Asian Harmonization Working Party

WORKING TOWARDS MEDICAL DEVICE HARMONIZATION IN ASIA

# FINAL DOCUMENT

**Title:** Guidance for Additional Considerations to support Conformity Assessment of Companion In vitro Diagnostic Medical Devices

**Authoring Group:** Work Group 2

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## 0.0 Preface

This document was produced by the Asian Harmonization Working Party. The AHWP would like to acknowledge and has considered the documents, "In Vitro Companion Diagnostic Devices" developed by US FDA and "Guideline for Approval and Evaluation of *In Vitro* Companion Diagnostic Devices" developed by the MFDS, Republic of Korea.

This document is intended to provide non-binding guidance for use in the regulation of companion IVD medical devices, and has been subject to consultation throughout its development.

## 1.0 Introduction

This document has been developed to encourage and support convergence of regulatory systems in the AHWP member economies. 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 IVD 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.

This guidance document is intended to guide staff of RAs and CABs who are assessing Companion In Vitro Diagnostic Medical Devices (IVD-CDx) for possible premarket regulatory pathways and assist manufacturers of the IVD-CDx to develop and demonstrate relevant performance characteristics for their products. 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.

This guidance should be read in conjunction with the AHWP documents on Essential Principles of Safety and Performance, Conformity Assessment, Labelling and Submission Dossier on IVD medical devices. It provides additional considerations specifically for IVD-CDx.

## 2.0 Rationale, Purpose and Scope

### 2.1 Rationale

Recent development of scientific technology has led to the development of personalized medicine for treatment. The process for selecting appropriate therapeutic products, based on a patient's characteristics has grown in importance. IVD-CDx provide information that is essential for the safe and effective use of a therapeutic product, for example such information can be based on the expression levels of genes, or the occurrence of any mutations. Guidance is required on the process for collecting, documenting and assessing the performance of an IVD-CDx in relation to the therapeutic product with which it is intended to be used.

### 2.2 Purpose

The purpose of this guidance is to provide a definition for IVD-CDx, and to provide guidance for manufacturers, RAs and CABs on additional requirements for the submission dossier and conformity assessment for IVD-CDx.

### 2.3 Scope

This guidance applies to IVD medical devices which are intended to provide information about certain patient characteristics in conjunction with the administration of a targeted therapeutic product, in order to:

- identify patients who are most likely to benefit from the therapeutic product;
- identify patients likely to be at increased risk for adverse reactions as a result of treatment with the therapeutic product;

There are two categories of IVD-CDx:

a) Newly developed IVD-CDx

Four approaches can occur in the development of a new IVD-CDx:

- simultaneous development of a new therapeutic product and a new IVD-CDx;
- development of a new IVD-CDx to be applied to a marketed therapeutic product;
- use of an IVD medical device which can be verified, validated and applied as an IVD-CDx to a targeted therapeutic product still under development; or

- use of an IVD medical device which can be verified, validated and applied as an IVD-CDx for a new indication of an approved therapeutic product.

b) Equivalent IVD-CDx

An equivalent IVD-CDx is a device that has the same intended use as an existing IVD-CDx.

## 3.0 References

1. *AHWP/WG2/PF002:2016. Principles of Conformity Assessment for In Vitro Diagnostic (IVD) Medical Devices*
2. *AHWP/WG2/PF003:2016. Submission Dossier for Demonstrating Conformity to the Essential Principles of Safety and Performance of In Vitro Diagnostic Medical Devices*
3. *AHWP/WG1a/F002:2013 Essential Principles of Safety and Performance of IVD Medical Devices*
4. *US FDA Guidance for Industry: In Vitro Companion Diagnostic Devices 2014*
5. *Korea MFDS guideline "Guideline for Approval and Evaluation of In Vitro Companion Diagnostic Devices" (2015/BI-2015-5-238)*
6. CLSI Harmonized Terminology database: http://htd.clsi.org/

## 4.0 Definitions

**Clinical cut-off:** The test value which determines the clinical decision for treatment, i.e. subjects with test results above the cut-off value are eligible for treatment, whereas those with test results below the cut-off value are not given the treatment.

Note 1: The clinical cut-off value is determined in the therapeutic product clinical trial.

Note 2: The role of the IVD-CDx is to determine the test value accurately.

**Companion In Vitro Diagnostic Medical Device (IVD-CDx):** means an In Vitro diagnostic medical device which is essential for the safe and effective use of a corresponding therapeutic product to:

a) identify, before and/or during treatment, patients who are most likely to benefit from the corresponding therapeutic product; or

b) identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding therapeutic product.

Note 1: except the products for compatibility evaluation for blood transfusion and transplant purposes.

Note 2: in specific cases, IVD-CDx may be used for monitoring response to treatment, but "therapeutic drug monitoring (TDM)" in general does not fall under the scope of IVD-CDx.

**Negative Percent Agreement (NPA)**: the percentage of agreement of the test method's ability to obtain negative results in concordance with negative results obtained by the comparative method.

Note: The proportion of correct calls by the assay for the absence of an analyte. The test method's ability to obtain negative results in concordance with negative results obtained by the comparative method.

**Positive Percent Agreement (PPA):** the percentage of agreement between positive test results with the positive results of the comparative method (usually non-reference standard); the percentage of agreement of the test method's ability to obtain positive results in concordance with positive results obtained by the reference method.

**Class of therapeutic product**: a set of therapeutic products that have similar chemical structures, and

- the same mechanism of action (i.e., bind to the same biological target), or
- a related mode of action, and are used to treat the same disease.

**Single arm study:** For the purpose of this document it is defined as a type of single group study where all subjects receive the same therapeutic product.

**Therapeutic product:** A therapeutic product is a product for use in humans in connection with preventing, diagnosing, curing or alleviating a disease, ailment, defect or injury, or influencing, inhibiting or modifying a physiological process.

## 5.0 Conformity Assessment of IVD-CDx

The IVD-CDx is a subset of IVD medical devices, which are developed and used in conjunction with therapeutic products. The requirements for IVD-CDx follow the AHWP general IVD medical device guidance, such as Essential Principles of Safety and Performance, Conformity Assessment, Labelling and Submission Dossier. However, the characteristics and application of IVD-CDx in conjunction with therapeutic products requires some specific considerations to be taken into account with respect to the AHWP general guidance for IVD medical device.

## 6.0 Specific Considerations to Essential Principles of Safety and Performance (EP)

IVD-CDx manufacturers need to take into account several specific considerations related to the Essential Principles specified in the AHWP document *AHWP/WG1a/F002:2013, Essential Principles of Safety and Performance of IVD Medical Devices.*

### 6.1 General Considerations

6.1.1 The intended use should include the trade name of the therapeutic product (including its active ingredient) to be used with the IVD-CDx.

6.1.2 The parameter for measurement and detection shall be clarified according to the following:

a) The name of gene, protein, etc. targeted shall be described;

b) If the IVD-CDx is to be used for the diagnosis of a specific genotype, when necessary, the corresponding genetic sequence/codon, mutation domain etc. shall be included.

6.1.3 If multiple types of specimen are mentioned in the intended use, data for each specimen type should be generated, in particular differences and potential limitations should be described, e.g. tissue versus serum/plasma.

6.1.4 Relationship of the IVD-CDx to the therapeutic product:

a) the clinical relationship of the use of the companion diagnosis for the corresponding therapeutic product, such as therapeutic target identification, efficacy, potential adverse reaction and dose adjustment administration, shall be considered;

b) the intended use of the corresponding therapeutic product should be considered.

6.1.5 For newly developed IVD-CDx, the clinical significance and clinical cut-off value of the IVD-CDx are evaluated in the clinical trial of the therapeutic product through screening with the IVD-CDx. Therefore, the IVD-CDx developer needs to obtain clinical research-related-information early enough from the therapeutic product manufacturers to cooperate with them appropriately.

6.1.6 For comparative testing with an existing IVD-CDx, a comparative testing report capable of confirming the correlation among the new and existing IVD-CDx should be generated.

It is preferable that the equivalence between the new and existing IVD-CDx is assessed with the same specimens collected from subjects who participated in a clinical trial of the relevant therapeutic product. However, if the same specimens cannot be secured, the equivalence trials can be conducted separately by using a smaller number of specimens collected and stored from a new subject group based on an equivalent selection condition compared to the clinical trial.

The appropriate level of positive percent agreement (PPA) or negative percent agreement (NPA) for IVD-CDx equivalence shall be applied by consideration of the characteristics of the disease, the patient number (functional case number capable of being confirmed realistically), confidence interval, etc.

## 6.2 Considerations for analytical performance

The manufacturer should consider the following specific aspects for analytical performance for IVD-CDx, in addition to those required for other IVD medical devices:

a) the specific mutation(s) the test can detect and the percentage of each of the mutant sequences;

b) the limit of detection expressed as the lowest amount of analyte or target cells;

c) the potential for cross-reactivity to other mutations;

d) the specimen information including method of sample collection, processing, storage etc.;

e) the possibilities of non-specific response and the countermeasure for it.

## 6.2 Considerations for clinical performance evaluation

The manufacturer should consider the following specific aspects for clinical performance for IVD-CDx, in addition to those required for other IVD medical devices:

a) the effect of the therapeutic product on the biomarker detected by the IVD-CDx;

b) the potential clinical pathway and treatment following the differential test result;

c) the potential benefit and risk to the patient.

### 6.3.1 Clinical performance studies

Clinical performance studies for IVD-CDx should consider the following specific aspects:

a) The clinical performance studies for IVD-CDx are based on interventional design. Such studies need to be conducted in accordance to the Declaration of Helsinki.

b) A randomized controlled trial (RCT) should be used for the clinical performance study of an IVD-CDx. If an enrichment design which excludes or includes the patient with a specific biomarker is used a documented justification should be provided. The RCT method after patient grouping into control and test by genetic test is not considered as the best choice for the replicated tests in both groups because of the decreased statistical significance and the resulting requirement for higher numbers of specimen requirement.

c) The prospective-retrospective study design may be used for the clinical performance study with left-over specimens. Comparative study with a reference method or randomized clinical study method using similar specimens can overcome the limitations for the causal relationship and a limitation derived from an insufficient number of specimens.

d) A single arm study may be used to determine the clinical performance of the IVD-CDx, if it satisfies the following conditions:

- the number of specimen is insufficient;
- the response rate i.e. partial response or complete response, can be utilized as a primary variable;
- the results for response rate of the similar cohort study which is not compared simultaneously are available.

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e) For the clinical performance study, the level of agreement, between the IVD-CDx and the existing IVD-CDx or the reference method, shall be described. The therapeutic product response using the IVD-CDx should be also described.

### 6.3 Labelling of IVD-CDx

The labelling for IVD-CDx should include the following in addition to the labelling requirements for the IVD medical devices as described in the AHWP document "Label and Instructions for Use for IVD Medical Devices":

a) An IVD-CDx that is intended for use with a therapeutic product must specify the therapeutic product(s) for which it has been approved or cleared for use. In some cases, if evidence is sufficient to conclude that the IVD-CDx is appropriate for use with a class of therapeutic products, the intended use/indications for use should name the therapeutic class, rather than each specific product within the class.

b) Once an IVD-CDx has been approved or cleared for use with a therapeutic product in one disease or setting, and evidence has become available that this IVD-CDx and the same therapeutic product can be used in another disease or setting, the intended use of the IVD-CDx in the labeling may be expanded.

c) When an IVD-CDx has been approved or cleared for use with one therapeutic product and evidence becomes available that use of the same device is essential for the safe and effective use of a different therapeutic product, the intended use of IVD-CDx may be expanded in the labelling to include the new therapeutic product.

## 7.0 Requirements for Submission Dossier of IVD-CDx

A submission dossier for IVD-CDx should include, in addition to the requirements specified in the AHWP *Submission Dossier Document For Demonstrating Conformity To The Essential Principles Of Safety And Performance Of In Vitro Diagnostic Medical Devices*, evidence related to additional requirements for the EP for IVD-CDx as described in Section 6 of this guidance.

## 8.0 Assessment of IVD-CDx Submission Dossier

IVD-CDx will be assessed in two different categories for regulatory approval:

a) Newly developed IVD-CDx

b) Equivalent IVD-CDx

### 8.1 Newly developed IVD-CDx

a) The efficacy of the therapeutic product related to the IVD-CDx should be reviewed by the RA or CAB responsible for the therapeutic product approval.

b) The IVD-CDx should be reviewed by the RA or CAB responsible for IVD medical device approval. The analytical performance characteristics of the IVD-CDx should be reviewed as described as *AHWP/WG2/PF002:2016, Principles of Conformity Assessment for In Vitro Diagnostic (IVD) Medical Devices*, with special focus on the characteristics that provide the selection criteria as demonstrated by the clinical study of the therapeutic product. In addition, the specific aspects of analytical performance as described in 6.2 of this guidance should be reviewed. This part of the submission dossier will be reviewed by the RA or CAB responsible for the IVD medical device approval.

c) The clinical performance of the IVD-CDx should be assessed by review of the therapeutic product manufacturer's demonstration of the statistical significance of the superiority of the response to the therapeutic product in the trial group screened by the IVD-CDx compared with the randomized patient group in accordance with current therapeutic product approval regulations. The specific aspects related to clinical performance and clinical performance studies as described in Section 6.3 should be reviewed. This part of the submission dossier will be reviewed by the RA or CAB responsible for IVD medical device and therapeutic product approval.

Note: If the therapeutic product and IVD-CDx are reviewed in parallel, it is important to share related information between applicants to synchronize the regulatory pathway and the approval timeline. Therefore, in such cases it is recommended that early phase combined pre-submission discussions are held with the IVD medical device and therapeutic product RAs.

8.2 Equivalent IVD-CDx

a) The analytical performance characteristics of the IVD-CDx should be reviewed as described as *AHWP/WG2/PF002:2016. Principles of Conformity Assessment for In Vitro Diagnostic (IVD) Medical Devices*. In addition, the specific aspects of analytical performance as described in 6.2 of this guidance should be reviewed. This part of the submission dossier will be reviewed by the RA or CAB responsible for the IVD medical device approval.

b) The comparative clinical performance data for the concordance between the equivalent product and the existing IVD-CDx should be reviewed. These performance data may include the correlation analysis between them. The specific aspects related to clinical performance and clinical performance studies as described in Section 6.3 should be reviewed. This part of the submission dossier will be reviewed by the RA or CAB responsible for the IVD medical device approval.