same Performance of the modified test system does not significantly change the analytical / clinical

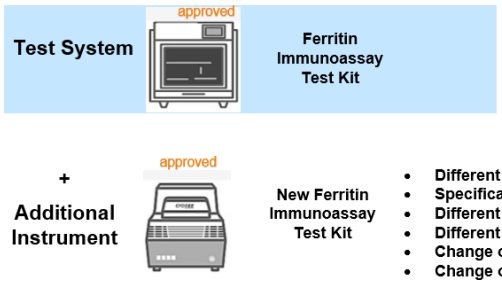
instrument family) meet the original test kit/assay specifications. 	validity of the approved test system **Validation/Verification Documentation** Risk assessment Validation and Verification Protocol Comparison table of the two instruments Acceptance criteria for each performance parameter comparison **Decision** Replacement Reagent Policy applies

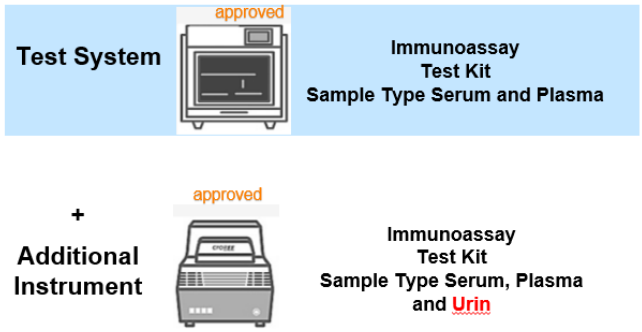
6.3 Examples – Not in Scope of Replacement Reagent or Instrument Family Policy

Example 6 **Neither Replacement Reagent nor Instrument Family Policy applies**	**Assessment** **Validation/Verification Documentation**
A manufacturer would like to add an additional member of an instrument to the instrument family. The application of the additional member of the family is not able to meet the low-end sensitivity claim of the original instrument. 	**Assessment** Performance of the modified test system does significantly change the analytical / clinical validity of the approved test system AHWP/WG2-WG1-WG3/F001:2019 *Categorisation of Changes to a registered Medical Device* **Decision** Not in scope of Replacement Reagent and/or Instrument Family Policy

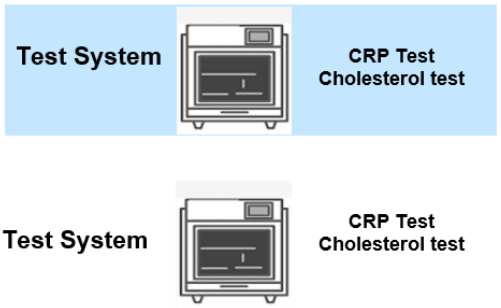
Example 7 **Neither Replacement Reagent nor Instrument Family Policy applies** AHWP/WG2-WG1-WG3/F001:2019 *Categorisation of Changes to a registered Medical Device applies*	**Assessment** **Validation/Verification** **Documentation**
The manufacturer would like to add a new instrument with an additional measurement technology e.g. HPLC which is not approved within the instrument family as the master instrument of the instrument family.  	**Assessment** Analysis principles of the new instrument on which Kit / Assay is used are different Design history files demonstrate that one instrument cannot be considered a modification of the other **Decision** Not in scope of Replacement Reagent and/or Instrument Family Policy

Example 8 **Neither Replacement Reagent nor Instrument Family Policy applies** AHWP/WG2-WG1-WG3/F001:2019 *Categorisation of Changes to a registered Medical Device applies*	**Assessment** **Validation/Verification** **Documentation**
A manufacturer is developing new test kits/assays or significantly change the test kits Examples are • Change of supplier of antibody with specification change • Significant specification change of primer • Different composition of the reagent • Change of test principle • Change of sample/reagent ratios Recommendation	**Assessment** Evaluate if it is a significant change of IVD Test Kit / Assay in regards of components and or test principle and if key components & fundamental test principle are different **Decision** Not in scope of Replacement Reagent and/or Instrument Family Policy

Example 9 **Neither Replacement Reagent nor Instrument Family Policy applies** AHWP/WG2-WG1-WG3/F001:2019 *Categorisation of Changes to a registered Medical Device applies*	**Assessment** **Validation/Verification** **Documentation**
A manufacturer is adding new sample type to the intended use of a test kits/assays, for example the test kits/assays were approved with serum and plasma samples and the manufacturer added urine as a new sample type. The manufacturer intends to use the Instrument Family Policy for this change. 	**Assessment** Change of intended use –clinical evidence for additional claim needed Change could affect the safety and/or performance of a medical device. **Decision** Not in scope of Replacement Reagent and/or Instrument Family Policy

Example 10 **Neither Replacement Reagent nor Instrument Family Policy applies** AHWP/WG2-WG1-WG3/F001:2019 *Categorisation of Changes to a registered Medical Device applies*	**Assessment** **Validation/Verification** **Documentation**

A manufacturer establish a new manufacturer site in a different country for a group of instruments and test kits/assays. The instruments or test kits/assays produced by (or for) having the same general architecture, design, tolerance limits, and capabilities, manufacturing process, product specification.  	**Assessment** This is a manufacturer site change and does not fall under the scope of a previously approved IVD Test kit/Assay (to be used in a specified instrument) to an additional or alternative approved instrument to expand the Test System or adding a new instrument to an instrument family **Decision** Not in scope of Replacement Reagent and/or Instrument Family Policy