Data requirements and assessment approach – including Companion Diagnostics (CDx)

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Acknowledgement of Country

I would like to acknowledge the Traditional Owners and Custodians of the lands on which we meet today and pay my respects to Elders past and present.

I would like to extend that acknowledgement and respect to any Aboriginal and Torres Strait Islander peoples here today.

Data requirements – Companion diagnostics (CDx)

Session outline

1. Definition of companion diagnostics (CDx)
2. Regulatory requirements
3. Assessment approach and Data requirements
4. Case study – in-house CDx IVD
5. Work in progress

What is a companion diagnostic (CDx)?

An IVD companion diagnostic (CDx) is an in vitro diagnostic (IVD) medical device which provides information that is essential for the safe and effective use of a corresponding medicine or biological.

The term 'IVD companion diagnostic' has been defined in the Therapeutic Goods (Medical Devices) Regulations 2002 came into effect on 1 February 2020:

• 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

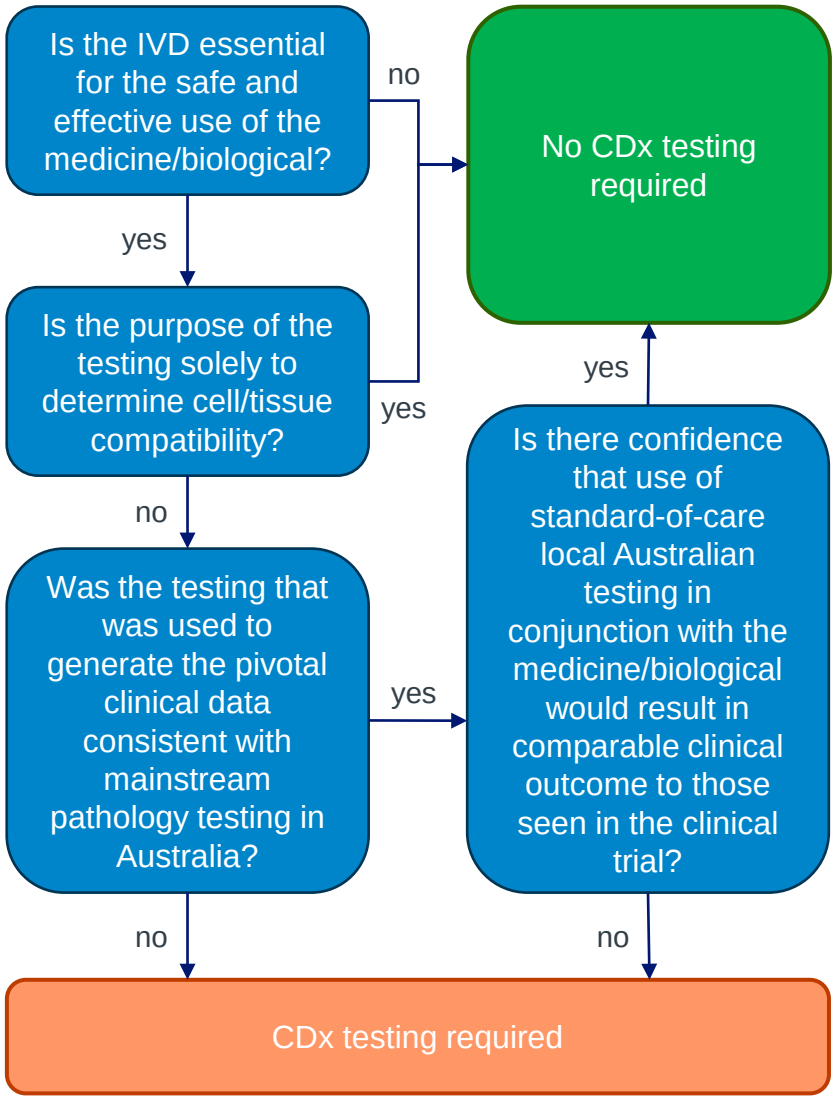
• It is not intended by the manufacturer to be used for the examination of the specimen merely to determine whether the medicine or biological is compatible with the individual (where the medicine or biological comprises blood, a blood component, cells, tissue or an organ from a donor other than the individual).

See more information on the TGA website: IVD companion diagnostics

What medicine or biological indications require CDx testing?

- The Product Information (PI) for the medicine or biological must state 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
- Wording in medicine or biological PI are determined during the medicine registration process
- CDx testing identification guide was developed to help identify whether a proposed medicine or biological indication requires CDx testing.

CDx testing identification guide



Regulatory requirements for CDx

All CDx are class 3 IVDs or class 3 in-house IVDs.

- New CDx regulations were introduced on 1 February 2020, transitional arrangements until May 2026
- A separate application for inclusion is now required for each CDx
- CDx entries in the ARTG will have a Unique Product Identifier (UPI) and a functional description for the device
- Concurrent applications for medicines/biologicals and CDx IVDs are encouraged. CDx cannot be approved, prior to medicines/biologicals being approved.

- Class 1-3 in-house IVDs do not require inclusion in the ARTG, however,
- Schedule 3, Part 6A of the Medical Devices Regulations require laboratories who manufacture Class 1-3 in-house IVDs to be accredited by NATA, and
- Meet the NPAAC standard *Requirements for development and use of in-house in vitro diagnostic medical devices (IVDs)*
- 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 (next week's presentation)

Essential Principles (EPs) overview

The Essential Principles are safety and performance requirements for medical devices, including in vitro diagnostic (IVD) devices.

- Laboratories must at all times have information available to demonstrate compliance with the Essential Principles
- Certification as part of the in-house notification form:

(b) the Class 1, 2 and 3 in-house IVD medical device comply with essential principles and NATA accreditation requirements; and

(c) I have available information to substantiate that compliance with the essential principles and NATA accreditation requirements.

Compliance with the NPAAC standard will be taken as compliance with the relevant essential principles for the safety and performance of an in-house IVD medical device

See more information on the TGA website: Essential Principles checklist (medical devices)

Essential Principles (EPs) overview

The Essential Principles are safety and performance requirements for medical devices, including in vitro diagnostic (IVD) devices.

- EP 1 : Use of medical devices not to compromise health and safety. Applies to all medical devices.
- EP 2 : Design and construction of medical devices to conform with safety principles. Applies to all medical devices.
- EP 3 : Medical devices to be suitable for intended purpose. Applies to all medical devices.
- EP 4 : Long-term safety. Applies to all medical devices for the intended lifetime of the devices, however long or short that may be.
- EP 5 : Medical devices are not adversely affected by transport or storage. Applies to all medical devices.
- EP 6 : Benefits of medical devices to outweigh any undesirable effects. Applies to all medical devices.
- EP 7 : Chemical, physical and biological properties. Applies to physical-form medical devices.
- EP 8 : Infection and microbial contamination. Applies to physical-form medical devices.
- EP 9 : Construction and environmental properties. Applies to all medical devices.
- EP 10 : Medical devices with a measuring function.
- EP 11 : Protection against radiation.
- EP 12 : Medical devices connected to or equipped with an energy source.
- EP 13 : Information to be provided with medical devices. Applies to all medical devices.
- EP 14 : Clinical evidence. Applies to all medical devices.
- EP 15 : Principles applying to IVD medical devices.

Assessment approach

The role of NATA and TGA in Class 1–3 in-house IVD conformity assessment

- NATA will assess the laboratory's quality management system against:
    - ISO 15189 (for a medical testing laboratory), or
    - ISO 17025 (for a non-medical testing laboratory as considered by NATA on a case-by-case basis).
- Technical documentation will be reviewed by NATA inspectors as part of laboratory accreditation, but the MD Regulations also allow us to request this documentation at any time (if required).
- The level of rigour for the review of selected Class 1-3 in-house IVDs will be commensurate with their risk class (i.e., higher risk Class 3 in-house IVDs will be subject to greater scrutiny than lower risk Class 1 in-house IVDs).
- MoU allows NATA to request assessors from the TGA to conduct NATA assessments (desktop reviews), subject to agreement from the laboratory.

Assessment approach

The medicine or biological determines the requirement for companion testing

- IVDs are often developed by different organisations to those involved in the development of medicines or biologicals.
- Ensure there is a concurrent submission for the relevant indication of the medicine or biological; or
- Medicine or biological is already included in the ARTG with an appropriate companion testing plan that provides the details of the laboratory who will conduct the testing using their in-house CDx IVD.
- 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.

Assessment approach

The intended purpose for the in-house CDx test must align with the approved indication for the medicine or biological.

- 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 *pembrolizumab* (medicine) to treat *NSCLC* (indication), testing of *FFPE samples* (sample type) to *detect expression of PD-L1* (purpose of test) is essential. Testing used in clinical practice should be adequately comparable to the testing used in the pivotal study(ies).”

Assessment approach

The intended purpose for the in-house CDx test must align with the approved indication for the medicine or biological.

- For in-house CDx tests, the intended use statement must include:
  - selection of patients for treatment with a particular medicine or biological; or
  - monitoring of patients who are being treated with a particular medicine or biological; or
  - both.

"The *PD-L1 assay* (in-house IVD) is intended to be used as a companion diagnostic to be ordered by Australian medical oncologists to identify *NSCLC patients* (indication) with *PD-L1 expression* (purpose of test), who may benefit from treatment with *pembrolizumab* (medicine) in combination with standard therapy."

Data requirements

Performance requirements for CDx – NPAAC Particular Requirements (and EPs)

- Design (EPs 1, 2 & 6)
- Production and Contracted Services (QMS)
- Analytical Performance (EP 15)
- Scientific Validity
- Clinical Performance (EP 14)
- Clinical Utility (EPs 14 & 15)
- Multivariate Index Assays (EP 12 & 15)
- Monitoring, Analysis and Improvement (QMS)
- Adverse Event Reporting and Recalls of Tests (Post-market)
- Documentation (QMS)

Data requirements

Clinical performance requirements for CDx

- Scenarios:
    1. Proposed CDx is the original CDx (same as the clinical trial assay)
    2. Proposed CDx is a transfer of the clinical trial assay to an Australian laboratory (subsequent CDx)
    3. A laboratory seeks to develop their own in-house IVD for use as a proposed CDx (subsequent CDx)

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.

Data requirements

Clinical performance requirements for CDx

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Substantial equivalence of the subsequent IVD with the original CDx must be demonstrated.

Data requirements

Requirements for Subsequent CDx IVDs:

Substantial equivalence of the subsequent IVD with the original CDx must be demonstrated.

- Bridging studies showing a high level of agreement in clinical performance between the clinical trial assay (CTA) 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 clinical sensitivity and specificity as well as positive and negative predictive values must be available for the relevant condition.

Data requirements

Clinical performance requirements for CDx – additional considerations

- All the specimen types claimed to be used with the device must be included in the clinical study. It is not acceptable to use specimen equivalence to leverage specimen type claims
- Information required for NGS tests:
  - End-to-end workflow,
  - Extraction methods,
  - Instruments/platforms and associated software
  - Details of the bioinformatic workflow used (e.g. sequence alignment process, germline filter, variant calling)
  - Details of the comparator method
  - Acceptable sequencing quality metrics
  - Summary of the prespecified clinical cut-off used to enrol patients

Data requirements

Analytical performance requirements for CDx

- Specimen stability (storage and transport)
- Specimen equivalence (for tests 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.

Case study – in-house CDx test

Aussie Lab adapts a Research Use Only (RUO) product to develop a subsequent CDx IVD intended to be used as an aid in selecting patients whose melanoma tumours carry BRAF V600 mutations, for treatment with *medicinemab*.

- *Aussie Lab* has entered into an agreement with the sponsor of *medicinemab* to provide CDx testing for Australian patients.
- The medicine's sponsor has already included *medicinemab* in the ARTG with a companion testing plan that includes using the CTA conducted in an overseas laboratory as an interim solution.
- *Aussie Lab* proposes to take a RUO product, a nucleic acid amplification test (NAAT) that can detect BRAF mutations and validate the test for use as a subsequent CDx in-house IVD.
- *Aussie Lab* must conduct the appropriate clinical and analytical validation studies to demonstrate that the subsequent CDx is substantially equivalent to the CTA, while complying with NPAAC standards (and EPs).

Case study – in-house CDx test

Aussie Lab adapts a Research Use Only (RUO) product to develop a subsequent CDx IVD intended to be used as an aid in selecting patients whose melanoma tumours carry BRAF V600 mutations, for treatment with *medicinemab*.

- In conducting the clinical studies, the medicine's sponsor provides access to some of the specimens used in the CTA. *Aussie Lab* must conduct an additional bridging study using specimens representative of those tested in the CTA from Australian patients and confirm agreement by testing these additional samples using the CTA.
- *Aussie Lab* also conducts all the necessary analytical validation.
- The results of the clinical and analytical validation demonstrate that the subsequent CDx is substantially equivalent to the CTA, and so *Aussie Lab* applies to have the test NATA accredited under the category of Molecular genetics - Companion diagnostic genetic testing.
- *Aussie Labs* must also meet its regulatory obligations by notifying the TGA by the 1 July of that year.

Work in progress

- TGA CDx list – currently includes commercial CDx
- Updated guidance for CDx to be released for public consultation soon.
- Updated guidance for Regulatory requirements for in-house IVDs to be published in coming weeks.

Coming up next week:

- NATA TGA IVD Information Session 3: Introduction of new In-house IVD notification form

Questions?

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Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration