|  |
| --- |
| IVD companion diagnostics (CDx) |
| Guidance on Australian regulatory requirements |
| Version 1.3, March 2024 |

Copyright

© Commonwealth of Australia 2024  
This work is copyright. You may reproduce the whole or part of this work in unaltered form for your own personal use or, if you are part of an organisation, for internal use within your organisation, but only if you or your organisation do not use the reproduction for any commercial purpose and retain this copyright notice and all disclaimer notices as part of that reproduction. Apart from rights to use as permitted by the *Copyright Act 1968* or allowed by this copyright notice, all other rights are reserved and you are not allowed to reproduce the whole or any part of this work in any way (electronic or otherwise) without first being given specific written permission from the Commonwealth to do so. Requests and inquiries concerning reproduction and rights are to be sent to the TGA Copyright Officer, Therapeutic Goods Administration, PO Box 100, Woden ACT 2606 or emailed to <[tga.copyright@tga.gov.au](mailto:tga.copyright@tga.gov.au)>.

**Table of Contents**

[IVD companion diagnostics (CDx) 1](#_Toc158650251)

[What are IVD companion diagnostics (CDx)? 4](#_Toc158650252)

[Which medicine or biological indications require CDx testing? 4](#_Toc158650253)

[How will CDx be regulated? 6](#_Toc158650254)

[Classification 6](#_Toc158650255)

[Use of a Unique Product Identifier (UPI) and separate applications for inclusion 6](#_Toc158650256)

[Applications for inclusion in the ARTG 6](#_Toc158650257)

[Mandatory application audit 6](#_Toc158650258)

[Concurrent submission for CDx and the corresponding medicine or biological 6](#_Toc158650259)

[Abridged evaluations and overseas evidence 7](#_Toc158650260)

[TGA CDx list 7](#_Toc158650261)

[What do medicine/biological sponsors need to do? 7](#_Toc158650262)

[Companion testing plan 8](#_Toc158650263)

[Post-approval actions 9](#_Toc158650264)

[Product Information (PI) 10](#_Toc158650265)

[What do device sponsors need to do? 10](#_Toc158650266)

[Instructions for use (IFU) 11](#_Toc158650267)

[Transitional arrangements 11](#_Toc158650268)

[Clinical performance requirements 12](#_Toc158650269)

[Clinical utility for subsequent CDx 13](#_Toc158650270)

[Analytical performance requirements 13](#_Toc158650271)

[Case studies 14](#_Toc158650272)

[Changes to CDx included in the ARTG 16](#_Toc158650273)

[In-house CDx IVDs 16](#_Toc158650274)

[Classification 16](#_Toc158650275)

[Notification to the TGA 16](#_Toc158650276)

[Evaluation of in-house CDx IVDs 17](#_Toc158650277)

[Clinical evidence 17](#_Toc158650278)

[Glossary and abbreviations 17](#_Toc158650279)

[Version history 19](#_Toc158650280)

## What are IVD companion diagnostics (CDx)?

An IVD companion diagnostic (CDx) is an [in vitro diagnostic (IVD) medical device](https://www.tga.gov.au/resources/resource/guidance/ivd-medical-devices-definitions-links) which provides information that is essential for the safe and effective use of a corresponding medicine or biological.[[1]](#footnote-2)

The term ‘*IVD companion diagnostic’* has been defined in the [*Therapeutic Goods (Medical Devices) Regulations 2002*](https://www.legislation.gov.au/Series/F2002B00237) (the Medical Devices Regulations) as:

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

## Which medicine or biological indications require CDx testing?

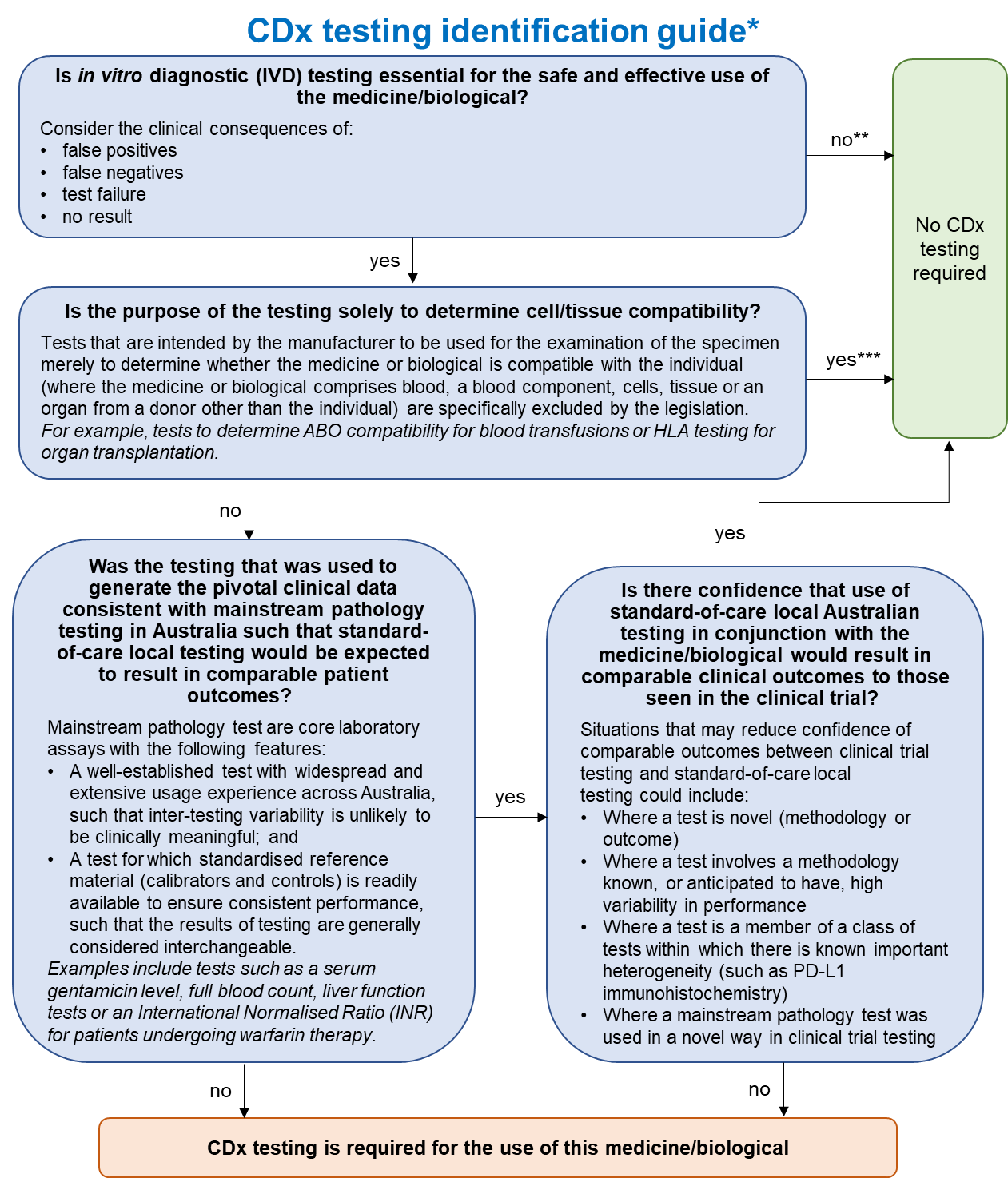
For every clinical indication of medicine, where IVD testing is essential for safe and effective use of that medicine, there are multiple factors that may determine the level of regulatory oversight of these devices.

Consistent with the regulatory definition, a CDx is an IVD that is essential for the safe and effective use of a corresponding medicine or biological, where both:

* the Product Information (PI) for the medicine (or Instructions for Use [IFU] for the biological) states that CDx testing is essential for the relevant use of the medicine or biological to be safe and effective, and
* the IVD claims that it is intended for the relevant use of the medicine or biological.

As the wording of the medicine or biological PI and the IFU are determined during the medicine registration process, the TGA has developed the CDx testing identification guide in [Figure 1](#Figure). The CDx testing identification guide helps to identify whether a proposed medicine or biological indication requires CDx testing, independently of PI or IFU wording. The intention of the identification guide is to assist in identifying tests that require inclusion in the Australian Register of Therapeutic Goods (ARTG) under the CDx framework for supply in Australia. This is to ensure the analytical and clinical performance of devices that are intended to conduct such testing are appropriate for use in conjunction with that medicine or biological.

**Figure 1. CDx testing identification guide**



\*Any queries that arise from the use of this identification guide, please contact TGA.

\*\*Examples of IVDs that are not captured under our definition of CDx include those consistent with FDA’s consideration of complementary diagnostics

\*\*\*Compatibility tests to determine which blood, blood components, blood products, cells, tissues or organs 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, the IVDs used in this testing are classified as Class 4 IVDs and subject to the highest standards of regulatory evaluation. Therefore, they are specifically excluded from the regulatory framework for CDx.

Note: CDx testing may be required for some therapeutic drug monitoring devices, not all. This will be determined during the application for the medicine.

## How are CDx regulated?

### Classification

In accordance with the classification rules set out in Schedule 2A of the Medical Devices Regulations, all CDx are class 3 IVDs or class 3 in-house IVDs.

### Use of a Unique Product Identifier (UPI) and separate applications for inclusion

The new CDx regulations were introduced on 1 February 2020. Under the CDx regulatory framework, new applications for inclusion of an IVD CDx in the Australian Register for Therapeutic Goods (ARTG) will be subject to an amendment as per Regulation 1.6, and will require a UPI, which is unique to the CDx device and is given by the manufacturer of the device. This means that a separate application for inclusion will be required for each CDx. In the ARTG inclusion form, you will be asked to identify if the application is for a CDx. If so, the UPI and a functional description for the device will need to be entered in the form. The UPI is the combination of words, numbers, symbols, or letters assigned by the manufacturer to uniquely identify an individual IVD (i.e. the device name).

### Applications for inclusion in the ARTG

Applications for inclusion of CDx in the ARTG must comply with the new Regulations. IVDs that were included in the ARTG prior to 1 February 2020 (including those covered under devices of kind) are subject to the [transitional arrangements](https://www.legislation.gov.au/Details/F2022L01300) and sponsors have until 26 May 2026 to submit a new application for inclusion for any devices that fit the definition of CDx.

### Mandatory application audit

Applications for inclusion of a CDx in the ARTG will be subject to a mandatory application audit under subparagraph 5.3(1)(j)(x) of the Medical Device Regulations, unless supported by a conformity assessment document issued by a notified body under the [European IVD Regulations (2017/746)](https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32017R0746) or by the TGA.

The TGA, on receipt of the application, will request the sponsor to submit the information required to conduct the application audit. Sponsors are expected to demonstrate conformity to the [Essential Principles](https://www.tga.gov.au/resources/resource/forms/essential-principles-checklist-medical-devices) of safety and performance through the preparation and submission of a technical file that shows how the IVD was designed, developed, and manufactured. Further details of the technical file required for an application audit can be found in [Application audit (technical file review) of IVD medical device applications](https://www.tga.gov.au/sites/default/files/ivd-application-audit.pdf).

### Concurrent submission for CDx and the corresponding medicine or biological

IVDs are often developed by different organisations to those involved in the development of medicines or biologicals.

Ideally, a CDx should be developed and an application for inclusion in the ARTG submitted to the TGA for each corresponding indication for use of a medicine or biological that requires CDx testing. However, this may not necessarily be possible within the same timeframe (or ever, if CDx testing is performed overseas). CDx testing may also rely on the use of [in-house CDx](#_In-house_IVDs_that) IVDs. All these factors may make it difficult to submit concurrent applications for a CDx and the relevant indication for use of a corresponding medicine or biological. Therefore, whilst it is strongly encouraged, concurrent submission and assessment of these applications is not mandated under the Australian legislation.

However, a device CDx application is predicated on the existence of the corresponding medicine or biological indication for use. A submission for ARTG inclusion of an IVD with an IFU that makes CDx claims cannot be made unless the relevant indication for use of a corresponding medicine or biological is approved or is under concurrent review by the TGA.

### Abridged evaluations and overseas evidence

The TGA will accept certification from a range of comparable overseas regulators and assessment bodies as evidence of compliance with the conformity assessment procedures. The [guidance on use of market authorisation evidence from comparable overseas regulators](https://www.tga.gov.au/resources/resource/guidance/use-market-authorisation-evidence-comparable-overseas-regulators-assessment-bodies-medical-devices-including-ivds) summarises the specific overseas assessments and approvals that can be used by applicants for supporting the basis for a possible abridged assessment of an application for a TGA conformity assessment certificate. The comparable overseas assessment and approvals can also serve as documentation for abridged assessment for applications for inclusion of CDx in the ARTG or for IVD assessment under the medicine application that requires companion testing.

Sponsors can request a [reduction in the audit assessment fee](https://www.tga.gov.au/how-we-regulate/manufacturing/medical-devices/conformity-assessment/conformity-assessment-bodies/tga-conformity-assessment-certification/reduction-assessment-fees-medical-devices) for medical device application, if they believe an abridged assessment is supported by the manufacturer’s evidence provided.

CDx are subject to additional requirements for assessment of technical documentation under the [EU IVD Regulation (IVDR) (2017/746](https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32017R0746))Annex IX (Full QMS) Section 5.2 and Annex X (Type Examination) section 3(k). Similarly, the FDA generally requires a full Premarket Assessment (PMA) for CDx. Therefore, sponsors can request TGA to consider abridgement of an application audit by providing overseas evidence that includes the overseas technical assessment report that complies with the requirements for CDx. This is also applicable for assessment of companion testing, as part of the medicine application.

### TGA CDx list

The [TGA CDx list](https://www.tga.gov.au/products/medical-devices/specific-types-medical-devices/tga-companion-diagnostics-cdx-list) is a published list of CDx that have been approved for supply in Australia under the CDx framework, along with the corresponding medicine or biological indication for which CDx testing is required. The list will initially identify commercially supplied CDx that are included in the ARTG, with plans to later include in-house CDx IVDs that have been notified to the TGA.

The list does not have formal regulatory status, but serves as a communication tool to assist clinicians, laboratories and other stakeholders who wish to know what CDx tests have been approved for supply in Australia.

The published list will include all commercially approved CDx testing, approved after introduction of the new CDx framework. However, information on medicine or biological indications that require CDx listing may not be comprehensively listed.

## What do medicine/biological sponsors need to do?

At the time of submission for a new indication for a medicine or biological (regardless of whether the active substance is new or already registered), the sponsor of the medicine or biological should use the CDx identification guide in [Figure 1](#ColumnTitle_4) to determine whether the indication requires CDx testing. If the sponsor is not sure, we recommend consultation with TGA by requesting a [pre-submission meeting](https://www.tga.gov.au/resources/resource/guidance/pre-submission-meetings-tga) with the Prescription Medicines Authorisation Branch.

For medicine or biological indications that require CDx testing, the medicine or biological submission must include:

* Data to support evaluation of the clinical and analytical performance of the IVD used in generating the pivotal data (the clinical trial assay)
* A companion testing plan

During review of a new indication that requires CDx testing, the TGA will perform a component evaluation of the clinical trial assay. Actual testing in real clinical usage may not be identical to the clinical trial testing, so the TGA CDx framework focusses on the ‘companionship’ between an indication for use of a particular medicine or biological and the core characteristics of the clinical trial testing using the clinical trial assay. The core characteristics of the clinical trial testing are those required for it to adequately guide safe and effective use of the medicine or biological. Subsequent IVDs seeking registration as a CDx for the same indication (seeking to be a subsequent CDx) would need to match these core characteristics. TGA will also review the medicine or biological sponsor’s companion testing plan.

### Companion testing plan

A companion testing plan is information provided by the sponsor of a medicine or biological product, relating to an indication that requires companion testing. The purpose of the plan is to provide reassurance that there is access to at least one adequate IVD for companion testing and ensure the Australian patients can be treated for that indication safely and effectively. All applications for registration of a new medicine or biological indication that require CDx testing must include a companion testing plan.

The plan only needs to identify one IVD that the TGA considers adequate. The companion testing plan is not meant to be a comprehensive description of all possible companion tests that are available in Australia at the time of medicine indication registration (or over subsequent time).

If the medicine sponsor is aware of a concurrent application for inclusion of a corresponding CDx in the ARTG (or notification of an in-house CDx IVD), the companion testing plan can simply consist of a cross-reference to the relevant details. Where a medicine's sponsor expects the testing to be conducted by an in-house CDx IVD, the companion testing plan could simply state this and provide information such as the name of the laboratory or laboratory network conducting the testing, the site addresses and the NATA accreditation number (if known).

The companion testing plan provides a mechanism for the TGA to evaluate the performance and validity of IVDs intended for companion testing, even when there is no concurrent application for inclusion of a CDx in the ARTG (or notification of an in-house CDx IVD). This approach recognises that there may be barriers to bringing a CDx to the Australian market for local supply, and Australian samples may have to be sent for testing internationally. While this is not preferred, the companion testing plan provides a mechanism for the TGA to appraise such testing and for a medicine or biological sponsor to take responsibility for it, until the registration or notification of a local testing option is possible.

|  |
| --- |
| **Please note:**  Sending of samples to an appropriately accredited overseas testing facility is considered acceptable by the TGA **only** if development of onshore testing with an ARTG-included or in-house (notified) CDx test is infeasible or incomplete. |

The IVD identified in the companion testing plan could be:

1. the clinical trial assay, or
2. a different IVD than the clinical trial assay (i.e., a ‘subsequent’ IVD).

If the IVD identified in the companion testing plan is the clinical trial assay, the TGA will assess the test performance during the component evaluation of the clinical trial assay. If there is no concurrent application for inclusion of a CDx in the ARTG (or notification of an in-house CDx IVD), the companion testing plan should contain the details of how the clinical trial assay is expected to be made available to Australian patients on an ongoing basis, for example, by sending samples to an appropriately accredited overseas testing facility.

If the IVD identified in the companion testing plan is a subsequent IVD, in addition to information about test availability and accreditation of destination laboratories, additional evidence is required to establish the performance and comparability of the subsequent IVD to the clinical trial assay. If there is no concurrent application for inclusion of a CDx in the ARTG (or notification of an in-house CDx IVD), the TGA will require this evidence on performance and comparability to be submitted by the medicine or biological sponsor; within the medicine application. The evidence should include:

* Device history, including any international regulatory approvals, rejections or withdrawals.
* Design and manufacturing information
* [Clinical performance](#_Clinical_performance_requirements)
* [Analytical performance](#_Analytical_performance), including validation of any controls/calibrators/reference materials or internal standards utilised.
* Risk analysis
* Stability
* Evidence of comparability to the clinical trial testing

The requirements for evidence of comparability are the same as for registration of a [subsequent CDx](#_Clinical_performance_requirements).

In lieu of a companion testing plan, a sponsor can submit a justification for why their proposed new indication does not require companion testing, and the TGA will consider the sponsor’s justification and work with the sponsor to determine whether the medicine requires companion testing. If a submission is identified where the TGA considers a proposed new medicine or biological indication does require companion testing, and a companion testing plan hasn’t been submitted, one will then be requested.

|  |
| --- |
| **Please note:**  A medicine or biological indication that requires CDx testing can be approved without a corresponding CDx test being on the ARTG (or notified to the TGA as an in-house IVD), as long as an adequate companion testing plan is in place. However, a commercial CDx must be included in the ARTG (or an in-house CDx must be notified to the TGA) before the device can be legally supplied in Australia. |

### Post-approval actions

When a medicine or biological indication that requires a CDx is approved, it will be published on the list of TGA-approved CDx. For indications where no CDx is included in the ARTG (or notified as an in-house CDx IVD), the list will reflect this, and there is scope for development of an Australian test.

For indications where no CDx is included in the ARTG (or notified as an in-house CDx IVD), a condition of medicine or biological registration, the medicine or biological sponsor must notify the TGA if there are any substantial changes to the companion testing plan. A delegate may choose not to impose such a condition if a related CDx device application is close to completion. The condition can also be removed later if a CDx is subsequently approved by the TGA (or notified to TGA, as part of the in-house IVD framework). A condition of registration can be removed without a fee.

For medicine or biological indications where a CDx is included in the ARTG (or notified as an in-house CDx IVD), conditions of registration relating to a companion testing plan are not needed.

If the TGA becomes aware that all existing (approved and notified) CDx for a given medicine or biological indication have become unavailable in Australia, the medicine or biological sponsor may be asked to provide a new companion testing plan for evaluation, and a new condition of registration regarding substantial changes to the testing plan may be added.

Data to support new or changed companion testing plans should be submitted by the medicine or biological sponsor through a [type H application, as](https://www.tga.gov.au/resources/resource/forms/prescription-medicine-registration-form) they require evaluation.

### Product Information (PI)

The Product Information (PI) for a medicine or the IFU (for a biological) will include a CDx ‘flag’ statement in line with the following for all **new** indications that require CDx testing:

*“IVD companion diagnostic (CDx) testing”*  
*“For safe and effective use of (medicine) to treat (indication), testing of (sample type) to (purpose of test) is essential. Testing used in clinical practice should be adequately comparable to the testing used in the pivotal study(ies).”*

It is recommended that the CDx flag statement be included as a subheading in section 4.4 of the PI (Special warnings and precautions for use). A single statement listing all relevant indications is preferred rather than a separate statement/new paragraph per indication.

TGA does not intend to retrospectively assess all existing medicine indications for whether or not they are indications requiring companion testing. Instead, we will do this for existing medicine indications only when we receive a relevant application from a device sponsor for a corresponding CDx device to be included in the ARTG.

The PI for medicines with existing indications that require testing that is consistent with companion testing according to the identification guide may contain other testing-related terminology (such as “validated test”). The flexibility in the legislation wording means that we can still consider those older indications to be ‘indications requiring companion testing’ without needing the new specific CDx ‘flag’ phrase to be in the PI. However, as the intention of the new flag phrase is to assist stakeholders to identify the medicine indications that correlate with registered CDx devices or notified NATA-accredited tests, we encourage sponsors of such indications to alter their PIs to add the new flag phrase. This can be done at a convenient time within an existing submission, and is encouraged but not mandated.

The CDx flag phrase for the medicine PI will not be included in the wording of the indication, to avoid implications for on-label versus off-label use based on test selection. Selection of patients that match the clinical indication description (including selection of clinical tools such as IVD diagnostic tests with which to do so) is within the remit of clinical practice. The intention of the TGA CDx framework is to provide additional information that stakeholders can use in their decision-making, including identifying where TGA has made a specific assessment of comparability between tests.

## What do device sponsors need to do?

Sponsors of a test seeking inclusion of a CDx in the ARTG must submit an IVD medical device application while the medicine or biological application is being considered, or at any time after approval of the medicine or biological. Instructions for the submission of IVD medical device applications can be found on [Medical device inclusion process](https://www.tga.gov.au/how-we-regulate/supply-therapeutic-good/supply-medical-device/medical-device-inclusion-process).

The medical device application must include data to demonstrate application of minimum applicable conformity assessment procedures and compliance with the relevant [Essential Principles](https://www.tga.gov.au/resources/resource/forms/essential-principles-checklist-medical-devices):

* Device history, including any international approvals, rejections or withdrawals.
* Design and manufacturing information
* [Instructions for use (IFU)](#_Instructions_for_use)
* [Clinical performance](#_Clinical_performance_requirements)
* [Clinical utility](#_Clinical_utility_for), if applicable
* [Analytical performance](#_Analytical_performance), including validation of any controls/calibrators/reference materials or internal standards utilised.
* Risk analysis
* Stability

The intended purpose in the application form for a CDx must exactly match the intended purpose in the IFU, as this is the source of the intended purpose for the ARTG certificate.

### Instructions for use (IFU)

The TGA uses the term ‘CDx claims’ to refer to statements about the IVD’s intended use:

* in the selection of patients for treatment with a particular medicine or biological; or
* in the monitoring of patients who are being treated with a particular medicine or biological; or
* in both selection and monitoring of treatment with a particular medicine or biological.

CDx claims in the IFU are expected to reference the International Non-proprietary Name (INN) of the corresponding medicine or biological.

IVDs that match the applicable core characteristics (of the clinical trial testing that supported registration of the relevant indication for use for the corresponding medicine or biological) will be allowed to make CDx claims in the IFU and be included in the ARTG as CDx for the relevant use of the corresponding medicine or biological. Approved CDx will be published on the [TGA CDx list](https://www.tga.gov.au/products/medical-devices/specific-types-medical-devices/tga-companion-diagnostics-cdx-list)*.*

Ambiguous claims in the IFU regarding whether a product is intended for use as a CDx are not acceptable.

**Examples of intended use statements consistent with CDx claims:**

* The primary use of the (*IVD name*) 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).
* 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 assay (*In-house IVD*) is intended to be used as a companion diagnostic to be ordered by Australian medical oncologists to identify ovarian cancer patients with homologous recombination deficiency (HRD), who may benefit from treatment with olaparib in combination with standard therapy as a maintenance therapy following first line chemotherapy.

|  |
| --- |
| **Please note:**  An IVD manufacturer cannot make CDx claims in the IFU unless the corresponding medicine or biological has been approved for the relevant use in Australia, or there are concurrent applications for approval of both the CDx and the relevant indication for use of the corresponding medicine or biological. The TGA does not require the decision dates for the two applications to align. |

### Transitional arrangements

Transitional arrangements apply to CDx that, on and after 31 January 2020:

* are included in the ARTG; or
* are the subject of an effective application for inclusion in the ARTG that has not been finally determined; or
* are not included in the ARTG but are covered by a current conformity assessment certificate issued by the TGA; or
* are not included in the ARTG but are covered by an effective application for a conformity assessment certificate that has not been finally determined; or
* are in-house IVDs that are Class 1, Class 2, or Class 3 in-house IVDs (noting that CDx will be Class 3 under the new Regulations).

A new application for inclusion that complies with the amended Regulations must be made before the transition end date of 26 May 2026, for continued supply of CDx.

### Clinical performance requirements

There are two ways that a CDx can be made available for supply in Australia:

1. Application for inclusion of the CDx in the ARTG
2. Development of an in-house CDx IVD and notification to the TGA

[Figure 2](#Fig2) describes the clinical performance requirements for an IVD that is intended to be used as a CDx, based on the way the IVD was developed with relation to the original CDx (the clinical trial assay).

**Figure 2: Clinical performance requirements in various scenarios**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Scenario | 1 | 2 | 3 | 4 |
| **Proposed CDx for inclusion in the ARTG is the original CDx (the same as the clinical trial assay)** | **Proposed CDx for inclusion in the ARTG is a subsequent IVD being developed commercially** | **Proposed CDx is a transfer of the clinical trial assay to an Australian laboratory,**  **i.e. in-house IVD** | **A laboratory seeks to develop their own in-house IVD for use as a proposed CDx** |
| Requirements | Clinical studies need to be well-designed. Aspects such as the prevalence of the target analyte, the statistical confidence and the adequate characterisation of all samples included in the study must be considered. | | | |
|  | Substantial equivalence of the subsequent IVD with the original CDx must be demonstrated. This will be contextualised by the core characteristics of the pivotal clinical trial testing, and could be based on:   * Bridging studies showing a high level of agreement in clinical performance between the clinical trial assay and the new CDx. Specimens used in bridging studies should be representative of those tested in the original pivotal clinical trials. * Re-testing the original clinical trial specimens with the new CDx to demonstrate high agreement with the original CDx results.   The TGA may consider other parameters when assessing whether there is substantial equivalence between a subsequent CDx and a clinical trial assay, such as the composition and nature of the tests. | | |
|  |  | In-house CDx IVDs must also comply with the validation requirements set out in the National Pathology Accreditation Advisory Council (NPAAC) standard. Refer to requirements for [in-house CDx](#_In-house_IVDs_that) IVDs. | |

### Clinical utility for subsequent CDx

Evidence of clinical utility must be provided for a subsequent IVD to be acceptable as a subsequent CDx. This involves a combination of clinical and analytical performance studies. The following sections regarding CDx clinical and analytical performance requirements should be read in conjunction with the guidance: [clinical evidence guidelines supplement: In vitro diagnostic (IVD) medical devices](https://www.tga.gov.au/resources/publication/publications/clinical-evidence-guidelines-supplement-vitro-diagnostic-ivd-medical-devices).

Applicants may use bridging and comparability studies to demonstrate comparability of analytical and clinical performance between the original CDx and the subsequent IVD. This would enable the pivotal studies that supported the indication approval of the original CDx to demonstrate the clinical utility data for approval of a subsequent CDx.

Alternatively, a non-inferiority clinical study with adequate statistical methodology and appropriate clinical endpoints could be performed establishing a direct link between the results of the subsequent CDx and patient outcomes for that medicine indication. The data would need to demonstrate that the clinical outcomes were not significantly different with use of the subsequent CDx to those that were obtained using the clinical trial assay in the original pivotal studies. Adequate clinical justification would be required for the statistical parameters in the study design, which should be pre-specified, including power and acceptance criteria (margins for concluding equivalence or non-inferiority).

### Analytical performance requirements

Analytical performance studies will be expected to include full validation of the following:

* Specimen stability (storage and transport)
* Specimen equivalence (for devices which intend to use more than one type of specimen)
* Sensitivity (limit of detection, limit of blank, limit of quantitation, as appropriate)
* Assay cut-off, or decision points for the assay
* Specificity (interference, cross-reactivity, inclusivity, any Hook Effect or prozoning, linearity or measuring range, precision, and accuracy)
* Quality control material (including reference materials or internal standards utilised)
* If it is a semi- or quantitative assay, calibration material must be available and expressed in acceptable or transferable units of measurement.

Full details of all studies conducted including experimental design and individual results for each individual sample utilised are required Summary details will not be accepted. For more information on the requirements of elaborated information, please refer to [depth of information to be provided](https://www.tga.gov.au/resources/resource/guidance/what-manufacturer-needs-know-about-conformity-assessment-and-declarations-conformity-ivds/depth-information-be-provided).

## Case studies

Below are four case study examples that may assist device sponsors in understanding clinical and analytical requirements when submitting a CDx application.

**Case study 1: Inclusion of IVD that has been used as the clinical trial assay for a medicine.**

|  |  |
| --- | --- |
|  | Paul is the sponsor of an IVD *‘PD-L1 Detect’* which detects Programmed Death Ligand 1 (PD-L1) in oesophageal squamous cell carcinoma to select patients for treatment with medicine *‘anticancermab*’ and intends to supply the IVD in Australia. Paul uses the [identification guide](#ColumnTitle_4) and determines *‘PD-L1 Detect’* is essential for the safe and effective use of *‘anticancermab*’, as it is not solely intended to determine cell/tissue compatibility and is not a mainstream pathology test. *‘PD-L1 Detect’* is the same clinical trial assay that was used in the pivotal clinical trial for *‘anticancermab’*. |
| Paul must apply for inclusion in the ARTG to supply *‘PD-L1 Detect’* in Australia as a CDx.  Paul is required to provide documentation to demonstrate the clinical and analytical performance of *‘PD-L1 Detect’*. Paul can leverage the clinical trial study to demonstrate clinical performance by submitting the complete clinical trial report.  To demonstrate analytical performance, Paul must also submit detailed reports of risk management analysis, stability (shelf-life, in-use, and transport), specimen stability, accuracy of measurement, analytical sensitivity, specificity (precision, cross-reactivity, and interference), range of the assay and validation of cut-off. The evidence provided must be in-line with the claims in the IFU for ‘*PD-L1 Detect*’. Refer to [clinical](#_Clinical_performance_requirements) and [analytical](#_Analytical_performance_requirements) performance requirements for additional information. | |

**Case study 2: Inclusion of a drug monitoring IVD that was not used as part of the clinical trial assay for a medicine (a subsequent IVD).**

|  |  |
| --- | --- |
|  | Shannon is a sponsor of an IVD *‘Medicinemab-ELISA’* which is used to monitor the concentration of *‘medicinemab’* in patients receiving treatment for genetic mutations that cause haemophilia A. Monitoring the levels of *‘medicinemab’* and dose adjustment is critical as too high or low concentrations in the patient can lead to complications. ‘*Medicinemab-ELISA*’ was developed as a subsequent IVD and it is intended to be used to adjust the dose of *‘medicinemab’.* Using the [identification guide](#ColumnTitle_4), Shannon has determined that *‘Medicinemab-ELISA’* is essential for the safe and effective use of *‘medicinemab’* and is not solely to determine cell/tissue compatibility and is not a mainstream pathology test. *‘Medicinemab-ELISA’* was not used in the pivotal clinical trial for the *‘medicinemab’*. |
| Shannon must apply for inclusion in the ARTG to supply *‘Medicinemab-ELISA’* in Australia as a CDx. Shannon is required to provide documentation to demonstrate the clinical and analytical performance.  To demonstrate clinical performance, Shannon must provide a bridging study to demonstrate the concordance between the *‘Medicinemab-ELISA’* and the assay used in the pivotal clinical trialfor *‘medicinemab’*. The bridging study includes the specimens used in the pivotal clinical trial re-tested with *‘Medicinemab-ELISA’* to assess percentage agreement with the clinical trial assay, including evaluation of the clinical decision points for dose adjustment. To demonstrate analytical performance, Shannon must submit detailed reports of risk management analysis, stability (shelf-life, in-use and transport), specimen stability, accuracy of measurement, analytical sensitivity, specificity (precision, cross-reactivity and interference), range of the assay and validation of cut-off. The evidence provided must be in-line with the claims in the IFU for *‘Medicinemab-ELISA’*. Refer to [clinical](#_Clinical_performance_requirements) and [analytical](#_Analytical_performance) performance requirements for additional information. | |

**Case study 3: Inclusion of a NGS panel IVD that was not used as part of the clinical trial assays for the medicines (a subsequent IVD).**

|  |  |
| --- | --- |
|  | Jenny is a sponsor of an IVD *‘NGS-Dx’* which is an NGS panel of 25 genes used to detect mutations and gene fusions in cancer-related genes. 9 out of 25 genes in the NGS panel are biomarkers which are essential for the selection of patients for use of medicines that have an approved indication in Australia requiring companion testing. ‘*NGS-Dx*’ was developed as a subsequent IVD and the device’s sponsor intends to supply *‘NGS-Dx’* in Australia*.* Using the [identification guide](#ColumnTitle_4), Jenny has determined that *‘NGS-Dx’* is essential for the safe and effective use of 9 different medicines, it is not solely to determine cell/tissue compatibility and is not a mainstream pathology test. *‘NGS-Dx’* was not used in any of the pivotal clinical trials for the 9 different medicines. |
| Jenny must apply for inclusion in the ARTG to supply *‘NGS-Dx’* in Australia as a CDx . Jenny is required to provide documentation to demonstrate the clinical and analytical performance.  To demonstrate clinical performance, Jenny must provide bridging studies to demonstrate the concordance or equivalence between the *‘NGS-Dx’* and the assays used in the pivotal clinical trialsfor the 9 medicines requiring companion testing. The comparability studies included the specimens used in the pivotal clinical trials re-tested with *‘NGS-Dx’* to assess percentage agreement with the clinical trial assays.  To demonstrate analytical performance, Jenny must submit detailed reports of risk management analysis, stability (shelf-life, in-use and transport), specimen stability and processing, accuracy of measurement, analytical sensitivity (coverage and call/detection/hit rates), specificity (inclusivity and interference), range of the assay, validation of cut-off and validation of any software/bioinformatics pipeline used to detect variant allele frequency, chimeric reads, copy number variants etc. The evidence provided must be in-line with the claims in the IFU for *‘NGS-Dx’*, i.e. a list of 9 genes with CDx claims and the corresponding medicines, and the other 16 genes that can be detected using *‘NGS-Dx’* with no CDx claims. Refer to [clinical](#_Clinical_performance_requirements) and [analytical](#_Analytical_performance) performance requirements for additional information. | |

**Case study 4: Inclusion of a medicine that does not require companion testing.**

|  |  |
| --- | --- |
|  | Chris is a sponsor of a medicine *‘antidysplasiamab’* which requires the detection of human epidermal growth factor receptor 2 (HER2) for first line use in patients with metastatic breast cancer. The clinical trial used an in-house IVD to identify HER2 (IHC 3+/ISH+) patients for treatment with *‘antidysplasiamab’*. Using the [identification guide](#ColumnTitle_4), Chris has determined that HER2testingis essential for the safe and effective use of *‘antidysplasiamab’*, it is not solely to determine cell/tissue compatibility, however, is a mainstream pathology test. |
| As part of the medicine’s application, TGA during evaluation determined that the proposed indication for *‘antidysplasiamab’* does not require companion testing. The TGA provided advice to Chris indicating that the TGA considers the identification of HER2-positive status in breast cancer was well established across pathology laboratories in Australia, and that a HER2-positive result would generally be expected to identify the same patients nation-wide, regardless of the brand of test used. No companion testing plan will be required. | |

## Changes to CDx included in the ARTG

All inclusions of CDx in the ARTG are subject to [automatic conditions which are imposed at the time a device is included in the ARTG](https://www.tga.gov.au/resources/resource/guidance/including-ivd-medical-devices-artg#automatic).

The sponsors of all CDx included in the ARTG are required to notify the TGA if they need to change any details of the device by completing the [Device Change Request](https://www.tga.gov.au/sites/default/files/2022-10/varying-entries-in-the-artg.pdf) form. Changes could include:

* A change in name (UPI) of the CDx
* A change to the intended purpose
  + Examples could include a change to the target or biomarker detected, addition of other targets or biomarkers to be detected, change in cut-off concentration or decision point for receiving the medicine/biological, expanded medicine/biological indications, addition of a new type of specimen or an addition/change to the function of the software used with the device. Please note: This list is not exhaustive but is intended to provide some examples only.
* Change to the manufacturer name or address.

Under the Medical Device Regulations, some CDx that have undergone mandatory application audit have additional conditions that apply automatically to the ARTG inclusion. Please contact [ivds@tga.com.au](mailto:ivds@tga.com.au) for further information or to seek clarity on any action required for changes to the CDx included in the ARTG.

## In-house CDx IVDs

Laboratory developed or “in-house” tests may be used as CDx. In-house IVDs that are intended for use as CDx are also subject to the regulatory changes (e.g. definition, classification rules) and a [transition period](https://www.legislation.gov.au/Details/F2022L01300) that is similar to other CDx is applicable.

### Classification

The classification rule which clarifies that all CDx are Class 3 IVDs applies equally to commercially supplied and in-house IVDs.

### Notification to the TGA

Class 1-3 in-house IVDs do not require inclusion in the ARTG, however, laboratories will need to identify their in-house CDx IVDs in the test list they provide to the TGA as part of the existing notification process.

The notification form that laboratories manufacturing in-house IVDs must complete will be amended to require them to indicate whether they have any in-house CDx IVDs. If so, laboratories will be required to specifically identify their CDx in the test list that they attach to their notification to the TGA. Guidance and updates on in-house CDx IVD notifications, and in-house IVD notifications in general, can be found at [Regulatory requirements for in-house IVDs](https://www.tga.gov.au/resources/resource/guidance/regulatory-requirements-house-ivds/what-house-ivd). This requirement will be mandatory from 27 May 2026 and the amended notification form will be available soon.

### Evaluation of in-house CDx IVDs

The conformity assessment procedures in Schedule 3, Part 6A of the Medical Devices

Regulations require laboratories who manufacture Class 1-3 in-house IVDs to be accredited by the

[National Association of Testing Authorities](https://nata.com.au/accreditation/) (NATA) as a testing laboratory and to meet the National Pathology Accreditation Advisory Council (NPAAC) standard, [*Requirements for development and use of in-house in vitro diagnostic medical devices (IVDs)*](https://www1.health.gov.au/internet/main/publishing.nsf/Content/health-npaac-dhaivd-2018) (the NPAAC standard).

Under NATA accreditation requirements, all Class 3 in-house IVDs will be evaluated for compliance with the NPAAC standard. Further consultation will be undertaken with NPAAC to determine whether there is a need to include additional information in this standard specific to the validation of in-house CDx IVDs. Under the [Memorandum of Understanding (MoU) between NATA and the TGA](https://www.tga.gov.au/resources/publication/publications/tga-nata-mou-relating-regulation-house-ivds), it is expected that NATA may request TGA’s assistance in the technical evaluation of the analytical and clinical performance of an in-house CDx IVD, due to the need to access proprietary information regarding clinical trial assay performance characteristics and its use in establishing the medicine or biological indication.

### Clinical evidence

Laboratories must comply with the validation requirements set out in the NPAAC standard and as noted above the TGA proposes to collaborate with NPAAC to ensure that the standard sufficiently addresses the clinical evidence requirements for in-house CDx IVDs.

## Glossary and abbreviations

|  |  |
| --- | --- |
| **Term** | **Description** |
| Bridging study | A study required to demonstrate equivalence to the clinical trial assay, when one or more factors relevant to clinical utility of the test varies between the clinical trial assay and the subsequent CDx. For example, a variation to the subject population or a change to the assay mechanism of the CDx. |
| CDx | In vitro diagnostic companion diagnostic. |
| Clinical trial assay (Original CDx) | The CDx assay used in the pivotal clinical trial of the associated medicine. |
| Clinical utility | The usefulness of the results obtained from testing with the IVD medical device and the value of the information to the individual being tested and/or the broader population. |
| Subsequent CDx/IVD | An IVD that is different to what was used in the clinical trial but is intended for the same medicine and indication. |
| In-house CDx | An IVD medical device that is:  (a) within the confines or scope of an Australian laboratory or Australian laboratory network:  (i) developed from first principles; or  (ii) developed or modified from a published source; or  (iii) developed or modified from any other source; or  (iv) used for a purpose, other than the intended purpose assigned by the manufacturer; and  (b) not supplied for use outside that laboratory or laboratory network.  Please refer to [guidance on in-house IVDs](https://www.tga.gov.au/resources/resource/guidance/regulatory-requirements-house-ivds). |
| Companion testing plan | A companion testing plan is information provided by the sponsor of a medicine or biological, relating to an indication that requires companion testing, that provides reassurance that Australian patients will be able to safely and effectively use the medicine as they will have access to at least one IVD that is adequate for companion testing. |

Version history

|  |  |  |  |
| --- | --- | --- | --- |
| Version | Description of change | Author | Effective date |
| V1.0 | Original publication | Medical Devices Branch | December 2019 |
| V1.1 | Reference to ‘proposed’ removed post approval of regulatory amendments | Medical Devices Branch | February 2020 |
| V1.2 | Update to reflect the extension in transition arrangements to 26 May 2026 for IVD companion diagnostics | Medical Devices Authorisation Branch | October 2022 |
| V1.3 | Updated guidance to include: Companion diagnostic identification guide, Case studies and performance requirements and further clarity on regulatory requirements | Medical Devices Authorisation Branch | March 2024 |

|  |
| --- |
| Therapeutic Goods Administration |
| PO Box 100 Woden ACT 2606 Australia  Email: [info@tga.gov.au](mailto:info@tga.gov.au) Phone: 1800 020 653 Fax: 02 6203 1605  [**https://www.tga.gov.au**](https://www.tga.gov.au) |
| Reference/Publication # |

1. See US FDA Food and Drug Administration guideline on [Companion Diagnostics](https://www.fda.gov/medical-devices/vitro-diagnostics/companion-diagnostics); and

   Clause 7 Article 2 of the EU IVDR, 2017-746 on [Companion Diagnostic](https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0746). [↑](#footnote-ref-2)