MDS – G26

Guidance on Companion Diagnostic IVDs

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Introduction

Purpose

The purpose of this document is to provide clarification on Companion Diagnostic (CDx) IVDs, specifically the requirements for development, conducting clinical studies, and obtaining Medical Devices Marketing Authorization (MDMA).

Scope

This document applies to:

- Local CDx manufacturers or Authorized Representative for overseas manufacturer who intend to perform clinical performance studies or to obtain MDM
- Establishments developing in-house CDx IVD assays**.**

Background

SFDA has issued this document in accordance to the following:

- Articles 7 and 8 of "Medical Devices Law" issued by the Royal Decree No. (M/54) dated 6/7/1442 AH.
- Requirements for Medical Device Marketing Authorization (MDS–REQ1).
- Requirements for Clinical Trials of Medical Devices (MDS–REQ2).
- Requirements for Post-Market Surveillance of Medical Devices (MDS–REQ11).
- Guidance on Innovative Medical Devices (MDS–G2).
- Guidance on the Development of IVDs for in-House Use (MDS–G22).
- Guidance on MDMA – Significant and Non-Significant Changes (MDS–G12).

What is a CDx IVD?

MDS–REQ1 defines a CDx as "a device which is essential for the safe and effective use of a corresponding medicinal product to:

- identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or
- 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 medicinal product."

Specific examples of CDx and IVDs that are not CDx are given in Annex (1).

The characteristics that define a CDx are:

- it is an IVD medical device or an in-house IVD medical device
- it is intended by its manufacturer to be used for the examination of a specimen from the body of an individual only when used:
  - to identify whether the individual would be likely to benefit from the use of a particular medicinal product; or
  - to identify whether an individual is likely to be at particular risk of a serious adverse reaction to the use of a particular medicinal product; and that is mentioned in the product information for the medicinal product as being essential for the safe and effective use of the corresponding medicinal product;
- that is not intended by the manufacturer to be used for the examination of the specimen merely to determine whether the medicinal product is compatible with the individual (where the medicinal product comprises blood, a blood component, cells, tissue or an organ from a donor other than the individual).

Annex (1) provides a flowchart to help manufacturers to determine whether an IVD is a Companion Diagnostics.

Following the classification rules stipulated in MDS-REQ1, Annex (5), 2.3, all CDx are classified as class C IVD under Rule 3 (f).

Development of CDx

Co-development: Ideally, the development of a new CDx is conducted at the same time as the development of the new medicinal product (a therapeutic product such as a medicine or biological drug) that the CDx is tied to. In the following, this approach is referred to as co-development. Under co-development, the clinical trials for the medicinal product are linked with the clinical performance studies for the CDx IVD and the development of the CDx is likely to be determined by the speed of drug development. The CDx manufacturer and the medicinal product manufacturer have to share information with each other to prepare the clinical trials (including the study protocols) for the IVD and the medicinal product and to obtain simultaneous marketing authorization.

Development of a CDx that is paired during the development of the medicinal product: Co-development of the CDx and the medicinal product may not always be feasible, e.g.:

- a new medicinal product is developed, and the CDx has already obtained MDMA for a different intended purpose;
- if during the development of a new medicinal product a major change in the development of the CDx occurred, such as a change of the analyte/biomarker, the test technology and/or the manufacturer of the Companion Diagnostic;
- development of a new CDx IVD for a medicinal product that has already obtained MDMA.

Under these circumstances, the clinical trials for the medicinal product and the CDx likely cannot be conducted simultaneously and it may not be possible to obtain simultaneous MDMA.

Follow-on CDx: A special case is the development of a new CDx that is targeting the same analyte/biomarker and the same medicinal product as a CDx that has already obtained MDMA. In this case, the clinical performance study for the CDx IVD will be performed after the clinical trials for MDMA of the medicinal product and may rely on comparison with the existing CDx.

MDMA Pathway for CDx IVDs

CDx IVDs are a subset of IVDs and therefore have to follow the general requirements for MDMA as stipulated in MDS-REQ1, including compliance with the Essential Principles of Safety and Performance for In-Vitro Medical Devices (Annex 2), the requirements for IVD Technical Documentation (Annex 4),and for Performance Evaluation, Performance Studies and Post-Market Performance Follow-up (Annex 7).

During the review of the application for MDMA, the SFDA Medical Devices sector will consult the SFDA sector for drugs who is responsible for review of the corresponding medicinal product.

MDMA of a new medicinal product that requires a CDx falls under the responsibility of the SFDA Drug sector and has to follow the requirements stipulated in "Regulatory Framework for Drugs Approval (DS-G-001). During the assessment of the application for MDMA, the SFDA Drug sector will consult the SFDA Medical Devices sector to ensure alignment with the review and MDMA of the corresponding CDx IVD.

Novel CDx IVDs may benefit from the dedicated pathway for Innovative Medical Devices as specified in MDS-G2.

For simultaneous submission of an application for MDMA for a CDx and an application for MDMA of the corresponding medicinal product, the medicinal product manufacturer and the CDx manufacturer are encouraged to consult with the relevant departments of the SFDA in the early development phase.

For simultaneous obtaining of MDMA of the CDx and the corresponding medicinal product, the medicinal product manufacturer and the CDx manufacturer are encouraged to consult with the relevant departments of the SFDA already in the early development phase.

Different Ways for Placing a CDx IVD on the Market or Putting into Service

Next to CDx offered as a distributed kit of reagents or distributed device, CDx can also be offered as a Laboratory Developed Test (LDT). LDTs or in-house tests are often used as CDx for targeted drug therapies and are tests that are developed and executed within a single laboratory or healthcare institution.

If the in-house test is developed and executed by a manufacturer within the KSA, the establishment shall obtain an establishment license from SFDA and meet the requirements specified in "Requirements for Medical Devices Establishments Licensing (MDS-REQ9)". MDMA can be obtained under the Points of Care (POC) Medical Devices Manufacturing scheme, according to the requirements defined in "Guidance for Points of Care (POC) Medical Devices Manufacturing (MDS-G9)" and "Guidance on the development of IVDs for in-house use (MDS-G22)".

LDTs or in-house tests performed outside of the KSA (by either a private laboratory or a healthcare institution) do not qualify as POC Medical Devices Manufacturing and shall follow the general process for MDMA.

Clinical Performance Studies of a CDx within a Medicinal Product Clinical Trial

For CDx: Clinical performance studies for CDx shall be performed according to the requirements defined in Annex (7) "Performance Evaluation, Performance Studies and Post-Market Performance Follow-up" of MDS-REQ 1 and if studies are conducted in the KSA shall comply with "Requirements for Clinical Trials of Medical Devices (MDS-REQ2)" and obtain study approval from the SFDA medical device sector.

For example, clinical trials shall comply with:

- The Implementing Regulations of the Law of Ethics of Research on Living Creatures;
- The Declaration of Helsinki;
- The standard of good study practice for clinical performance studies of in vitro diagnostics medical devices (ISO 20916) or any other similar standard.

As described above, the clinical performance study for a CDx may be linked with a clinical trial for a new medicinal product. If the study is conducted in the KSA, the clinical trial for the medicinal product shall comply with the requirements stated in "Regulations and Requirements for Conducting Clinical Trials on Drugs (DS-G-014)" and obtain study approval from the SFDA drug sector. At the same time, a separate study approval shall be obtained for the CDx clinical performance study from the SFDA medical devices sector. Both sectors will coordinate to ensure parallel review and approval of the linked studies.

For medicinal product part : In case of a clinical trial for a new medicinal product with a linked CDx is conducted in the KSA but the clinical performance study for the CDx with testing of patient samples from the KSA is conducted in a centralized laboratory outside of the KSA, the study protocol for the clinical performance study still shall be submitted to the SFDA medical device sector for review and approval.

Refer to Annex (2) of MDS–REQ2 for additional considerations for use of CDx and other IVDs in a medicinal product clinical trial.

Analytical and Clinical Performance Expectations

CDx shall meet the requirements for analytical and clinical performance set in Annex (2) of MDS–REQ1, "Essential Principles of Safety and Performance for In-Vitro Medical Devices, 9.1 Performance characteristics".

Refer to MDS-G22 for detailed guidance on the requirements for evaluation of analytical and clinical performance.

Clinical evidence for CDx consists of scientific validity, analytical performance and clinical performance. The clinical evidence shall support the intended use of the Companion Diagnostic, including all intended specimen types, the intended user and use environment and the intended population. For CDx that are used in combination with other devices (e.g. instruments, reagents for nucleic acid extraction, software for interpretation of PCR curves) performance shall be established in combination with these other devices. For CDx that include multiple biomarker tests, analytical performance should be established for each biomarker.

For a novel CDx using a new biomarker, it may not be possible to establish scientific validity (the association of the analyte with the clinical condition) based on peer-reviewed scientific literature. Instead, the manufacturer may rely on feasibility studies or conduct a clinical performance study to establish the scientific validity of the new marker. For novel Companion Diagnostic, data from a clinical performance study shall be submitted to establish the clinical performance of the new Companion Diagnostic. Before starting the clinical performance study, analytical performance and scientific validity should already be established. The study design will evaluate the performance of the CDx in comparison with the response of the patients to the new medicinal product.

A follow-on CDx refers to a new CDx test targeting the same analyte/biomarker and medicinal product as an already authorized CDx with MDMA, scientific validity may be established based on peer-reviewed scientific literature describing the original CDx test. Analytical performance shall be established for the new CDx test, including establishing the cut-offs of the follow-on product. Clinical performance studies shall be conducted for CDx and may rely on comparison of the new CDx with the existing CDx as comparator. Preferably, the comparison between the new and the existing CDx test should be assessed with the same specimens collected from subjects who participated in a clinical trial for the related medicinal product. However, if this is not feasible, the comparison study should be conducted based on comparison of specimens collected from a new subject group based on equivalent subject selection criteria to the original clinical trial for the medicinal product.

Labelling of CDx and the related Medicinal Product

The intended purpose and the IFUs of a CDx shall state the function of the device as companion diagnostic, the International Non-proprietary Name (INN) of the associated medicinal product for which it is a CDx test and the intended target population (see MDS-REQ1 Annex (2) 20.4.1.C) and Annex (4) 1.c)). The CDx manufacturer may also choose to include the brand name of the approved medicinal product in the Instructions for Use. This approach is illustrated by the following examples:

- PD-L1 expression in tumor cell (TC) membrane as detected by [IVD name] in NSCLC is indicated as an aid in identifying patients for treatment with KEYTRUDA® (pembrolizumab).
- The primary use of the [IVD name] test is the detection of the BRAF V600 mutations in DNA extracted from formalin-fixed, paraffin-embedded human melanoma and papillary thyroid carcinoma (PTC) tissue. In melanoma, it is intended to be used as an aid in selecting patients whose tumors carry BRAF V600 mutations, for treatment either with ZELBORAF® (vemurafenib) alone, or for treatment with COTELLIC® (cobimetinib) in combination with ZELBORAF® (vemurafenib).

The IFUs of the associated medicinal product shall state the CDx as being essential for the safe and effective use of that particular medicinal product. It is expected that the product information of the medicinal product will generally include generic references to CDx IVDs that are approved for that purpose rather than a specific manufacturer's IVD. This approach is illustrated by the following examples:

- KEYTRUDA® (pembrolizumab) is indicated as monotherapy for the first-line treatment of patients with NSCLC expressing PD-L1 [tumor proportion score (TPS) ≥1 %] as determined by a validated test, with no EGFR or ALK genomic tumor aberrations.
- Zelboraf is indicated for the treatment of unresectable stage IIIC or stage IV metastatic melanoma positive for a BRAF V600 mutation. Before taking Zelboraf, patients shall have BRAF V600 mutation-positive tumor status confirmed by a SFDA approved assay performed by an accredited laboratory.

Post Market Surveillance and Vigilance

CDx IVDs shall comply with the general requirements for post-market surveillance of medical devices stipulated in “Requirements for Post-Market Surveillance of Medical Devices (MDS-REQ11)”, including investigating and reporting complaints and adverse events to the NCMDR.

CDx IVDs that are used in clinical studies shall comply with the requirements for reporting and investigating serious adverse events or device deficiencies stipulated in “Requirements for Clinical Trials of Medical Devices (MDS-REQ2)”.

Due to the relationship between the CDx product and the related medicinal product the CDx IVD manufacturer and the medicinal product manufacturer should also notify each other in case of serious adverse events and in case of events that could have led to a serious adverse event.

As part of the investigation of complaints, adverse events and device deficiencies, the CDx manufacturer should evaluate if the complaint or adverse event is related to the CDx product (device related) or to the associated medicinal product (drug related). This evaluation shall be documented, including justification, and could be based on the methodology for adverse event categorization described in ISO 20916:2024, Annex G.

Changes to CDx after MDMA

Changes made to CDx after MDMA shall be reported and notified to the SFDA according to the requirements specified in "Guidance on MDMA – Significant and Non-Significant Changes (MDS-G12)".

The following examples represent significant changes that may occur due to the specific nature of CDx with guidance on the required additional clinical evidence:

- Change from centralized testing to a distributed reagent kit

  The evaluation of this change requires establishing analytical performance for the distributed kit, including confirming the cut-offs. A clinical performance study is needed to compare the performance of the distributed kit to the performance of the centralized test as comparator, with a similar study design as for a follow-on Companion Diagnostics. Refer to Annex (2) for the considerations for the study design of such a bridging study. In addition, due to the different use conditions, stability and shipment studies will be required.

- Addition of new specimen types to the intended use, e.g. the addition of liquid biopsy samples to a test with MDMA for tissue samples

  If a new specimen type is added to the intended use of a Companion Diagnostic, next to concordance between the two specimen types the accuracy of predicting drug response for the new specimen type is required. This evaluation may be performed retrospectively, i.e., subjects are selected for medicinal product prescription based on the test results of the existing specimen type, and samples from the new specimen type collected prior to administration of the medicinal product are tested to confirm response to the medicinal product. The considerations for the study design are similar to the consideration for a bridging study (refer to Annex (2) for details).

- Addition of a new medicinal product to the intended use of a Companion Diagnostic

  The intended use of a CDx could be expanded to include a new medicinal product without any change to the CDx IVD itself. In this case, the clinical performance of the CDx for the new medicinal product has to be established, similar as for the development of a new Companion Diagnostic.

- Addition of a generic drug to the intended use of a Companion Diagnostic

  If a new medicinal product with the same active ingredient, i.e. a generic drug, is added to the intended use of a CDx there will be no change to the INN. If the equivalence of the generic drug with the existing medicinal product has been established and the generic drug has obtained MDMA, this change is not considered a significant change to the CDx IVD.

Annexes

Annex (1): Determining whether an IVD is a Companion Diagnostics

The flowchart below is intended to help manufacturers to determine whether an IVD is a CDx; this should be followed for each intended purpose of the device.

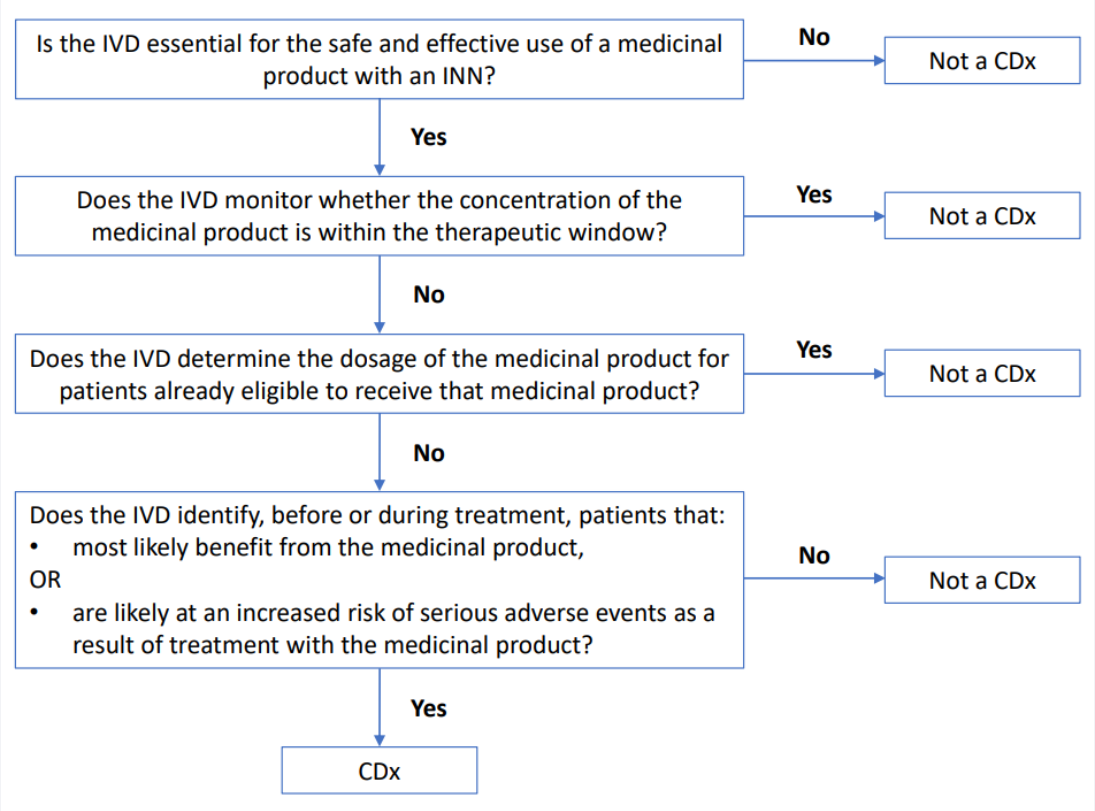

Figure 1: Decision tree to determine if an IVD is a Companion Diagnostic

For illustration, five examples of specific CDx are given below:

- A device intended for the qualitative detection of anaplastic lymphoma kinase (ALK) protein in formalin-fixed, paraffin-embedded (FFPE) non-small cell lung carcinoma (NSCLC) tissue, intended as an aid in identifying patients eligible for treatment with crizotinib or ceritinib.
- A device intended for the quantitative detection of BCR-ABL1 transcripts and the ABL1 endogenous control mRNA in peripheral blood specimens from patients previously diagnosed with t(9:22) positive chronic myeloid leukemia, during treatment with nilotinib.
- A qualitative immunohistochemical device using monoclonal mouse Anti-PD-L1, intended for use in the detection of PD-L1 protein in FFPE NSCLC and gastric or gastroesophageal junction (GEJ) adenocarcinoma tissues, that is indicated as an aid in identifying patients for treatment with pembrolizumab.
- A device intended for the demonstration of individuals homozygous for the non-functional DPYD variant DPYD*2A, that typically have complete dihydropyrimidine dehydrogenase (DPD) deficiency. The DPYD gene encodes DPD, an enzyme that catalyzes the rate-limiting step in fluorouracil metabolism. Capecitabine, a

chemotherapy agent used in the treatment of colon cancer, metastatic colorectal cancer, and metastatic breast cancer, is a prodrug that is enzymatically converted to its active form, fluorouracil. Individuals who are carriers of non-functional DPYD variants, may not be able to metabolise capecitabine at normal rates, and are at risk of potentially life-threatening capecitabine toxicity, such as bone marrow suppression and neurotoxicity.

- A next-generation sequencing (NGS) based device to evaluate KRAS/NRAS genetic variants to determine the presence of mutations affecting the efficacy of vectibix for treatment of metastatic colorectal cancer.

While the majority of CDx are related to cancer therapies, there are also examples of CDx in other disease areas, e.g. a device that is intended to detect antibodies against a viral vector that is employed to deliver gene therapy in patients with severe hemophilia A.

There are many IVDs that share some of the characteristics of a CDx and might seem to be included under that definition. However, that is not the intention of the regulatory framework and it is important that those IVDs are not confused with companion diagnostics. For an IVD to be regulated as a CDx it shall meet all of the criteria set out in the regulatory definition of IVD companion diagnostic.

Some examples of IVDs that are not CDx are considered below.

- Complementary diagnostics: Based on the definition used by the FDA, complementary diagnostics are diagnostic procedures that are recommended for the safe and effective use of a medicinal product but are not mandatory for use.

  Note that complementary diagnostics are not defined under the SFDA regulation.

  An example of a complementary diagnostic device is as follows:

  - A device for detection of PD-L1 expression in tumor cell (TC) membrane in NSCLC that may be associated with enhanced survival from nivolumab.

- Compatibility tests for blood products, tissues or organs: Compatibility tests to determine which blood, tissue or organ products can be safely transfused or transplanted to a patient have a long history of use in clinical and laboratory practice. Due to the high personal risk arising from transfusion or transplantation of incompatible products, these IVDs are classified as Class D IVDs and subject to the highest standards of regulatory evaluation and are specifically excluded in the definition of Companion Diagnostics.

- Drug monitoring tests: IVDs that are intended to be used for monitoring treatment with a medicinal product (e.g. an antibiotic or anti-epileptic) in order to ensure that the concentration of relevant the substance in the human body is within the therapeutic window are not considered to be companion diagnostics.

- Diagnostic tests: IVDs are used in the diagnosis of many diseases, conditions or ailments. Therapies are frequently initiated as a result of these diagnoses. These

diagnostic tests are not IVD CDx where they apply to all patients or a sub-population of patients unless the test is specified in the product information or IFU of a medicinal product as being essential for the safe and effective use of that medicinal product.

Annex (2): Considerations for Use of CDx and Other IVDs in a Medicinal Product Clinical Trial

The use of CDx and IVDs in a clinical trial for a medicinal product can have various purposes with a different risk profile. The list below provides an assessment of the study design, risk for the patient and requirements for study approval.

1. Use of a CDx / IVD for patient inclusion / exclusion

   Interventional study design, an incorrect test result may result in an incorrect therapy decision, requires study approval for the medicinal product and as Clinical Performance Study.

2. Use of a CDx / IVD for guiding therapy selection / patient management

   Interventional study design, an incorrect test result may result in incorrect patient management, requires study approval for the medicinal product and as Clinical Performance Study.

3. Use of a CDx / IVD for patient stratification

   Interventional study design for medicinal product, CDx / IVD test results are not used to guide therapy decisions, an incorrect test result does not have a direct risk for the patient. Requires study approval for the medicinal product only, unless the sample collection for the CDx / IVD poses additional risk to the study participants.

4. Use of a CDx / IVD for that has already obtained marketing authorization

   a) within its intended use

      No additional risks to the patient. Requires study approval for the medicinal product only.

   b) outside its intended use

      A CDx / IVD used outside its intended use is considered a new device, requires study approval for the medicinal product and as Clinical Performance Study.

5. Use of a CDx / IVD to evaluate exploratory end points

   No direct risk to the patient. Requires study approval for the medicinal product only, unless the sample collection for the CDx / IVD poses additional risks to the study participants.

These considerations and requirements are also applicable to CDx and IVDs that are Clinical Trial Assays (CTA). A CTA is an investigational use only assay that is used in a medicinal product trial for diagnostic purposes but is not intended to be fully developed into a companion diagnostic.

Figure 2 illustrates two different study designs for the use of a CTA in a medicinal product trial. If the CTA is used for patient selection or allocation of patients to a specific treatment, the CTA has a medical purpose and the study requires approval as Clinical Performance Study (A)). If the CTA is used for patient stratification, meaning that the test result is not used for treatment allocation but only to ensure that patients that test positive / negative for the CTA are evenly spread across the treatment arms (B)). In this case the CTA is not used for a medical purpose

and does not require approval as Clinical Performance Study, unless the sample collection poses additional risks to the patients.

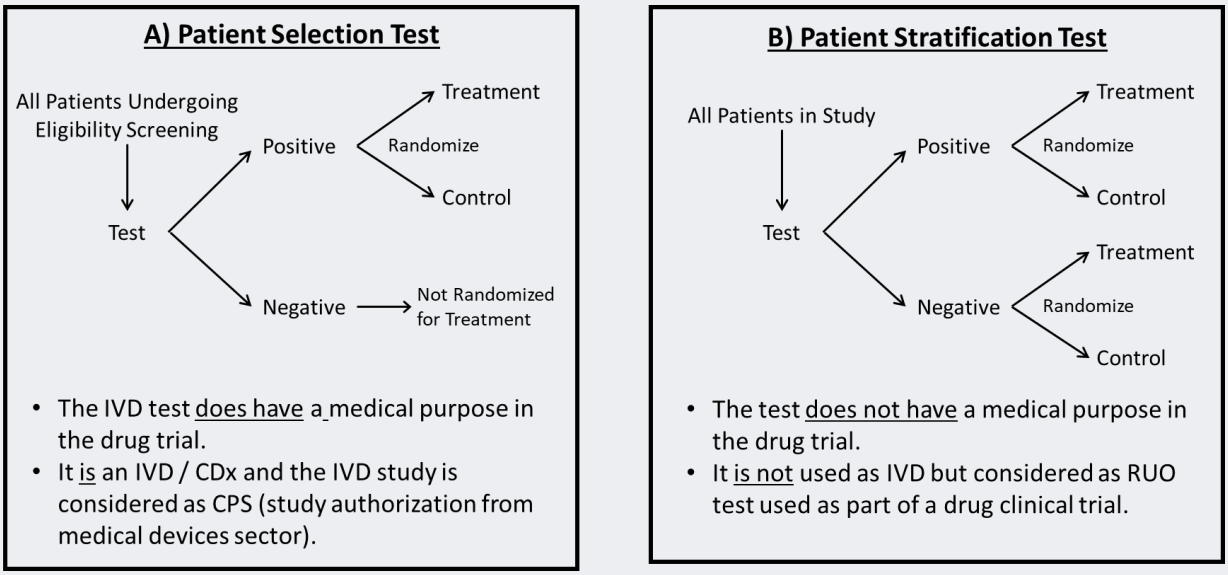

Figure 2: Clinical trial design - CTA use for patient selection (A)) versus CTA use for patient stratification (B)).

If the CTA is later converted to a CDx assay or reagent kit for commercialization, a bridging study between the CTA and the final CDx product will be needed. The development, performance evaluation and marketing authorization of this CDx product could be initiated by either the CTA manufacturer, the medicinal product company or another IVD manufacturer (in cooperation with the medicinal product manufacturer).

The bridging study shall demonstrate concordance (agreement) between the final CDx and the CTA used in the pivotal clinical trial for the medicinal product. Preferably, the bridging study should use the original clinical trial samples. The statistical analysis plan should consider differences between the two tests that can lead to discordant results and the impact of missing samples/test data.

Annex (3): Definitions & Abbreviations

KSA	Kingdom of Saudi Arabia
SFDA	Saudi Food and Drug Authority
Analytical Performance	The ability of a device to correctly detect or measure a particular analyte.
Biological (Drug)	A substance that is made from a living organism or its products and is used in the prevention, diagnosis, or treatment of cancer and other diseases. Biological drugs include antibodies, interleukins, and vaccines. Also called biologic agent and biological agent.
Clinical performance	The ability of a device, resulting from any direct or indirect medical effects which stem from its technical or functional characteristics, including diagnostic characteristics, to achieve its intended purpose as claimed by the manufacturer, thereby leading to a clinical benefit for patients, when used as intended by the manufacturer.
Companion Diagnostic (CDx)	A device which is essential for the safe and effective use of a corresponding medicinal product to: a) identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal 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 medicinal product.
Complementary Diagnostic	A diagnostic procedure that is recommended for the safe and effective use of a medicinal product, but is not mandatory for use of the medicinal product.
CPS	Clinical Performance Study
Clinical Trial Assay(CTA)	An investigational use only assay (test) that is used during (drug) clinical trials but not intended to be commercialized. Typically, a predictive biomarker assay that is either a prototype form of a planned IVD kit, or a laboratory-developed test.
IFU	Instructions for Use
INN	International Non-proprietary Name, an official generic and nonproprietary name given to a pharmaceutical substance or an active ingredient.
IVD	In vitro diagnostic medical device
LDT	Laboratory developed test, also called in-house developed test
MDMA	Medical Devices Marketing Authorization
Medicinal Product	Also called drug, therapeutic product or pharmaceutical substance. May refer to small molecule compounds, biological drugs and other active ingredients used for pharmacological therapy.
POC	Point of care

Research Use Only (RUO)	A device for research purposes that does not have an IVD intended use
Scientific Validity	The association of an analyte or marker with the clinical condition