Australian Government
Department of Health
Therapeutic Goods Administration

IVD companion diagnostics

Guidance on proposed regulatory requirements

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TGA Health Safety Regulation

Contents

What are IVD companion diagnostics?

An IVD companion diagnostic 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.[1] It is proposed that the term '*IVD companion diagnostic'* will be defined in the *Therapeutic Goods (Medical Devices) Regulations 2002* (the Medical Devices Regulations) from 1 February 2020.

It is proposed that Australia's definition of IVD companion diagnostic will align with the US FDA's definition and the definition in the European Union Regulation (EU) 2017/746. The characteristics that define a companion diagnostic 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:
  - 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
- that 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
- that 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).

Consistent with this regulatory definition, the Instructions for Use of an IVD companion diagnostic must stipulate the corresponding medicine or biological, and vice versa. The following sections discuss these requirements.

Instructions for Use (IFU) of an IVD companion diagnostic

Consistent with the proposed regulatory definition of an IVD companion diagnostic, the IFU shall stipulate how the IVD is intended for use with the corresponding medicine or biological. It must make clear that the IVD is intended for 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.

For clarity it is expected that the IFU shall reference the International Non-proprietary Name (INN) of the corresponding medicine.

[1] See US FDA Food and Drug Administration guideline on Companion Diagnostics

The following examples of approved IFUs are used to illustrate these requirements:

- 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).

An IVD manufacturer cannot make claims in the IFU that the IVD is intended for use as a companion diagnostic unless the particular medicine or biological has been approved for use in Australia, or there are concurrent applications for approval of both the IVD companion diagnostics and the particular medicine or biological. This will allow for collaborative evaluation of clinical evidence by relevant sections of the TGA prior to inclusion of the IVD companion diagnostic on the ARTG, but it does not require concurrent approval dates for the IVD companion diagnostic and the related medicine or biological.

Product information for corresponding medicines and biologicals

The proposed regulatory definition of an IVD companion diagnostic is predicated on the device being mentioned in the product information (PI) for the medicine, or the IFU of a biological as being essential for the safe and effective use of that particular medicine or biological.

It is expected that the product information will generally include generic references to IVD companion diagnostics that are approved for that purpose rather than a specific manufacturer's IVD. This could be either a commercially supplied or an in-house IVD companion diagnostic. However, approval of each medicine or biological is ultimately dependent on the clinical evidence submitted, and the specific references to IVD companion diagnostics may be negotiated on a case-by-case basis.

To illustrate this proposed approach, the following examples are provided:

- 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 must have BRAF V600 mutation-positive tumour status confirmed by a TGA approved assay performed by a NATA accredited laboratory.
- KEYTRUDA® (pembrolizumab) is indicated as monotherapy for the first-line treatment of patients with NSCLC expressing PD-L1 [tumour proportion score (TPS) ≥1%] as determined by a validated test, with no EGFR or ALK genomic tumour aberrations.

Once the proposed new Regulations are fully implemented (i.e. from 1 July 2022), references to "a validated test" may no longer be acceptable and instead the PI of a medicine may refer to 'TGA approved IVD companion diagnostic'. References to "TGA approved" assay or IVD are taken to mean IVDs that are included on the ARTG or in-house IVDs that have been notified to the TGA by NATA accredited laboratories.

IVDs that are not companion diagnostics

There are many IVDs that share some of the characteristics of a companion diagnostic 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 companion diagnostic it must meet all of the criteria set out in the regulatory definition of IVD companion diagnostic. Some IVDs that are not companion diagnostics are considered below.

Complementary diagnostics

Drawing on information published by the FDA, a *complementary diagnostic* is considered to be a test that aids in the benefit-risk decision-making about the use of a medicine or biological, where the difference in benefit-risk is clinically meaningful. Complementary diagnostic information is included in the information supplied with a medicine or biological.[2]

Complementary diagnostics are distinct from companion diagnostics in that they provide additional information about the use of a medicine or biological but are **not essential** for the safe and effective use of that medicine or biological. This distinction will be made clear in the product information for a medicine or the IFU for a biological as well as the IFU for the IVD companion diagnostic.

An example of a complementary diagnostic claim is as follows:

- PD-L1 expression in tumor cell (TC) membrane as detected by (IVD name) in NSCLC **may be associated with** enhanced survival from OPDIVO® (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, 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 IVD companion diagnostics.

Drug monitoring tests

IVDs that are intended to be used to monitor treatment with a therapeutic drug (e.g. an antibiotic or anti-epileptic) are not companion diagnostics unless the test is specified in the PI of the medicine as being **essential** for the safe and effective use of that medicine.

As an example, the following information is drawn from the product information for B. Braun Gentamicin (ARTG 280508) to illustrate why such IVDs are not companion diagnostics:

- under Indications, it is noted that "therapy may be instituted before obtaining results of susceptibility tests"; and
- under Precautions, it is noted that "peak and trough levels (of gentamicin) should be constantly monitored …"

As another example, the following information is drawn from the PI of Carbamazepine Sandoz (ARTG 78217):

- under Dosage for Epilepsy it is noted that "determination of plasma concentrations may help in establishing the optimum dosage";

[2] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5355969/

While various tests are referred to in the PI of these medicines, the use of the terms "may" and "should" rather than "must" confirm that these tests are not **essential** for the safe and effective use of the medicine.

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 companion diagnostics where they apply to all patients or a sub-population of patients unless the test is specified in the PI of a medicine or the IFU of a biological as being **essential** for the safe and effective use of that medicine or biological.

As an example, the following information is drawn from the PI of Zepatier (ARTG 259928):

- Under Therapeutic Indications it states that "Zepatier is indicated for the treatment of Chronic Hepatitis C genotype 1 or 4 infection in adults"; and
- Under Special Warnings and Precautions for Use it is noted that "the efficacy of Zepatier has not been established in patients infected with HCV genotypes 2, 3, 5 and 6".

Thus while HCV genotyping tests are indicated to select patients for this treatment, the PI does not state specifically that HCV genotyping is essential for the safe and effective use of the medicine.

How will IVD companion diagnostics be regulated?

Classification

The classification rules set out in Schedule 2A of the Medical Devices Regulations make it clear that all IVD companion diagnostics are Class 3 IVDs or Class 3 in-house IVDs.

Applications for Inclusion in the Australian Register of Therapeutic Goods (ARTG)

Applications for inclusion of IVD companion diagnostics in the ARTG that are submitted after 31 January 2020 must comply with the new Regulations. IVD companion diagnostics that are included in the ARTG immediately prior to the commencement date are subject to the transitional arrangements and sponsors have until 30 June 2022 to submit a new application for inclusion.

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

From the 1 February 2020, new applications for Inclusion of an IVD companion diagnostic in the ARTG will be subject to an amendment at Regulation 1.6, namely that the UPI given to the device by its manufacturer is a characteristic that determines a kind of device that is an IVD companion diagnostic. This means that a separate application for Inclusion will be required for each IVD companion diagnostic. In the application form you will be asked to identify if the application is for an IVD companion diagnostic. 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).

Mandatory application audit

From 1 February 2020 applications for Inclusion of an IVD companion diagnostic in the ARTG will be subject to a mandatory application audit under amendments at subparagraph 5.3(1)(j)(x).

Clinical evidence

Clinical evidence guidelines for IVDs are currently in draft and are expected to be ready for publication in early 2020. These guidelines will include specific references to clinical evidence for IVD companion diagnostics.

Abridged evaluations and overseas evidence

Since August 2018 the TGA has accepted certification from an expanded range of comparable overseas regulators and assessment bodies as evidence of compliance with the conformity assessment procedures. Guidance on the TGA website summarises the general requirements for evidence which must accompany an application for Inclusion of medical devices including IVDs. A link to the legislative instrument on Information that must accompany an application for Inclusion can also be found on the TGA website via the Therapeutic Goods Determinations page. Sponsors can request a reduction in the audit assessment fee if they believe an abridged assessment is supported by the manufacturer's evidence provided.

IVD companion diagnostics are subject to additional requirements for assessment of technical documentation under the EU IVD Regulation 2017/746 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 IVD companion diagnostics.

The TGA is aligning the regulatory requirements for IVD companion diagnostics with the EU and the FDA. Therefore, for abridgement of an application audit to be considered, overseas evidence must include the technical assessment report to EU or FDA requirements for IVD companion diagnostics.

Conditions on inclusion and variations

Under the Medical Device Regulation 5.12 certain conditions apply automatically to the ARTG Inclusion of IVD medical devices that are subject to mandatory application audit under paragraph 5.3(1)(j). The provisions of the Medical Device Regulation 5.12 will apply to IVD companion diagnostics that are included in the ARTG from 1 February 2020. For the purposes of the Medical Device Regulation 5.12 a change that must be notified may include:

- A change in name (UPI) of the IVD companion diagnostic; or
- A change to the intended purpose to detect different biomarkers or additional biomarkers; or
- A change to the intended purpose to:
  - Add a new therapy (whether another IVD companion diagnostic or a complementary diagnostic claim);
  - Add a new specimen type (e.g. tissue, circulating tumour cells);
  - Add a new target patient population for whom the IVD is intended to be used.

Transitional arrangements

Transitional arrangements apply to IVD companion diagnostics that, on 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 (noting that IVD companion diagnostics will be Class 3 under the new Regulations).

A new application for inclusion that complies with the amended Regulations must be made before 30 June 2022, for continued supply after 1 July 2022 of IVD companion diagnostics that are covered by the transitional arrangements. For these transitioning IVD companion diagnostics, the application fee under Item 1.5(h) in Part 1 of Schedule 5 will be waived.

IVD companion diagnostics which are not covered by the proposed transition period must comply with the new Regulations from 1 February 2020.

Concurrent submission and assessment of applications for an IVD companion diagnostic and the corresponding medicine or biological

Ideally, an IVD companion diagnostic and its corresponding medicine or biological should be developed contemporaneously, with the clinical performance of the IVD companion diagnostic and suitability of the biomarker established using data from the clinical trial of the medicine or biological. Concurrent submission and assessment of applications for an IVD companion diagnostic and the corresponding medicine or biological, while not mandated under Australia's legislation, is highly recommended.

It is expected that there will be circumstances where concurrent applications for approval of an IVD companion diagnostic and its corresponding medicine or biological does not occur, e.g.:

- a new medicine is submitted for approval and the IVD companion diagnostic has already been included on the ARTG for a different intended purpose; or
- an application is submitted for a new IVD companion diagnostic for a medicine that has already been approved for supply in Australia (and there are other IVD companion diagnostic for the same biomarker on the ARTG).

IVD companion diagnostics are generally developed by different manufacturers from those developing medicines/biologicals and not necessarily within the same timeframe; or a manufacturer of a therapeutic good may partner with a diagnostic device manufacturer to modify an existing IVD diagnostic device to accommodate the intended use as a companion diagnostic. Further there may not be a commercially available IVD companion diagnostic and testing may rely on the use of in-house IVD companion diagnostic. All of these factors may make concurrent submission of applications more difficult to achieve.

Assessment of applications for an IVD companion diagnostic

The TGA will review an application for an IVD companion diagnostic within the context of, and in conjunction with, its corresponding medicine or biological to ensure a comprehensive evaluation of the benefits and associated risks of the therapeutic goods when used for their

intended purpose and indications. The assessment of both the safety and performance of the device and suitability and clinical validity of the biomarker would be carried out collaboratively between the relevant sections within the TGA.

It is anticipated that applications will be submitted for an IVD companion diagnostic where the medicine or biological has been approved for use with an alternative IVD companion diagnostic which detects the same biomarker. If the IVD companion diagnostic was not used in the clinical trials of the approved medicine or biological the performance data should include the results of concordance studies which demonstrate comparable clinical and analytical performance of the new IVD companion diagnostic with the reference test.

The validity of the clinical claims being made in relation to the use of an IVD companion diagnostic cannot be fully assessed without consideration of the evaluation of the corresponding medicine or biological which will determine whether the use of the IVD is considered essential for the safe and effective use of the medicine or biological. Therefore, companion diagnostic claims for an IVD cannot be approved in the absence of an application for, or approval of, the corresponding medicine or biological.

In-house IVDs that are companion diagnostics

Laboratory developed or "in-house" tests are often used as companion diagnostics for targeted therapies. In-house IVDs that are intended for use as companion diagnostics are also subject to the regulatory changes (e.g. definition, classification rules) and a similar transition period as outlined in the previous section.

Classification

The classification rule which clarifies that all IVD companion diagnostics are Class 3 applies equally to in-house and commercially-supplied 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 IVD companion diagnostics in the test list they provide to the TGA as part of the 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 IVD companion diagnostics. If so, laboratories will be required to specifically identify their IVD companion diagnostics in the test list that they attach to their notification to the TGA. This requirement will be mandatory from 1 July 2022 and the amended notification form will be available from this date.

Evaluation of in-house IVD companion diagnostics

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 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)* (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 for the validation of in-house IVD companion diagnostics. Under a Memorandum of Understanding (MoU) between NATA and the TGA, NATA can request TGA assistance in the technical evaluation of analytical and clinical performance of an in-house IVD and it is anticipated that this may occur with some in-house IVD companion diagnostics.

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 IVD companion diagnostics.

Publication of a list of IVD companion diagnostics approved by the TGA

The TGA intends to publish on its website a list of IVD companion diagnostics that have been approved for supply in Australia. It is intended that the list will include in-house IVD companion diagnostics that have been notified to the TGA in addition to IVD companion diagnostics included on the ARTG. The list will not be complete until the end of the proposed transition period on 1 July 2022 but consideration will be given to publishing an interim list before that date. The published list will not have formal regulatory status but will serve as a communication tool to assist clinicians and other users who wish to know what IVD companion diagnostics are approved for supply in Australia.

This is in line with the US FDA's list of cleared or approved companion diagnostic devices (In Vitro and Imaging Tools).

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Medical Devices Branch	December 2019

Therapeutic Goods Administration

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