Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Regulatory requirements for in-house IVDs

Version 3.0, May 2024

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Introduction

Australian laboratories that manufacture in-house in vitro diagnostic medical devices (IVDs) are required to meet regulatory requirements (that commenced on 1 July 2010) to legally supply* their in-house IVDs in Australia.

The IVD regulatory framework has the following features:

- IVDs must comply with a set of Essential Principles for the quality, safety, and performance of the IVD.
- A risk-based classification scheme requiring different levels of regulation for each class of device.
- There is a choice of procedures (known as conformity assessment procedures), based on the risk classification, to be applied by manufacturers to demonstrate initial and on-going compliance with the Essential Principles.
- Compliance with recognised standards is used as a means to demonstrate that the Essential Principles and conformity assessment procedures have been met.
- It includes provisions for post market activities, including monitoring and adverse event reporting.

Laboratories, the Therapeutic Goods Administration (TGA) and the National Association of Testing Authorities (NATA) are involved in ensuring the regulatory requirements of in-house IVDs are met.

There is a Memorandum of Understanding (MoU) between NATA and the TGA that describes the interaction, role and responsibilities of both parties in relation to the regulation of in-house IVDs.

This guidance explains how laboratories that manufacture in-house IVDs can meet these requirements.

**Supply means making the test available and reporting patient/client results of the test.*

In-house IVD

'In-house' IVDs are pathology tests that has been developed (or modified) **within a laboratory (or laboratory network)** to carry out testing on human samples, where the results are intended to assist in clinical diagnosis or be used in making decisions concerning clinical management.

IVDs developed in-house but **supplied* outside** of the laboratory or laboratory network, **fall outside the definition of 'in-house IVD'.**

These are commercially supplied IVDs and must be included in the ARTG prior to being supplied outside of the laboratory or laboratory network.

**Supply in this context means supply of the actual device, not the testing service outside of the laboratory or laboratory network.*

The regulations are not limited to medical testing laboratories but extend to all laboratories that manufacture in-house IVDs in Australia.

All tests manufactured by a laboratory for a therapeutic purpose (e.g., diagnostic tests, screening tests, tests for susceptibility or predisposition to disease; tests for monitoring a disease or exposure to toxic metals and chemicals), regardless of

whether they attract a Medicare rebate, are still subject to the requirements of the in-house IVD regulatory framework.

In-house tests that are developed by a laboratory for research purposes only (i.e., where there is no reporting of patient/client results) are not IVDs.

In-house IVDs are defined in Regulation 1.3 of the MD Regulations, and there are three broad situations where a laboratory is considered to have manufactured an in-house IVD.

Developed from first principles

An in-house IVD is considered to be developed from first principles (de novo) when a laboratory or laboratory network is responsible for the design and production of the in-house IVD, and includes:

- design control through assignment of the specifications for the in-house IVD, as well as planning and development processes
- assembly, processing and packaging of components that make up the in-house IVD
- assigning the intended purpose through the information supplied with the in-house IVD (i.e., the instructions for use or laboratory-controlled documents)

Developed or modified from a published source

These include in-house IVDs that are produced by a laboratory or laboratory network:

- in accordance with scientific literature, or
- from the design specifications or method for an in-house IVD manufactured by another laboratory, or
- from the design specifications of any other source.

They also include the assembly of commercially supplied components, some or all of which may not be regarded as IVDs because they are:

- not finished products, or
- not presented for use as an IVD in the information provided with the device (i.e., manufacturer's labels and instructions for use) and in the advertising, or
- marked "for research use only" (RUO), "investigational use only" (IUO) or "analyte specific reagent" (ASR)

While RUO, IUO and ASR products may be commercially supplied, they are not intended by the manufacturer to be used for an in vitro diagnostic purpose and will not be included on the Australian Register of Therapeutic Goods (ARTG).

Therefore, the use of these items to develop a test for the purpose of reporting clinical results for a patient means the test would be captured by the in-house IVD regulations

The laboratory is responsible for one or more of the following:

- assembly, processing and packaging of components purchased separately to produce the in-house IVD
- assigning the intended purpose through the information supplied with the in-house IVD (e.g., the instructions for use, laboratory-controlled procedures)
- supplying the in-house IVD under the laboratory's name (e.g., ABC Pathology Legionella total antibody assay).

**Supply means making the test available and reporting patient/client results of the test.*

Modifications to commercially supplied IVDs

Commercially supplied IVDs become in-house IVDs when:

- they are used for a clinical purpose other than that intended by the manufacturer
- a physical component of the commercial IVD is modified, substituted or removed
- the IVD is not used in accordance with the manufacturer's instructions for use (i.e., modifications to the instructions for use that could affect the performance of the device and would require validation).

The laboratory must document any changes made to a commercially supplied IVD and be able to demonstrate that the changes have been appropriately validated to ensure that the assay performs safely and effectively.

Requirements for the validation of class 1–3 in-house IVDs are specified in the National Pathology Accreditation Advisory Council (NPAAC) standard, *Requirements for the development and use of in-house in vitro diagnostic medical devices.*

If a laboratory imports a commercially supplied IVD directly from an overseas supplier, even when intending to modify that IVD so it becomes an in-house IVD, then the laboratory is the sponsor of the IVD.

Before importing the IVD, the laboratory must apply for inclusion of the commercial IVD in the ARTG. See Including IVD medical devices in the ARTG.

Examples

Modifications that then create an in-house IVD include:

- dilution of a component reagent to a concentration other than that specified by the manufacturer.
- substitution of one or more components supplied in a kit, or that are intended by the manufacturer to be used as part of the assay, with an alternatively sourced or laboratory-prepared component.
- substitution of the manufacturer's specified controls with alternative control material.
- modification of the cut-off value, or the calculation specified by the manufacturer for determining the cut-off value, for an assay.
- use of a commercial IVD with a specimen type not specified in the manufacturer's instructions for use.
- use of a monitoring assay to provide a diagnostic result.

Modifications that are NOT likely to create an in-house IVD include:

- utilising variations, alternatives or optional steps included by the manufacturer in the instructions for use or other information provided with the device.
- use of alternative controls where the manufacturer has specified in the instructions for use or other information provided with the device that these can be used.
- use of an alternative reference range that is relevant to the test population, established using a documented process.

These types of modifications would not result in an in-house IVD for regulatory purposes, but laboratories should ensure that any modifications are appropriately verified in accordance with the laboratory's quality management system and accreditation requirements.

Laboratory networks

Laboratory networks are a group of laboratory organisations that operate under a single quality management system (QMS).

A laboratory network is defined in Regulation 1.3 of the MD Regulations.

The QMS must be managed centrally, and applied uniformly across all work locations which manufacture and use the in-house IVD. However, some local work instructions may be necessary due to location-specific requirements.

As a minimum requirement, the following elements of the QMS must be managed centrally:

- management review
- internal quality audits
- corrective and preventive action
- complaints
- changes to the quality system documentation for key elements.

Laboratory organisations with appropriate NATA corporate/multisite accreditation can be considered a laboratory network and can manufacture and distribute in-house IVDs within their network.

Conformity assessment procedures for in-house IVDs

Conformity assessment ensures that the manufacturing processes used to make an in-house IVD (and the in-house IVD itself) comply with the regulatory requirements for quality, safety, and performance.

The class of an IVD determines the conformity assessment procedures a manufacturer can apply to ensure that the device is appropriately assessed, with higher class devices requiring more stringent conformity assessment procedures than lower class devices.

For in-house IVDs, there are different conformity assessment procedures (requirements) for:

- Class 1–3 in-house IVDs
- Class 4 in-house IVDs.

The first step in determining the relevant regulatory requirements is to identify all in-house IVDs, and determine whether they are class 1-3 or class 4 by referring to Classification of IVD medical devices.

Class 1-3 in-house IVDs

These do not need to be included in the Australian Register of Therapeutic Goods (ARTG) as they are currently exempt as per Item 2.10, Part 2, Schedule 4 of the MD Regulations.

However, laboratories that manufacture class 1-3 in-house IVDs must comply with the conformity assessment procedure in Part 6A, Schedule 3, of the MD Regulations.

They are also required at all times to have information available to demonstrate compliance with the Essential Principles.

To comply

To meet the requirements of this procedure, the laboratory (manufacturer) must fulfil the following criteria.

Accreditation requirements

- Be accredited by the National Association of Testing Authorities (NATA), as:
- a medical testing laboratory to ISO 15189 Medical laboratories - Particular requirements for quality and competence[1], or
- a non-medical testing laboratory to ISO 17025 - General requirements for the competence of testing and calibration laboratories[2]
- Meet the NPAAC standard: Requirements for the Development and Use of In-house In Vitro Diagnostic Medical Devices

The role of NATA 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).

The medical testing laboratory accreditation program is administered by NATA in conjunction with the Royal College of Pathologists of Australasia (RCPA). NATA/RCPA accreditation to ISO 15189 is available to laboratories performing tests in various fields of human pathology including anatomical pathology (histology and cytology), chemical pathology, cytogenetics, haematology, immunohematology, immunopathology, microbiology, molecular genetics, non-clinical biomarkers and assisted reproductive technologies.

Information about the medical testing laboratory accreditation program is on NATA (see Human Pathology).

Review of technical documentation

- NATA inspectors will review the technical documentation for a representative sample of in-house IVDs (e.g., those that are changed or newly introduced since the time of last inspection).

[1] Australian standard AS ISO 15189-2013 is identical to, and has been reproduced from, ISO 15189-2012.

[2] Australian standard AS ISO 17025-2005 is identical to, and has been reproduced from, ISO/IEC 17025-2005.

- The technical documentation will be reviewed for compliance with the NPAAC standard, *Requirements for the Development and Use of In-house In Vitro Diagnostic Medical Devices.*

Compliance with the NPAAC standard will be taken as compliance with the relevant Essential Principles for the safety and performance of an IVD medical device. For more information on Essential Principles. See the Essential Principles checklist for medical devices (including IVDs).

- 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).
- NATA may notify us of any compliance issue that has or may lead to the death or serious deterioration in the state of health of a patient, user of the in-house IVD, or another person.

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).

Notification of class 1-3 in-house IVDs

Initial notification

Laboratories that commence manufacturing class 1-3 in-house IVDs must submit an initial (i.e., first) notification to use **by 1 July of the next financial year** (or within 20 working days of this date).

You can notify us at any time prior to this date, but if new in-house IVDs are introduced in the intervening period, you will need to re-notify us to cover the new in-house IVDs before this date.

Re-notification

Re-notification applies to those laboratories that already have a current notification in place but have introduced new class 1-3 in-house IVDs since this time.

If your laboratory introduces new class 1-3 in-house IVDs, re-notification to the TGA is required prior to 1 July of the next financial year (or within 20 working days of this date).

In practice this means that the introduction of an in-house test or test procedure used by a laboratory for a new determination or examination that is required to be added to the laboratory's NATA test list also requires notification to us (by 1 July of the next financial year).

Examples of when re-notification is not required

- Change to an existing in-house test or test procedure that has previously been notified to us and does not require addition to the laboratory's existing NATA test list.
- Manufacture of an existing in-house IVD has ceased. It is expected that this information would be updated in the next notification for the introduction of any new in-house IVDs.
- Re-notification is not required if your laboratory has not introduced any new class 1-3 in-house IVDs since your previous notification.

How to identify your class 1-3 in-house IVDs in a single notification

The electronic notification form will no longer ask you to select from predetermined broad categories that cover the types of class 1-3 in-house IVDs in use in your laboratory.

Instead, this information will be captured as part of the standardised In-house IVD notification template (an Excel spreadsheet) that laboratories must complete and attach as part of the notification form.

The first time that your laboratory completes the In-house IVD notification template, you will be required to include all accredited tests.

This includes the tests already notified to the TGA previously and any new tests, as applicable.

In future notifications, you will only need to update the existing In-house IVD notification template by inserting new rows for new test notifications. In submitting new tests for notification, laboratories should remove (or delete rows) for tests that are no longer accredited or being performed.

This newly developed In-house IVD notification template will enable us to collect the required information in a suitable format that is useful for the purposes of identification and reporting.

For testing laboratories, this will avoid duplication, as they will now be required to provide the information on the in-house test only in the excel sheet and not in both the excel sheet and the electronic IVD in-house notification form.

Information to be attached to your notification – standardised In-house IVD notification template

To identify your class 1-3 in-house IVDs, you must attach a copy of the completed In-house IVD notification template.

This is a standardised template that your laboratory is required to complete and maintain for notification to the TGA.

The information required includes:

- Header:
    - Name of the laboratory network (if applicable) and the NATA accreditation number of the facility
    - The laboratory name (header): insert extra rows for multiple laboratories if part of a laboratory network.
    - NATA site identifier number
- Column A: Test name
- Column B: Site identifier - if the test is performed as part of a laboratory network, enter the site numbers where this test is performed. Column C: Category - select from the drop down list the category of the test.
- Column D: CDx - select yes or no to identify whether the test is a companion test or companion diagnostic (CDx). If you are uncertain whether the test is a companion diagnostic, refer to guidance on CDx IVDs.
- Column E: Notification year - Enter the year of notification for a previously notified test, or the current year for a new or updated test.
- Column F: Indication/Determination: Provide general information regarding the nature and purpose of the test (or test group). For CDx tests, list the indication including disease status and the medicine/biological requiring companion testing.
- Column G: Specimen - List all specimen (sample) types validated for use with the test.
- Column H: Instruments - List any instrument(s) to be used with the test, including model numbers (if known).

- Column I: Software - Any software that is separate to instrument/analysers, including version number (if known).
- Column J: Commercial test - If applicable, the commercial test from which the in-house test was developed, including manufacturer and device name of the commercial test.
- Column K: Modification - For in-house IVDs developed from commercially supplied devices, provide a description of the modification, e.g. additional sample type, modification to process, new indication, etc.
- Column L: LDT - select yes or no to identify a laboratory developed test (LDT), either from first principles or from a Research Use Only (RUO) kit.
- Column M: Class - select the class of the in-house IVD, either 1, 2 or 3.
- Column N: Comments - Any additional comments regarding the test.

You are required to add only one test per row and can create copies of the class 1-3 in-house IVD notification template tab for each department as required.

The below image is a snapshot of the standardised In-house IVD notification template with a CDx example.

Test name	Site Identifier	Category	CDx	Notification year	Indication/Determination	Specimen	Instruments
Name of the test	*List the identifier number(s) for the sites where this test is performed*	*Category of testing performed*	*Is this a Companion Diagnostic test?*	*Please indicate if this is a new device; a change to a device; or a previously notified device (state year of notification)*	*Please provide general information regarding the nature and purpose of the in-house IVD test (or test group). For CDx tests, list the indication including disease status and medicine/biological product*	*All specimen types validated for use with the test*	*Instrument(s) to be used with the test, including model number if known*
BRAF Detect Assay	2632, 5485	Molecular Genetics	Yes	2024	The BRAF Detect Assay is intended to be used as aid in selecting patients whose melanoma tumours carry the BRAF V600 mutation, testing in FFPE tissues prior to treatment with medicinemab.	Formalin fixed paraffin embedded (FFPE)	PCR instrument

Software	Commercial test	Modification	LDT	Class	Comments
Software separately supplied to the instrument(s), including version number if known	*If applicable, the commercial test from which the in-house test was developed (including manufacturer and device name)*	*For in-house IVDs developed from commercially supplied devices, please provide a description of the modification, e.g. additional sample type, modification to process, new indication, etc*	*If developed from first principles or a Research Use Only (RUO) kit (and not from an existing commercially supplied device), please indicate if the device is a laboratory developed test (LDT) - Y/N*	*Select the class of IVD (i.e. Class 1 - 3 in-house IVD)*	*Add any comments you would like to include*
Software embedded in PCR instrument, mutation mapper software (stand alone RUO)	N/A	N/A	Yes, RUO	Class 3 in-house IVD	

Examples of in-house tests and procedures which could be found on the In-house IVD notification template include but are not limited to:

- multiple in-house IVDs that form part of or are used for the same test procedure (e.g., identified on the NATA test list as in-house culture media, in-house stains for general histology)
- a single in-house test to detect a specific marker, analyte or pathogen (e.g., an in-house IVD to detect meningococcal disease)
- a single in-house test to detect multiple specific markers, analytes or pathogens (e.g., a multiplex PCR for respiratory pathogens)
- an in-house test procedure that incorporates a combination of individual markers, analytes or pathogens using the same testing platform or technology, and which are interpreted together in order to determine a specific condition (e.g., an in-house test to determine haematological malignancy using a panel of CD markers used in flow cytometry)
- an in-house CDx test to detect specific biomarkers, analytes or for drug monitoring to be used as a companion test for a medicine or biological

If you have any issues completing the electronic notification form for your in-house IVD, or have questions regarding completing the In-house IVD notification template, contact us for assistance at: IVDs@tga.gov.au

Submitting your notification

To submit a notification, the laboratory or an authorised person acting on behalf of the laboratory, must be a TGA 'client'.

Information on how to become a client, and gain access to TGA Business Services (TBS), is available at TGA Business services: getting started with the TGA.

User guidance for submission of the Laboratory's notification

User guidance to assist with the submission of the initial notification, as well as the re-notification process through updating the existing notification is available at Class 1-3 in-house IVDs: using the online application form

Notification fees

Current notification fees are available in the TGA summary of fees and charges.

- A notification fee applies to the initial notification, and to any subsequent re-notifications, and only one fee is charged per notification.

All class 1–3 in-house IVDs manufactured by a laboratory (or a laboratory network) can be entered in the in-house IVD notification template in a single notification.

Once the notification is submitted

- Once submitted (and the notification fee processed), the laboratory's details will be recorded in the class 1-3 in-house IVD notification database.
- Laboratory will receive an acknowledgment of the notification and will be able to view* their notification via their TBS account.
- As outlined in the user guidance for Class 1-3 in-house IVDs: Using the online application form, a staff member would have been nominated as the Administrator for the organisation's account. The laboratory is responsible for ensuring the contact details of the administrator are updated and

current by completing the Updating organisation administrator form and sending it through to ebs@health.gov.au

**The class 1-3 in-house IVD notification database is not publicly viewable.*

Class 4 in-house IVDs

Laboratories that manufacture class 4 in-house IVDs must:

- include them in the ARTG
- comply with the conformity assessment procedures in Part 1 or Part 6B, Schedule 3, of the MD Regulations.

To do this, laboratories have a choice of two (2) pathways:

1. Obtaining TGA conformity assessment certificates prior to applying for inclusion of their class 4 in-house IVDs in the ARTG;
   or
2. Using their existing NATA accreditation to ISO 15189, or their TGA Manufacturing licence, to apply directly for inclusion of their class 4 in-house IVD in the ARTG.

TGA conformity assessment

The pathway for manufacturers of class 4 in-house IVDs to obtain TGA conformity assessment certificate is available **before** they can apply for ARTG inclusion.

This pathway is for the manufacturers of class 4 in-house IVDs that:

- don't currently hold valid NATA accreditation or a TGA issued licence to manufacture therapeutic goods, and
- don't intend to obtain either of these in the future.

For this procedure, the laboratory will need to apply to TGA for a:

- quality management system (QMS) certificate for the laboratory
- design examination (DE) certificate for each class 4 in-house IVD.

Assessment process

- TGA will conduct an assessment for compliance with ISO 13485:2016 Medical devices - Quality management systems - Requirements for regulatory purposes. This details the requirements for a quality management system for the design and manufacture of medical devices.

  This process may also involve an on-site inspection.
- As part of conformity assessment, we will also assess the technical documentation (i.e., analytical and clinical performance data) for the class 4 in-house IVD to assess compliance with the Essential Principles for safety and performance.
- If successful, we will issue the laboratory with a TGA Conformity Assessment QMS certificate and a DE Certificate for the class 4 in-house IVD.

Once issued, the laboratory can then apply for inclusion of the class 4 in-house IVD in the ARTG with TGA conformity assessment certificate as the evidence.

For further information on TGA conformity assessment, see:

- Conformity assessment overview (IVDs)

- What a manufacturer needs to know about conformity assessment (IVDs)

Using existing NATA accreditation or TGA Manufacturing licence

In this pathway, a laboratory can apply directly to include their class 4 in-house IVD in the ARTG (i.e., without needing a TGA conformity assessment certificate) if they are either:

- Are accredited by NATA to ISO 15189 as a medical testing laboratory; and comply with the NPAAC standard, *Requirements for the development and use of in-house IVDs.*
- Hold a current TGA issued Manufacturing licence that authorizes the carrying out of a step in the manufacture of blood, blood components and plasma derivatives, human cell and tissue based therapeutic goods; **and** the laboratory satisfies the requirements in the Australian Code of Good Manufacturing Practice for Blood and Blood Components, Human Tissues and Human Cellular Therapy Products.

Mandatory application audit

As part of the ARTG inclusion application, the application will be subject to a mandatory application audit, where we will assess the analytical and clinical evidence for the class 4 in-house IVD to determine compliance with the relevant Essential Principles prior to ARTG inclusion.

If a class 4 in-house IVD is based on the modification of a commercially supplied class 4 IVD already included in the ARTG, only the changes made to the commercially supplied IVD and the relevant validation document will be assessed.

Laboratories may also be required to provide evidence that they have appropriate procedures in place that allow them to monitor the on-going performance of the device and report any adverse events or problems associated with its use (see Post market responsibilities).

For more information on including class 4 in-house IVDs in the ARTG, see:

- What a sponsor needs to know about conformity assessment (IVDs)
- Including IVD medical devices in the ARTG

Fees for class 4 in-house IVDs

Current fees are available in the TGA summary of fees and charges, and the total fees payable will vary depending on the chosen pathway.

The assessment fees reflect the maximum payment **if the full fees were applied**. In majority of circumstances, a full assessment would not be required, and the fees could be reduced.

For example, if a laboratory has developed a class 4 in-house IVD by modifying a commercially supplied class 4 IVD (that has been previously assessed by us), then only the changes made to the commercially supplied product would need to be assessed and the assessment fees could be reduced.

TGA conformity assessment

If a laboratory chooses to obtain TGA conformity assessment certificates prior to applying for inclusion in the ARTG, then the following fees will apply:

- Application fee for TGA conformity assessment certificate
- A full quality management system inspection fee* (fee for evaluation of the QMS) *Additional fees may apply if an on-site inspection is required.

- A design examination fee for each class 4 in-house IVD (fee for evaluation of the technical documentation)
- Application fee for inclusion in the ARTG

Using existing NATA accreditation to ISO 15189 or TGA manufacturing licence

If a laboratory chooses to apply directly for inclusion in the ARTG based on already having NATA accreditation to ISO 15189 or a TGA issued Manufacturing licence, then the following fees will apply:

- Application fee for inclusion in the ARTG
- Application audit assessment fee for class 4 in-house IVDs (fee for evaluation of the technical documentation)

There is no annual charge for class 4 in-house IVDs.

The fees and charges are detailed in Schedule of fees and charges.

Ongoing responsibilities

All in-house IVDs must comply with the applicable conformity assessment procedures and Essential Principles. You are required to maintain evidence of compliance at all times, as outlined in the relevant guidance.

You are also required to maintain records and details of instances of supply and use of the tests.

The TGA may require you to submit such information at any time.

For all classes of in-house IVDs, laboratories must implement a post-market system for the ongoing monitoring of the performance of their in-house IVDs (e.g., via quality assurance programs and internal quality control) and to notify us of any adverse events.

In addition, reports need to be made to us in relation to:

- malfunction or deterioration in characteristics or performance
- and any inadequacy in the design, production, labelling, instructions for use or advertising materials of the kind of device.

The MD Regulations require laboratories that manufacture in-house IVDs to have a QMS in place that allows them to:

- monitor the performance of their IVDs by systematically reviewing the application of quality control (QC) procedures and participation in external quality assurance (EQA) programs
- apply necessary corrective action if any failures (or potential failures) are detected in relation to the performance of the in-house IVD
- report any adverse events relating to the safety, quality or performance of their in-house IVDs to us.
- notify us* of any malfunction or deterioration in a class 4 in-house IVD that has led the laboratory to take steps to cease using or recover the device if it has been disseminated within a laboratory network.

** Send this notification to the TGA Recalls Unit in accordance with the requirements of the Uniform Recall Procedure for Therapeutic Goods (URPTG).*

The NPAAC standard (Sections 9 and 10 - Particular requirements – monitoring, analysis and improvement and Particular requirements – adverse event reporting and recalls) provides guidance on the necessary monitoring and post market activities for in-house IVD manufacturers.

Adverse events

An adverse event includes an event that leads to:

- the death of a patient
- a serious injury or serious deterioration to a patient, user or other person, including a life-threatening illness or injury
- permanent impairment of a body function
- permanent damage to a body structure
- a condition necessitating medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure.

Typical causes of adverse events

- design issues
- deficiencies in instructions
- defective components
- performance failures
- user/systemic errors

Reporting adverse events

The MD Regulations prescribe that information must be reported to us about events related to the use of medical devices (including in-house IVDs) that represent:

- a serious threat to public health
- the death of a person
- a serious deterioration in the health of a person.

Regulation 5.7 prescribes the timeframes where information about adverse events must be reported to us:

Event (or other occurrence)	Timeframe required for reporting (after the person becomes aware of the event or occurrence)
Represents a serious threat to public health	48 hours
Led to the death, or a serious deterioration in the state of health of a person* **a patient, a user of the device, or another person*	10 days
Where a recurrence might lead to the death or a serious deterioration in the state of health, of a person* ** a patient, a user of the device, or another person*	30 days

For more information, see Report a medical device adverse event (sponsor/manufacturer).

Exemptions for in-house IVDs

Therapeutic goods legislation provides exemptions for IVDs that are used for evaluation or experimental purposes, or to deal with emergencies.

Exemptions for experimental purposes

Schedule 4 Part 2 of the MD Regulations sets out the provisions for exempting medical devices for experimental purposes.

Laboratories that need access to an unapproved commercially supplied IVD or need to develop a class 4 in-house IVD for experimental purposes, should contact us to discuss the requirement for an exemption.

Exemptions to deal with emergencies

Part 4-6A of the Act allows for certain therapeutic goods be stockpiled to deal with possible future emergencies or made available urgently to deal with actual emergencies.

For example, class 4 in-house IVDs that have been developed by laboratories to detect an emerging infectious disease may be exempted from the need to be included on the ARTG in the national interest, to deal with a possible emergency.

Laboratories that manufacture in-house IVDs for these purposes should contact us to discuss the requirement for an exemption.

This type of exemption **can only be initiated by the Government** (i.e., not by an individual laboratory) in the event of an actual public health emergency or potential emergency.

Case studies

Below are four case study examples that may assist manufacturers of in-house IVDs in Australia to meet regulatory requirements.

Case study 1:

Imaginary Labs intends to transfer technology from an overseas laboratory that is currently conducting companion diagnostic (CDx) testing for patients expected to receive Adeno-Associated Virus 5 (AAV5) gene therapy.

The test is a neutralising anti-AAV5 antibody assay (*nAb AAV5 Assay*) intended to be used as an aid in selecting patients with Factor IX mutations prior to treatment and is essential for the safe and effective use of the gene therapy. The testing being performed overseas is the clinical trial assay (CTA) and the gene therapy product has already been included in the ARTG with a companion testing plan.

Imaginary Labs enters into an agreement with the sponsor of the gene therapy product (*Sponsor G*) and prepares to validate and accredit the use of the *nAb AAV5 Assay* as a new in-house CDx IVD. The *nAb AAV5 Assay* is a transfer of the CTA and is therefore a subsequent CDx.

Imaginary Labs uses TGA guidance and the classification rules to determine that the *nAb AAV5 Assay* will be a Class 3 in-house IVD. Using the guidance for Regulatory requirements for in-house IVDs , the NPAAC standard for in-house IVDs and the CDx performance requirements,, they begin to design and develop validation studies to demonstrate the clinical and analytical performance of the *nAb AAV5 Assay*.

In conducting the clinical validation studies, *Sponsor G* provides access to some of the specimens used in the CTA, however, the sample numbers are not statistically significant. *Imaginary Labs* 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.

Imaginary Labs also completes analytical validation for *nAb AAV5 Assay* including:

- specimen stability and storage for the intended sample type of serum,
- analytical sensitivity in the form of limit of detection, expressed as titre ratio,
- analytical specificity, for example, endogenous and exogenous substances that may be present in serum samples, cross-reactivity to other AAV antibodies,
- assay cut off, expressed as titre ratio,

- repeatability and reproducibility,
- accuracy and cross-contamination,
- validation of the internal control materials.

The results of the clinical and analytical validation demonstrate that the *nAb AAV5 Assay* is substantially equivalent to the CTA, therefore, *Imaginary Labs* applies to have the test NATA accredited under the category of Immunopathology - Companion diagnostic testing.

Once accreditation has been issued, the laboratory begins to conduct companion testing for the indication approved for the gene therapy product. *Imaginary Labs* must meet their regulatory obligations by notifying the TGA by the 1 July of that year of their new CDx test, maintain documentation related to post-approval activities and report any adverse events.

Case study 2:

Orange Labs is currently using a commercial kit, *Uric Acid Detect*, that is listed in the ARTG with the intended purpose of detecting uric acid levels in serum, plasma, and urine specimen types. *Orange Labs* wants to use *Uric Acid Detect* to test joint aspirate fluid as a sample type. However, this sample type is not intended to be used by the manufacturer of the commercial kit. *Orange Labs* must validate and accredit the use joint aspirate fluid with *Uric Acid Detect* as an in-house IVD.

Orange Labs uses TGA guidance and the classification rules to determine that their in-house uric acid test will be a class 2 in-house IVD. Since *Uric Acid Detect* is already ARTG included, the laboratory is required to undertake clinical and analytical studies to demonstrate equivalent performance of the test when using joint aspirate fluid as a specimen type.

Orange Labs conducts a clinical study using simultaneously collected patient joint aspirate fluid and plasma samples to demonstrate equivalent performance. The clinical study contains statistically significant sample numbers and provides detailed descriptions of the samples collected and tested.

Orange Labs also completes a specimen equivalence study as part of the analytical validation for joint aspirate fluid specimens which includes limit of detection (LoD) for analytical sensitivity, potentially interfering substances for analytical specificity and specimen storage and transport.

The results of the clinical and analytical validation demonstrate that the use of joint aspirate fluid is an acceptable specimen type and applies to have the test NATA accredited as an in-house IVD. Once accreditation has been issued, the laboratory begins to conduct testing using the newly validated specimen type. *Orange Labs* must meet their regulatory obligations by notifying the TGA by the 1 July of that year of their new in-house IVD, maintain documentation related to post-approval activities and report any adverse events.

Case study 3:

Hypothetical Laboratories develops a device to screen blood donor products for the presence of Treponema pallidum. Based on the intended use of the device and the classification rules provided by Schedule 2A of the Regulations, the manufacturer determines that the device is a class 4 IVD.

The manufacturer uses the 'Clinical evidence guidelines supplement: In vitro diagnostic (IVD) medical devices' guidance to understand how the TGA interprets regulations and how manufacturers can comply with them. The manufacturer also identifies IVD medical device standards that are most relevant and appropriate to their device such as the common specifications for certain class D in vitro diagnostic medical devices in accordance with Regulation (EU) 2017/746 and CLSI EP19-ED2:2015 A Framework for Using CLSI Documents to Evaluate Clinical Laboratory Measurement Procedures. Based on these standards the manufacturer develops a plan to validate the safety, quality, and performance of the treponema pallidum device for its intended use in donor screening.

Based on the validation plan, the manufacturer assembles panels of samples (negative, low positive, moderate positive and strong positives) and standards (for e.g., WHO international standard), ensuring that the materials selected are appropriate, have known values and are stable during storage.

The manufacturer also identifies a state-of-the-art comparator method that would be used as a method comparator to assess the performance of the device.

The manufacturer conducts flex and robustness studies to establish the testing procedure and characteristics.

The manufacturer then establishes the analytical performance of the using the in-house developed test over multiple days, including analytical studies such as establishing equivalence between various sample types, sample stability, precision, analytical sensitivity (limit of detection), validation of cut-off, analytical specificity (interferences and cross-reactivity). The manufacturer additionally establishes the clinical performance of the device with each sample type intended to be used. Clinical performance studies include the validation of clinical sensitivity, seroconversion and clinical specificity. All discordant results are further evaluated. The manufacturer also verifies the suitability of diluent, control and calibration materials for use with the device. The laboratory seeks approval from NATA for the inclusion of the new in-house IVD under their laboratory's accreditation.

Hypothetical Laboratories must meet their regulatory obligations by submitting an application for inclusion of their new Class 4 in-house IVD medical device in the ARTG.

After submission of the application and payment of the application fee the TGA will select the application for a mandatory audit. The TGA will also request the provision of all documentation that is relevant to the Class 4 device, including the manufacturer's validation of the device's performance characteristics.

Alternatively, *Hypothetical Laboratories* may also submit an application for certification under Part 1 and Clause 1.6 of Part 1 of Schedule 3 of the Regulations for Conformity Assessment and Design Examination certification.

Once the device is included in the ARTG as a Class 4 in-house IVD, the manufacturer must maintain documentation related to post-approval activities and report any adverse events.

Case study 4:

Illusionary Labs develops a *de novo* assay as a new in-house IVD, *Preimplantation Genetic Testing (PDT) Detect*. The *PDT Detect* assay is intended to be used as aid in detecting life-threatening or debilitating mutations in patient embryos prior to implantation as part of the *in vitro* fertilisation procedure.

The *PDT Detect* assay is a NGS panel test that can detect 80 different human genetic variants related to congenital and development abnormalities. *Illusionary Labs* needs to validate the entire panel of genes in the assay to have the *PDT Detect* assay accredited as an in-house IVD.

Illusionary Labs uses TGA guidance and the classification rules to determine that their *PDT Detect* assay will be a Class 3 in-house IVD. Using the guidance for Regulatory requirements for in-house IVDs and the NPAAC standard for in-house IVDs, they begin to design and develop validation studies to demonstrate the clinical and analytical performance of *PDT Detect*.

In conducting the clinical validation studies, *Illusionary Labs* must ensure their study is well-designed. Aspects such as the prevalence of the target analytes, the statistical confidence and the adequate characterisation of all samples included in the study must have been considered.

Illusionary Labs also completes analytical validation for *PDT Detect* including:

- specimen stability and storage for the intended sample type of DNA/RNA extracted from blastomere cells,
- validation of the extraction process from blastomere cells (quality of the DNA/RNA input),
- analytical sensitivity in the form of coverage and read depth,
- assay cut offs, as appropriate,
- inclusivity analysis of the primer and probe sequences for the target analytes,
- repeatability and reproducibility,
- accuracy, and
- validation of the control materials developed as part of the assay.

The results of the clinical and analytical validation demonstrate that *PDT Detect* performs adequately and demonstrates compliance with the NPAAC standard and EPs. Therefore, *Illusionary Labs* applies to have the test NATA accredited under the category of Molecular genetics. NATA accreditation involves a sampling method where specific analytes are selected and reviewed as being representative of other similar assays using the same technology.

Once accreditation has been issued, the laboratory begins to conduct testing. *Illusionary Labs* must meet their regulatory obligations by notifying the TGA by the 1 July of that year of their new class 3 in-house IVD, maintain documentation related to post-approval activities and report any adverse events.

In subsequent years, *Illusionary Labs* decides to add new genetic variants to the *PDT Detect*. *Illusionary Labs* has already obtained accreditation for the panel from NATA and does not need to be audited for the additional genetic variants. However, the in-house IVD is being used for a different purpose than that which was previously notified to the TGA and an additional in-house IVD notification is required for the year in which the new genetic variants are included in the *PDT Detect* assay.

Relevant legislation

The legislation applicable to in-house IVDs is:

- Therapeutic Goods Act 1989
- Part 6A, Schedule 3, of the Therapeutic Goods (Medical Devices) Regulations 2002 (for class 1-3 in-house IVDs)
- Part 1 or Part 6B, Schedule 3, of the Therapeutic Goods (Medical Devices) Regulations 2002 (for class 4 in-house IVDs)
- Part 2 and Part 4-6A, Schedule 4, of the Therapeutic Goods (Medical Devices) Regulations 2002 (for Exempt devices)

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	IVD section	January 2012
V2.0	Updated to reflect recent amendments to regulatory requirements	IVD section	March 2016
V2.1	Updated to remove transition information which ended July 2017 and include more information about what constitutes an in-house IVD	IVD section	May 2018
V2.2	Included link to MoU and updated broken links for NPAAC publication and TGA fees and charges	IVD section	September 2018
V3	Updated to include: In-house notification template instructions Repeal of Regulation 4.1 information and Addition of case studies	Medical Devices Authorisation Branch	April 2024

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Reference/Publication #