Global Harmonization Working Party
Towards Medical Device Harmonization

PROPOSED FINAL DOCUMENT

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

Authoring Group: Work Group 2, Pre-market: IVD

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Preface

This document was produced by the Global Harmonization Working Party. The GHWP 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 GHWP 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 In Vitro Companion 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 GHWP has prepared this guidance document. Comments or questions should be directed to the Chair of GHWP Work Group 2 whose contact details may be found on the GHWP web page.

This guidance should be read in conjunction with the GHWP 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, proteins, or the occurrence of any mutations. Guidance is required on the process to demonstrate safety and 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 define IVD-CDx and guide manufacturers, Regulatory Authorities (RAs) and conformity Assessment Bodies (CABs) on requirements for submission and conformity assessment for IVD-CDx performance.

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;
- Monitor response to treatment with the therapeutic product for the purpose of adjusting treatment (e.g., determination of the dosage, the timing of administration, and discontinuation of the administration schedule, dose, discontinuation) to achieve improved safety or effectiveness;
- Identify patients in the population for whom the therapeutic product has been adequately studied, and found safe and effective, i.e., there is insufficient information about the safety and effectiveness of the therapeutic product in any other population.

Note: The tests performed to determine donor-recipient matching (blood, blood composition, cells, tissues, and organs) are not included. However, the Human Leukocyte Antigen (HLA) analysis method falls within the scope of the IVD-CDx when the HLA analysis method is essential for the safe and effective use of therapeutic products rather than intended to determine donor-recipient matching.

3.0 Categories of IVD-CDx development

3.1 Novel IVD-CDx

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

- Contemporaneous development of a new therapeutic product and a new IVD-CDx;
- Development of a novel IVD-CDx used for previously approved therapeutic product.

3.2 Follow-on IVD-CDx

A follow-on companion diagnostic is a device using, either the same or different technology, that is intended to be used with the therapeutic product in the same indication of use and patient population, as in the labelling of the original companion diagnostic. However, the development of a follow-on companion diagnostic device may not have a therapeutic partner to conduct a new additional clinical trial, or the availability of the patient samples from the original clinical trial is limited, where the original IVD-CDx was developed and the therapeutic product were evaluated together.

3.3 Changes and additions of the purpose of use on IVD-CDx

a) Addition of types of samples for in vitro companion diagnostic devices that have previously been approved (e.g., tissue sample → tissue sample or liquid sample)

b) Addition of new therapeutic products of which the response is predictable to an existing (previously approved) in vitro companion diagnostic devices' intended use.

(e.g., Drug A → Drug A or Drug B)

c) As in vitro companion diagnostic devices that have previously been approved have multiple drugs whose correlation with response in vitro companion diagnostic devices can be established, they are integrated into one specific group name.

(e.g., Drug A, B, C, D → Drug Alphabet)

4.0 References

AHWP/WG2/PF002:2016 Principles of Conformity Assessment for In Vitro Diagnostic (IVD) Medical Devices

AHWP/WG2/PF003:2016 Submission Dossier for Demonstrating Conformity to the Essential Principles of Safety and Performance of In Vitro Diagnostic Medical Devices

AHWP/WG1a/F002:2013 Essential Principles of Safety and Performance of IVD Medical Devices

US FDA Guidance for Industry: In Vitro Companion Diagnostic Devices 2014

Korea MFDS guideline "Guideline for Approval and Evaluation of In Vitro Companion Diagnostic Devices" (2015/BI-2015-5-238, 2022/Guideline-1267)

CLSI Harmonized Terminology database: http://htd.clsi.org/

US FDA Guidance for Industry: Developing and Labeling in vitro companion diagnostic devices for a specific group of oncology therapeutic products 2020

US FDA Guidance for Industry and Food and Drug Administration Staff (Draft): Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product (2016)

US FDA Guidance for Industry (Draft): Use of Circulating Tumor DNA for Early-Stage Solid Tumor Drug Development (May 2022)

5.0 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'

Cut-off for an IVD-CDx: 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.

[Ref. *US FDA Guidance, Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product (2016)]*

In Vitro Companion Diagnostic Medical Device (IVD-CDx): Means an In vitro diagnostic medical device which provides information that 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;

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;

c) Monitor response to treatment with the therapeutic product for the purpose of adjusting treatment (e.g., determination of the dosage, the timing of administration, and discontinuation of the administration) to achieve improved safety or effectiveness; or

d) Identify patients in the population for whom the therapeutic product has been adequately studied, and found safe and effective, i.e., there is insufficient information about the safety and effectiveness of the therapeutic product in any other population.

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 or adjusting treatment, but "therapeutic drug monitoring (TDM)" in general does not fall under the scope of IVD-CDx.

[Ref. *US FDA Guidance, In Vitro Companion Diagnostic Devices (2014); MFDS Guidance, Guideline for Approval and Evaluation of In Vitro Companion Diagnostic Devices (2022)]*

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.

-[Ref. *CLSI Harmonized Terminology database]*

Positive Percent Agreement (PPA): The percentage of agreement of the test method's ability to obtain positive results in concordance with positive results obtained by the comparative method.

[Ref. *CLSI Harmonized Terminology database]*

Comparative method: In a method evaluation experiment, a well-characterized method that serves as the basis for assigning the true concentration of an analyte in a sample.

Note 1: The method(s) being used to validate the new automated system, also known as a comparator method;

Note 2: The comparative method(s) may be a reference standard or a nonreference standard.

[Ref. *CLSI Harmonized Terminology database]*

Reference method: A methodology that has exact and clear descriptions of the necessary conditions and procedures that provide sufficiently accurate and precise laboratory data for it to be used to assess the validity of other test methods.

[Ref. *CLSI Harmonized Terminology database]*

Specific group of therapeutic products: The specific group refers to the indication that the therapeutic products have in common which is captured in the therapeutic products' labelling (including sections other than the indications and usage section).

Note: See section 7.2.3. b)-3) for additional information about integrating multiple therapeutic product names into one specific group name in the labelling of IVD-CDx.

[Ref. *US FDA Guidance Developing and Labelling in vitro companion diagnostic devices for a specific group of oncology therapeutic products (2020)]*

Therapeutic product (as used in this guidance): Includes therapeutic, preventive, and prophylactic drugs and biological products.

[Ref. *US FDA Guidance, In Vitro Companion Diagnostic Devices (2014)*]

Liquid biopsy: Liquid biopsy is a technique used for the diagnosis and observation of diseases such as cancer by analyzing liquid samples rather than analyzing solid biological tissues. The biggest advantage of liquid biopsy is that it is a non-invasive sample collection method. Blood and body fluids such as serum, plasma, exosomes, circulating tumor cells (CTC), cerebrospinal fluid (CSF), urine, and saliva are used as samples.

[Ref. *MFDS Guidance, Guideline for Approval and Evaluation of In Vitro Companion Diagnostic Devices (2022)*]

Circulating tumor DNA (ctDNA): Circulating tumor DNA is tumor-derived fragmented DNA shed into a patient's bloodstream that is not associated with cells.

[Ref. *US FDA Guidance for Industry (Draft): Use of Circulating Tumor DNA for Early-Stage Solid Tumor Drug Development (2022)*]

6.0 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 GHWP 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 GHWP general guidance for IVD medical device.

7.0 Considerations to Essential Principles of Safety and Performance

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

7.1 General Considerations

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

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

- The name of gene, protein, clone (in case of mAb) etc. targeted shall be specified;
- 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.

c) 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.

d) Relationship of the IVD-CDx to the therapeutic product:

- 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;
- the specific intended use of the corresponding therapeutic product should be considered

e) It is desirable to use a risk-based approach for the approval and review of an IVD-CDx. Accordingly, the review should be focused on the following matters.

- Purpose of use of an IVD-CDx;
- Level of confidence in safety and effectiveness;
- Level of risk associated with false positive and negative results of an IVD-CDx

f) In the case of contemporaneous development of therapeutic product and IVD-CDx, pharmaceutical companies and medical device manufacturers must prepare for clinical trials by sharing information with each other and obtain approval for the protocol for therapeutic product and IVD-CDx separately for each.

g) For simultaneous approval of therapeutic product and IVD-CDx both of which were contemporaneously developed, IVD-CDx developers are guided to help them to match the timing of the clinical development of therapeutic product and the submission date of the application form. Therefore, pharmaceutical companies and IVD-CDx manufacturers are encouraged to consult with relevant departments of authority in the early development phase.

7.2 Specific considerations according to IVD-CDx Categories

7.2.1. For Novel IVD-CDx

a) The review of the clinical effectiveness of an IVD CDx determines if the response to a therapeutic product is more favorable (statistically significant) in the patient group screened by applying the IVD CDx than in the randomized patient group (compliance with the license conditions, the safety, and efficacy of the therapeutic product) and evaluate the clinical performance of the IVD CDx (sensitivity, specificity, or equivalence to reference methods).

b) In the case of the recent simultaneous clinical evaluation on IVD-CDx and targeted therapy, the clinical design in which patients who showed a positive result for IVD-CDx are divided into a test group (targeted therapy) and a control group (placebo, chemotherapy, etc.) and compared each other is common, but the clinical evaluations on some of the second-line treatments are designed for evaluation in the test group only without a control group.

c) In the case of IVD-CDx for which a tissue sample or liquid biopsy can be used, the performance evaluation including drug reactivity of oncogenes in the tissue of primary cancer and liquid biopsy should be performed in the same patient. In addition, comparative analysis data with other test methods are reviewed to prove the test results of circulating tumor DNA.

- In general, companion diagnostics on solid tumor using liquid biopsy shows low sensitivity compared to tissue samples, so if there is no evidence to refute it, it is reasonable to select tissue samples with priority. However, if the collection of a tissue sample is rather a big risk to the patient, liquid biopsy can be used for the test alternatively, but if the test result is negative, it is reasonable to conduct the retest with a tissue sample (Avoid missing treatment opportunities due to false negative result).

Note: When developing a new IVD-CDx that can be used with either tissue samples or liquid biopsies, it is important to evaluate not only the concordance between specimen types, but also the accuracy of predicting drug reactivity through liquid biopsy testing. However, drug reactivity through liquid biopsy testing can be confirmed retrospectively (when a patient is prescribed a drug based on the results of a tissue sample, and the liquid biopsy collected before the drug is taken is tested to confirm drug reactivity).

d) Review the analytical performance (sensitivity, specificity, accuracy, reproducibility, linearity, etc.) of IVD-CDx. In addition, if multiple biomarker tests, such as multiple sites of mutation, are required, analytical performances of each biomarker should be ensured.

- Analytical performance should be assessed after the sampling method and criteria(area of tissue, tumor ratio within the tissue, thickness of tissue, etc.)

have been validated, and validation data should be reviewed along with the appropriateness of the criteria during acceptance and audit.

Note: Nucleic acid extraction kits are used to extract genes, including variants associated with drug response, and the nucleic acid extraction kits must be notified or approved by the authorities. Particularly for liquid biopsies (blood), the quality of circulating tumor DNA has a significant impact on test results because the amount of circulating tumor DNA is very low and nucleic acids are damaged while circulating in the human bloodstream. Therefore, it is recommended that quantitative and qualitative assessment of extracted nucleic acids be performed. It is also recommended that internal quality controls to measure the amount of amplifiable nucleic acids among the damaged nucleic acids be included in the IVD-CDx being developed.

7.2.2. For Follow-on product equivalent to the first approved IVD-CDx

a) When developing a follow-on product that is equivalent to the previously approved IVD-CDx with clinical evidence in conjunction with the therapeutic products, you will need to evaluate its clinical performance through comparison study (correlation and concordance between the original and the follow-on products). However, drug response studies that were required for approval of the original approved product are not required for approval of the follow-on product.

   Note 1: 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 specimens collected and stored from a new subject group based on an equivalent selection condition compared to the clinical trial.

   Note 2: If there is a previously approved IVD-CDx using two types of samples (e.g., tissue or liquid biopsy) and comparison testing is performed using this as a control IVD-CDx, only the degree of agreement between them (between the approved IVD-CDx and follow-on product with each specimen type; between sample types of test IVD-CDx) can be evaluated without the drug response studies.

b) Analytical performance (sensitivity, specificity, accuracy, reproducibility, linearity, etc.) of follow-on IVD-CDx.

   Note: It is important to note that IVD-CDx does not determine the presence or absence of a specific biomarker (mutation), but rather predicts the presence or absence of drug response, and the limit of detection (LOD) is not related to the accuracy in predicting drug response (e.g., If a qPCR-based product with a clinical evaluation of drug response prediction is first approved as an IVD-CDx, and a subsequent droplet digital PCR-based product with a great limit of detection is developed, it is not possible to say that the drug response prediction accuracy of the subsequent product exceeds that of the first licensed product without an evaluation of drug response prediction for that drug.). Therefore, it is necessary to confirm that the cut-offs of the original approved IVD-CDx clinically evaluated

concurrently with the corresponding drug and the cut-offs of the follow-on product are quantitatively equivalent.

7.2.3. Addition of new specimen types or new drugs to the intended use

a) Addition of new specimen type to the intended use

If you are changing an IVD-CDx that only uses tissue specimens to additionally use liquid biopsies, you will need to evaluate the concordance of drug response prediction between the same specimen types from same patient and review the appropriateness of the concordance level. You will also need evidence to support its qualification by comparing the performance of genetic testing on liquid biopsies to other testing methods.

Note: If you add a specimen type to the intended use of an IVD-CDx using only tissue specimens that also allows for the use of liquid biopsies, you should evaluate the accuracy of predicting drug response beyond concordance between specimen types. However, the accuracy of predicting drug response from liquid biopsies can be evaluated retrospectively (i.e., subjects are selected for drug prescription based on the results of the tissue specimen, and liquid biopsies collected prior to drug administration are tested to confirm drug response).

b) Addition of a companion drug to the intended use

- Addition of new therapeutic product

If IVD-CDx, which can predict reactivity to a specific therapeutic product (A), is approved, and the purpose of the use is expanded to predict the reactivity of new drug (B) without any changing the IVD-CDx itself, the clinical performance of IVD-CDx on a new drug (B) should be reviewed from the same perspective as for the case where a new IVD-CDx is developed.

Note: These considerations apply to the addition of new disease into the previously approved intended use of IVD-CDx.

- Addition of generic drug

In the case of adding a generic drug (A′) for an original drug (A), if there is data demonstrating its equivalence with existing drugs, the generic drug can be added without a separate clinical performance evaluation in relation to the prediction of drug response.

- Integration of names of multiple anticancer drugs into one special group name

If IVD-CDx can predict drug responses to multiple anticancer drugs, you can consolidate multiple anticancer drug names into one representative group name in the Intended Use field.

(1) If multiple drugs with predictable reactivity are listed as Drug A, Drug B, Drug C, Drug D, Drug E, Drug F, etc. in the IVD-CDx's Intended Use, the

characteristic equivalence levels of the different anticancer drugs can be considered collectively, and only drugs with higher equivalence levels can be listed under one common group name.

*** Checklist of characteristics when unifying special group names**

Check mechanism of drug action, interactions (concentration of biomarkers or genomic volumes by concentration or variant type) between drugs and biomarkers (targets of drugs, proteins identified by IVD-CDx, or specific gene states), cut-off identity of IVD-CDx by each drug response prediction, and effects of biomarkers identified by IVD-CDx to cancer cells in the patient subjected to prescription.

(2) (Labelling for performance) Although names of multiple anticancer drugs are consolidated into a specific single group name in the “Intended Use” section, the drug response in patients identified by IVD-CDx is presented for each anticancer drug in the “Performance” section. However, if the IVD-CDx is approved without clinical trials for the drug, and it is intended to change the specific single group name listed in the 'Intended Use' section to be equivalent to the previously approved drug, the results of additional drug response and correlation tests are not required, and the test results are not described in the 'Performance' section.

(3) If a follow-on IVD-CDx is changed to use a special group name for an Intended Use prior to the initially approved product, the descriptions of drug response testing and correlation testing in the "Performance" section may be omitted in Performance section, but the data for the above validation may be required the same as for previously licensed IVD-CDx.

Considerations for integrating multiple anticancer drug names into a single special group name:

1. Can a single IVD-CDx (identifying the appropriate patient group for potential treatment) be described in grouping multiple anticancer drugs into a specific group?

2. Are sufficient studies on the mechanism of action of the specific group of anticancer drugs designed for use with the IVD-CDx, and interactions between biomarkers and drugs identified with IVD-CDx based on the variation in the molecular structure available?

3. Are there sufficient clinical experience with at least two anticancer drug treatments for indications with the same biomarker secured?

4. Has the analytical performance of the IVD-CDx been tested for each biomarker providing indication information?

5. Has the clinical performance of IVD-CDx been tested with the indicated treatment? (Clinical performance may be tested by

prospective or prospective/retrospective methods, but the cut-off level between anticancer-related drugs in the special group should be confirmed)

Example of integrating multiple anticancer drug names into a single special group name:

In non-small cell lung cancer (NSCLC), EGFR exon 19 deletion mutation or exon 21 (L858R) substitution mutation promotes phosphorylation of EGFR, leading to the promotion of cancer cell proliferation. Therefore, similar target anticancer drugs (afatinib, erlotinib, gefitinib, osimertinib, dacomitinib) that inhibit it can be collectively referred to as a single group name called tyrosine kinase inhibitor (TKI).

However, drugs that **only act on exon 20 (T790M) substitution mutations** due to TKI resistance cannot be included in the above TKI.

※ *Osimertinib (Tagrisso): At first approval, it was approved as a second-line treatment for patients with a history of TKI first-line therapy and cancer of exon 20 (T790M) substitution mutation, but it was expanded through further clinical study as first-line treatment for patients with exon 19 deletion mutations or exon 21 (L858R) substitution mutations.*

7.3 Detailed of the Performance Test

The safety, efficacy, and efficiency of therapeutic products requiring CDx are directly affected by the performance of IVD-CDx.

7.3.1. IVD-CDx in a pharmaceutical trial

Since the clinical significance of IVD-CDx and the establishment and evaluation of clinical cut-offs are performed using clinical trials of drugs conducted on patients identified by IVD-CDx, IVD-CDx developers need to obtain information related to the drug's clinical trials from pharmaceutical companies in advance and cooperate with them.

In the case of applying for IND approval of the protocol on the therapeutic product, if the use of an unauthorized IVD-CDx is included in it for the purpose of CDx of the therapeutic product, the IDE approval of the protocol on the clinical performance of IVD must be obtained separately.

In addition, the clinical significance and cut-off values of the IVD-CDx should be described for the premarket approval, based on the clinical performance of the associated therapeutic product, including the name of the therapeutic product, test name, test methods, and test results.

7.3.2. A test on the evaluation of equivalence of IVD-CDx

a) Evaluation of IVD-CDx equivalence

If an equivalent product is being developed, as there is a previously approved product with an evaluation on clinical performance that was tested together with the therapeutic product, it is possible to replace the evaluation on the prediction of drug reactivity with the evaluation of the equivalence with the previously approved product (clinical performance evaluation-correlation).

b) Precautions for equivalence tests of an IVD-CDx

Ideally, equivalence tests of an IVD-CDx should be carried out using the samples collected from the subjects who participated in the clinical trials of a corresponding therapeutic product, but the samples may not be available for various reasons. If that is the case, leftover samples or newly collected samples from a different subject group can be used for separate equivalence tests among IVD-CDx as long as the sample and subject selection criteria used in the original clinical trials are satisfied. The sample should be maintained in a similar manner to the previous trial, and it is recommended that prior arrangements be made with the approval authority to ensure that the sample are properly maintained with respect to timing of sample collection, quality of lesions, and fixation and storage conditions.

c) The criteria for positive or negative agreements required to be considered appropriate for IVD-CDx should be reviewed in consideration of the characteristics of the disease, the number of patients (realistically verifiable cases), and the confidence interval. The validity of such criteria should be referred to the authority.

7.3.3. Considerations for analytic performance evaluation

Analytic Performance evaluation of IVD-CDx may include the following:

a) Accuracy;
b) Precision;
c) Specificity;
d) Measuring range and linear line segments, such as quantitative range or detection limits;
e) Analytical Cut-off;
f) Reference materials and in-house reference materials;
g) Information about the sample being collected, including sampling method, processing method, and storage method;
h) Possibility and its inhibition of non-specific reactions such as reaction conditions and analysis conditions;

i) Potential misjudgments due to contamination and measures to eliminate them.

Note: In addition, if you want to change the approval for the applied device and test method, you must provide sufficient results of the verification data to ensure that the analytical method can be measured/detected equally before and after the change through the verification of the analytical method.

7.3.4. Considerations for evaluating clinical performance

a) Evidence that the prognosis was affected by the status of the biomarker

This can be used as an alternative to determine the effect of treatment on prognosis. To obtain evidence, you need to compare the outcomes of treatment in patients with and without a positive biomarker.

b) Evidence showing the impact of the proposed test on the health of patients

It should be checked whether patients were identified with the IVD-CDx test, were randomized, and patients with similar health conditions were appropriately assigned to the study treatment group and the usual care group. It is important to obtain high-quality, direct evidence and determine statistical significance. To get these, it is important to assess all of clinical safety, effectiveness, and efficiency.

8.0 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 GHWP document "*Label and Instructions for Use for IVD Medical Devices*".

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 specific group of therapeutic products, the intended use/indications for use should name the therapeutic product group, rather than each specific product within the group.(refer the 7.2.3.c)

9.0 Requirements of Submission Dossier of IVD-CDx

A submission dossier for IVD-CDx should include, in addition to the requirements specified in the GHWP *Submission Dossier Documents 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 7 of this guidance.

10.0 Assessment of IVD-CDx Submission Dossier

10.1 IVD-CDx will be assessed in three different categories for regulatory approval

a) Newly developed IVD-CDx;

b) Equivalent IVD-CDx;

c) Addition of new specimen types or new drugs to the intended use

10.2 Novel 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 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 section 7 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 7 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.

10.3 Follow-on 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 section 7 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 7 should be reviewed. This part of the submission dossier will be reviewed by the RA or CAB responsible for the IVD medical device approval.

10.4 Addition of new specimen types or new drugs to the intended use

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 section 7 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) For addition of new specimen type, the comparative clinical performance data between sample types obtained from same patients should be reviewed. For addition of new therapeutic products, the clinical performance of the IVD-CDx with the new drug should be reviewed from the same perspective as if a new IVD-CDx were being developed. The specific aspects related to clinical performance and clinical performance studies as described in Section 7 should be reviewed. This part of the submission dossier will be reviewed by the RA or CAB responsible for the IVD medical device approval.