REQUIREMENTS FOR THE DEVELOPMENT AND USE OF IN-HOUSE IN VITRO DIAGNOSTIC MEDICAL DEVICES (IVDs)

(Third Edition 2014)
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*Requirements for Medical Pathology Services*

Australian Government Department of Health
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The National Pathology Accreditation Advisory Council (NPAAC) was established in 1979 to consider and make recommendations to the Australian, state and territory governments on matters related to the accreditation of pathology Laboratories and the introduction and maintenance of uniform Standards of practice in pathology Laboratories throughout Australia. A function of NPAAC is to formulate Standards and initiate and promote guidelines and education programs about pathology tests.

Publications produced by NPAAC are issued as accreditation material to provide guidance to Laboratories and accrediting agencies about minimum standards considered acceptable for good Laboratory practice.

Failure to meet these Standards may pose a risk to public health and patient safety.
Scope

The Requirements for the Development and Use of In-house Diagnostic Medical Devices (In-house IVDs) document is a Tier 3B NPAAC document and must be read in conjunction with the Tier 2 document Requirements for Medical Pathology Services. The latter is the overarching document broadly outlining Standards for good medical pathology practice where the primary consideration is patient welfare, and where the needs and expectations of patients, Laboratory staff and referrers (both for pathology requests and inter-Laboratory referrals) are safely and satisfactorily met in a timely manner.

Whilst there must be adherence to all the requirements in the Tier 2 document, reference to specific Standards in the document are provided for assistance under the headings in this document.

This document outlines the principles and assessment criteria by which in-house IVDs must be designed, developed, produced, validated and monitored for use by medical laboratories in Australia.

It is a requirement that all in-house IVDs be assessed by NATA to this Standard. In-house IVDs that fall into the TGA Classes 1, 2, and 3 risk categories require assessment to this Standard for accreditation purposes in order to be listed on the TGA in-house IVD notification database, and Class 4 in-house IVDs require assessment to this Standard for accreditation purposes. Additionally, in-house IVDs that fall into Class 4 require assessment by TGA to the relevant conformity assessment procedures prescribed in the Therapeutic Goods (Medical Devices) Regulations 2002 in order to be listed on the Australian Register of Therapeutic Goods (ARTG).

It is a basic principle of Laboratory practice that test methods should be validated prior to use and that the level of validation should be commensurate with the risks associated with the IVD, either to the user, to the health of the patient whose sample is being tested, or to public health in general. The provision of appropriate resources, design, production, validation and continual monitoring of a device, including a device being used for purposes not intended by the manufacturer, is addressed in this document.

Validation of an in-house IVD by a Laboratory using this Standard does not allow that IVD to be supplied as a validated IVD to any other Laboratory, unless that other Laboratory is part of the same Laboratory network.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ARTG</td>
<td>Australian Register of Therapeutic Goods</td>
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<td>AS</td>
<td>Australian Standard</td>
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<td>CLSI</td>
<td>Clinical and Laboratory Standards Institute</td>
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<td>EGAPP</td>
<td>The Evaluation of Genomic Applications in Practice and Prevention</td>
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<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
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<td>ISO</td>
<td>International Organization for Standardization</td>
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<td>In-house IVD</td>
<td>In-house In Vitro Diagnostic Medical Device</td>
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<td>MIA</td>
<td>Multivariate Index Assay</td>
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<td>NATA</td>
<td>National Association of Testing Authorities</td>
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<td>NPAAC</td>
<td>National Pathology Accreditation Advisory Council</td>
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<tr>
<td>QC</td>
<td>Quality Control</td>
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<td>QS</td>
<td>Quality System</td>
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<td>RCPA</td>
<td>Royal College of Pathologists of Australasia</td>
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<tr>
<td>RUO</td>
<td>Research Use Only</td>
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<tr>
<td>TGA</td>
<td>Therapeutic Goods Administration</td>
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### Definitions

<table>
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<tr>
<th>Term</th>
<th>Definition</th>
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<tr>
<td>Accuracy</td>
<td>means closeness of the agreement between the result of a measurement and a true value of the measurand. (International vocabulary of basic and general terms in Metrology (VIM) draft 2004 revision, definition 3.5) If the true value cannot be determined, then an accepted value may be used as a substitute</td>
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<tr>
<td>Adverse event</td>
<td>means an event arising from the use of an IVD medical device that might lead, or might have led, to the death or serious deterioration in the state of health of a patient, a user of the IVD medical device or another person</td>
</tr>
<tr>
<td>Analytical performance</td>
<td>means the ability of an IVD medical device to detect or measure a particular analyte</td>
</tr>
<tr>
<td>Clinical Evidence for an IVD medical device</td>
<td>means all the information that supports the scientific validity and performance for its use as intended by the manufacturer</td>
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<tr>
<td>Clinical utility</td>
<td>means 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.</td>
</tr>
<tr>
<td>Clinical Performance</td>
<td>means the ability of an IVD medical device to yield results that are correlated with a particular clinical condition/physiological state in accordance with the target population and the intended user.</td>
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<td>Conformity assessment</td>
<td>means a process undertaken by an accreditation body to assess the competence of a Laboratory or organisation, based on particular Standard(s) and/or other normative documents, and for a defined scope of accreditation. (Derived from ISO/IEC 17011:2004 – Conformity assessment - General requirements for accreditation bodies accrediting conformity assessment bodies)</td>
</tr>
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<td>In vitro diagnostic medical device (IVD)</td>
<td>means a medical device that is: (a) a reagent, calibrator, control material, kit, Specimen receptacle, software, instrument, apparatus, equipment or system, whether used alone or in combination with another diagnostic product for in vitro use; and (b) intended by the manufacturer to be used in vitro for the examination of a Specimen derived from the human body, solely or principally for: (i) giving information about a physiological or pathological state or a congenital abnormality; or (ii) determining safety and compatibility with a potential recipient; or (iii) monitoring therapeutic measures; and (c) not a product that is: (i) intended for general Laboratory use; and (ii) not manufactured, sold or presented for use as an IVD medical device.</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
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<td><strong>In-house IVD</strong></td>
<td>means an IVD medical device that is: (a) within the confines or scope of an Australian medical Laboratory or Australian medical 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 medical Laboratory or medical Laboratory network.</td>
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| **Imprecision**             | means the dispersion of independent results of measurements obtained under specified conditions. Imprecision is expressed numerically as standard deviation or coefficient of variation projects. (Harmonized Terminology Database of the Clinical and Laboratory Sciences Institute)  

*Note: The term ‘imprecision’ is used rather than ‘precision’ because the common measures used, such as standard deviation and coefficient of variation, are in fact measures of imprecision.* |
<p>| <strong>Intended purpose</strong>        | means the purpose for which the manufacturer of the device intends it to be used, as stated in: (a) the information provided with the device; or (b) the instructions for use of the device; or (c) any advertising material applying to the device. (d) technical documentation describing the mechanism of action of the device |
| <strong>Medical Laboratory Network</strong> | means a network of Laboratory organisations that operate under a single Approved Pathology Authority (APA) with a single quality management system for which: (a) the activities of the network span more than one field of testing or program; or (b) the network operates at multiple sites within a field or involves a combination of multiple sites or programs. |
| <strong>Modified IVD</strong>            | means any IVD medical device that is: • used for a purpose other than that intended by the original manufacturer; or • not used in accordance with the manufacturer’s instructions for use or the methodology described. |
| <strong>A Multivariate Index Assay (MIA)</strong> | means an IVD medical device that - (a) combines the values of multiple variables using an interpretation function to yield a final, patient-specific result (such as a score or an index etc.) that is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease, and (b) provides a result whose derivation is non-transparent and cannot be independently derived or verified by the end user. |</p>
<table>
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<tr>
<th>Requirements for Medical Pathology Services (RMPS)</th>
<th>means the overarching document broadly outlining standards for good medical pathology practice where the primary consideration is patient welfare, and where the needs and expectations of patients, Laboratory staff and referrers (both for pathology requests and inter-Laboratory referrals) are safely and satisfactorily met in a timely manner.</th>
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<tr>
<td>The standard headings are set out below –</td>
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<td>Standard 1 – Ethical Practice</td>
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<td>Standard 2 – Governance</td>
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<td>Standard 3 – Quality Management</td>
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<td>Standard 4 – Personnel</td>
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<td>Standard 5 – Facilities and Equipment</td>
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<td>A – Premises</td>
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<td>B – Equipment</td>
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<td>Standard 6 – Request-Test-Report Cycle</td>
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<td>A – Pre-Analytical</td>
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<td>B – Analytical</td>
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<td>C – Post-Analytical</td>
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<td>Standard 7 – Quality Assurance</td>
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| Scientific validity                               | means the association of an analyte to a clinical condition/physiological state.                                                                                                                                                                |
| Validation studies                                 | means validation studies which provide objective evidence that an in-house method or modified standard method is fit for the purpose and satisfies the particular requirements for its specific use. Commercial applications designated by the manufacturer ‘for research purposes only’ are considered in-house methods |
| Verification studies                               | means verification studies which are typically less extensive and demonstrate the user’s ability to achieve the published performance characteristics of a method under the user’s own test conditions |
Introduction

This document, *Requirements for the Development and Use of In-house In Vitro Diagnostic Medical Devices*, together with the *Requirements for Medical Pathology Services*, sets out the minimum requirements for best practice for the development and/or use of in-house IVDs.

The fundamental principle embodied in this document is that all in-house tests must be produced in a manner whereby they are safe and perform as intended. This Standard assures this by introducing requirements for the design, production, verification and validation of in-house IVDs.

These Requirements have been developed with reference to current Australian legislation and other standards from the International Organization for Standardization (ISO) including:

AS ISO 15189 *Medical laboratories – Requirements for quality and competence*

This document should be read within the national pathology accreditation framework including the current versions of the following NPAAC documents:

**Tier 2 Document**
- *Requirements for Medical Pathology Services*

**Tier 3A and all Tier 3B Documents**

**Tier 4 Documents**
- *Requirements for Laboratory Testing for Antibodies to the Human Immunodeficiency Virus (HIV) and the Hepatitis C Virus (HCV)*
- *Requirements for Medical Testing of Human Nucleic Acids*
- *Requirements for Medical Testing of Microbial Nucleic Acids*

**Tier 5 Documents**
- NATA Medical Testing Field Application Document - Requirements for Accreditation
- ISO 13485 *Medical Devices – Quality Management Systems – Requirements for Regulatory Purposes*
- ISO 14971 *Medical Devices – Application of Risk Management to Medical Devices*

In addition to these Standards, Laboratories must comply with the relevant state and territory legislation (including any reporting requirements).
In each section of this NPAAC document, points deemed important for practice are identified as either ‘Standards’ or ‘Commentaries’.

- A Standard is the minimum requirement for a procedure, method, staffing resource or facility that is required before a Laboratory can attain accreditation — Standards are printed in bold type and prefaced with an ‘S’ (e.g. S2.2). The use of the verb ‘must’ in each Standard within this document indicates a mandatory requirement for pathology practice.

- A Commentary is provided to give clarification to the Standards as well as to provide examples and guidance on interpretation. Commentaries are prefaced with a ‘C’ (e.g. C1.2) and are placed where they add the most value. Commentaries may be either normative or informative, depending on both the content and the context of whether they are associated with a Standard or not. Note that when comments are expanding on a Standard or referring to other legislation, they assume the same status and importance as the Standards to which they are attached. Where a Commentary contains the verb ‘must’ then that Commentary is considered to be normative.

Please note that any Appendices attached to this document may be either normative or informative in nature and should be considered to be an integral part of this document.

Please note that all NPAAC documents can be accessed at the Health Website.

While this document is for use in the accreditation process, comments from users would be appreciated and can be directed to:

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CANBERRA ACT 2601

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Email: npaac@health.gov.au
Web: Department of Health

Requirements for the Development and Use of In-House In Vitro Diagnostic Medical Devices (IVDs)
**Background**

In Australia, all in vitro diagnostic medical devices (IVD medical devices or IVDs) that are intended to be used for a therapeutic purpose are subject to regulation under the *Therapeutic Goods Act 1989*. A new regulatory framework for IVDs was implemented on 1 July 2010, following amendments made to the *Therapeutic Goods (Medical Devices) Regulations 2002* (the Regulations) to include IVDs as a subset of medical devices.

The changes made to the legislation apply to all IVDs, including in-house IVDs, and require that all manufacturers of IVDs certify that their products are safe, perform appropriately for their intended purpose, and are manufactured to a high standard of quality. This is achieved by complying with a set of Essential Principles (EPs) which identify performance levels required, hazards to be addressed, or issues to be considered. The Essential Principles for safety and performance form the basis of the IVD regulatory framework and are set out in Schedule 1 of the Regulations (see Appendix A).

The degree of regulatory review each IVD is required to undergo is determined by assessing the risk posed to the health of the individual or to the public through use of that IVD. By applying a set of classification rules that take into account the likelihood of harm and the severity of that harm, products are assigned to one of four risk categories, as follows:

- **Class 1 IVD** – No public health risk or low personal risk
- **Class 2 IVD** – Low public health risk or moderate personal risk
- **Class 3 IVD** – Moderate public health risk or high personal risk
- **Class 4 IVD** – High public health risk

The classification rules for IVDs are detailed in Schedule 2A of the Regulations (see Appendix B). It is the manufacturer's responsibility to determine the classification of each IVD and consideration must be given to its intended use and the overall significance of the final result. The classification rules are relevant to both commercially supplied and in-house IVDs, and except in those cases where a special rule exists, if more than one classification rule applies the IVD must assume the highest classification level.

The classification of the IVD will determine the minimum conformity assessment procedure(s) that a manufacturer must apply to demonstrate compliance with the Essential Principles. The appropriate conformity assessment procedure is further established on the basis of either commercial or in-house manufacture. More detailed information relating to classification of IVDs is available in the TGA guidance document *Classification of IVD Medical Devices*.

**In-house IVDs**

In-house IVDs are separated into two groups for the purposes of determining the appropriate conformity assessment procedure:

- Class 1–3 in-house IVDs; and
- Class 4 in-house IVDs.
Manufacturers of in-house IVDs that are classified as a Class 1 in-house IVD, Class 2 in-house IVD or Class 3 in-house IVD are required to follow the set of conformity assessment procedures detailed in Schedule 3 Part 6A of the Regulations, and as outlined in the TGA document *The Regulatory Requirements for In-House IVDs in Australia*.

Responsibility for review of each Laboratory’s compliance with the requirements rests principally with NATA, and will be carried out in conjunction with their routine Laboratory accreditation visits.

The key requirements for Class 1-3 in-house IVDs are summarised as follows:

- Laboratories manufacturing in-house IVDs are required to notify to the TGA at least annually, all in-house IVDs manufactured. The details will be maintained by the TGA in a repository.
- Laboratories manufacturing in-house IVDs must be accredited as a medical testing laboratory by NATA Laboratory Accreditation Scheme, or by a body determined by the TGA.
- A Laboratory that manufactures in-house IVDs must meet *AS ISO 15189 Medical laboratories – Requirements for quality and competence*.
- A Laboratory that manufactures in-house IVDs must meet *Requirements for the Development and Use of In-house In Vitro Diagnostic Medical Devices (IVDs)*.
- Laboratories must maintain suitable documentation which can be used to demonstrate that each in-house IVD complies with the applicable provisions of the NPAAC Standards and the overarching standard *Requirements for Medical Pathology Services*. Information must include details of the design, development, production, validation and monitoring for each device.
- Laboratories must maintain a post-marketing system that monitors the performance of each in-house IVD, implements corrective action as appropriate to address deficiencies in design and production, and notify the TGA of any adverse events arising from the use of the in-house IVD.

Manufacturers of in-house IVDs that are classified as Class 4 in-house IVDs will be subject to the same level of regulatory control, by the TGA, as applied to the commercial Class 4 IVDs. Further information about conformity assessment procedures for high risk IVDs are available on the TGA website [www.tga.gov.au](http://www.tga.gov.au).

**Transition period for in-house IVDs**

Laboratories manufacturing Class 1 – 3 in-house IVDs for their own use must comply with this NPAAC standard, and must also comply with relevant TGA requirements as detailed in TGA regulations.
Criteria for assessment of in-house IVDs

Standards outlined in this document, used for the assessment of in-house IVDs, have been separated into eleven sections:

1. General requirements
2. Particular requirements – design
3. Particular requirements – production and contracted services
4. Particular requirements – analytical performance
5. Particular requirements – scientific validity
6. Particular requirements – clinical performance
7. Particular requirements – clinical utility
8. Particular requirements – multivariate index assays
9. Particular requirements – monitoring, analysis and improvement
10. Particular requirements – adverse event reporting and recalls

Laboratories should note that the particular requirements outlined in Sections 2 to 11 are intended to ensure that the quality system implemented by all accredited Laboratories under AS ISO 15189, extends to the particular requirements surrounding the production or manufacture of an in-house IVD.

Laboratories that design, produce, and use in-house IVDs need to ensure that their current Quality System (QS) covers these requirements. The extra requirements of the QS to cover activities surrounding in-house IVDs may be summarised as:

- management responsibility
- resource management
- planning and production
- monitoring, analysis and improvement.

It is expected that most of these requirements will be met by modification of the existing QS within the laboratory. Extension of the QS requirements to cover in-house IVDs is considered in Section 2 through to Section 11 in this document.
1 General requirements

(Refer to Standard 1, Standard 2 and Standard 3 in Requirements for Medical Pathology Services)

S1.1 The work environment must be conducive to ensuring that the design, production, and utilisation of in-house IVDs meet the regulatory requirements of this document.

S1.2 An in-house IVD must not be used in the provision of any service by a laboratory unless it has been validated according to these Requirements (except as outlined in S1.3 below).

C1.2(i) In-house IVDs, or commercial tests endorsed by the manufacturer as ‘for research use only’ or ‘not for diagnostic use’, or elements of such tests that are supplied as ‘analyte-specific reagents’ must be validated in accordance with this document if they are to be used in the management of a specific patient, or used to produce a result on a specific patient that may be used for patient management.

C1.2(ii) An IVD is considered to be for research use only when the test results produced using that IVD are neither used for nor intended to be used for patient management.

S1.3 If an in-house IVD cannot be fully validated, and there is no reasonable access to an alternative validated assay, and it is used in one or more of of the circumstances described in C1.3(i), then the report issued with the test result must contain the following statement:

“The test used cannot be fully validated to the current NPAAC Requirements because … [insert a brief reason] … and the results should be interpreted accordingly. For further information please contact the Laboratory.”

C1.3(i) Incompletely validated in-house IVDs may only be used clinically in the following circumstances:

(a) for a new or uncommon condition where its rarity precludes the Laboratory from fulfilling all validation requirements, or

(b) an uncommon application where it is not possible to fulfill all validation requirements, or

(c) a matter of urgency for a disease that poses a serious risk to public health.

C1.3(ii) The Laboratory must have a documented plan for validation.

C1.3(iii) Where an in-house IVD has been used in the circumstances described in S1.3, there must be validation records available to the extent possible.

C1.3(iii) Where an in-house IVD has been used in the circumstances described in S1.3(c), validation must be completed as soon as possible.
S1.4 If any modification is made to a commercial IVD or an existing in-house IVD, it must be treated as a new in-house IVD, and the modification must be validated in accordance with this document.

C1.4(i) This must include changes to intended use (including sample type) or indications for use.

C1.4(ii) Where an IVD has been modified, the validation steps required are determined by the nature of the modification. It must be demonstrated that the changes have been properly assessed and show that the assay continues to perform safely and effectively.

S1.5 Where a Laboratory develops an in-house IVD, that IVD must only be used in that laboratory or its own laboratory network.

C1.5(i) If a Laboratory supplies an in-house IVD that has been manufactured in-house to a Laboratory outside of its own Laboratory network, then that IVD must be assessed as a commercial IVD, and as such, must meet the requirements for commercially supplied IVDs as set out in the Therapeutic Goods (Medical Devices) Regulations.

C1.5(ii) This Standard does not prevent collaboration in the design and development of IVDs or exchange of clinical samples as these are not captured by the definition of an in-house IVD.
2 Particular requirements – Design

(Refer to Standard 3 and Standard 5 in Requirements for Medical Pathology Services)

S2.1 The Laboratory must have and maintain a QS that ensures that all phases in the design, production, utilisation, storage, packaging and transport of in-house IVDs within the Laboratory are sufficient and fully documented to ensure that any in-house IVD so produced is suitable for the purpose for which it was designed.

C2.1 For each in-house IVD, there should be a file containing documents defining IVD specifications, production processes and QS requirements.

S2.2 The IVD must be designed and produced so that when used under the conditions and for the purposes intended, all reasonable measures have been taken to minimise the risk of compromising the health and safety of the patient, the user or any other person.

S2.3 The design and construction of the IVD must conform to the Essential Principles (as outlined in Appendix A), taking account of best practice, where this includes identifying and eliminating risks associated with use (including disposal), and ensuring that adequate protection measures are in place.

C2.3(i) The Laboratory must ensure that the safety of the patient, the operator, and other staff is not compromised by the design, the production, or the use of the validated IVD, through compliance with all state and territory occupational health and safety requirements.


S2.4 The IVD must be designed and produced in a way that ensures it is safe to use over the intended life of the device.

S2.5 Where parts of the in-house IVD are to be purchased from an external source, the Laboratory must ensure that the products purchased will meet the requirements as specified in the design protocol.
3 Particular requirements – Production and Contracted Services

(Refer to Standard 3, Standard 4 and Standard 5 in Requirements for Medical Pathology Services)

Planning, scheduling resources, and purchasing are all part of the manufacture of in-house IVDs as are procedures for monitoring these processes.

S3.1 The Laboratory must establish documented procedures to ensure that products sourced for use in the routine production of in-house IVDs conform to specified requirements and are traceable.

S3.2 The Laboratory must ensure that sub-contracted services that affect the in-house IVD are controlled.

S3.3 Where work environment conditions are critical for the development, production, validation, or use of the in-house IVD, the Laboratory must monitor and control these work environment conditions.

S3.4 Senior staff must have significant diagnostic or research experience with new test development and validation. The depth and complexity of this experience must be commensurate with the range and complexity of IVD development undertaken in the Laboratory.

C3.4 The presence of experienced supervisors and trainers is essential, given their critical involvement in error detection, error correction and problem solving.

S3.5 The Laboratory must plan and carry out the production of in-house IVDs under controlled conditions from design, manufacture and validation of the proposed product to its release for routine use.

C3.5 Controlled conditions include:

i) identification of different stages of assay development, including routine production

ii) implementation of review, verification and validation of the above by designated personnel

iii) documented requirements (e.g. batch size, acceptable performance limits)

iv) identification and use of reference materials and reference measurement procedures

v) identification and use of suitable equipment (i.e. appropriate for use and calibrated)

vi) identification and use of monitoring and measuring processes and devices

vi) planned and documented specifications and processes for the release of the product, and for the receipt of the product at the site of routine storage prior to product use
vii) planned and documented specifications and processes for any packaging and labelling of the final product, accessories or components

viii) planned and documented specifications, processes and records if cleanliness of the environment is critical, as for a production step where sterilisation is required

S3.6 The Laboratory must establish procedures to verify the suitability of the in-house IVD for use in the setting in which it will normally be used.

S3.7 Records relating to production batches and the status of an in-house IVD, or a component thereof, must be traceable and retained for a minimum of 3 years beyond the date of their valid use or 5 years from the date of manufacture.

(a) the Laboratory must maintain records of each batch produced. This must include records of all components of the batch, and any other information relevant to the successful use of the batch in the routine environment.

(b) each batch, and each component within the batch, must be assigned a unique identifier and must be available for the purposes of traceability.

(c) at each stage of production, the product status must be identifiable. A batch of an in-house IVD awaiting final release validation must be clearly identified as such. A batch that has been deemed acceptable for routine use (i.e. validation criteria have been passed) should be identified as such.

(d) if a component within a batch is changed, then that batch must be considered as a new batch and will require re-validation.

S3.8 The Laboratory must establish procedures to ensure that conditions preserving the effectiveness of an in-house IVD are not compromised.

C3.8 Documented procedures or work instructions for the production of the in-house test and its routine use that mitigate variations influencing the efficacy of the assay are required.

S3.9 The Laboratory must ensure that any validation and monitoring measures required for verification of the processing steps are identified, validated and documented.

S3.10 If a batch, or part thereof, is distributed within a Laboratory network, then procedures or instructions must also be issued relating to the transport, receipt and use of the test at its destination. Such instructions should refer to the packaging, transport, handling, storage and identification of the in-house IVD.
4 Particular requirements – Analytical Performance
(Refer to Standard 3, Standard 6B and Standard 7 in Requirements for Medical Pathology Services)

The analytical performance of an in-house IVD medical device is its ability to detect or measure a particular analyte.

S4.1 The stability of the analyte being measured must be determined under the sample storage conditions being utilised.

S4.2 The suitability of an IVD must be demonstrated for use with each Specimen type to be tested under the collection and transport conditions used by the laboratory.

S4.3 The minimum Specimen handling and IVD storage conditions must be determined and documented for the end-users of the in-house IVD.

S4.4 The accuracy and imprecision of in-house IVDs must be determined by at least one of the following methods applicable to the relevant biological material:

(a) the use of certified reference material
(b) comparison with a definitive method or a reference method
(c) performance of recovery experiments
(d) use of validated in-house reference material
(e) performance in external proficiency-testing programs or Laboratory sample exchange programs

C4.4 The materials used in this analysis may include known positive and negative control samples or proficiency material, or be from patients of known clinical states. The threshold for detection of an analyte can be determined by the repeat analysis of samples with results near the cutoff of sensitivity for the IVDs.

S4.5 Sufficient numbers of Specimens and appropriate statistical tools must be employed in the development phase in order to achieve the confidence levels required to satisfy both the analytical performance and the required clinical utility of the test.

C4.5(i) In general, validation of analytical performance requires that the reference interval, analytical sensitivity, limits of detection, analytical specificity, accuracy, imprecision, linearity, and freedom from interference be addressed. Laboratories should strive to achieve the best test performance relevant to the intended clinical use of the IVD.

It is not possible to be prescriptive about the required sensitivity and specificity, nor about the number of Specimens involved, because these will vary with the intended use and with the significance of false results. Where there are significant guidelines available, these should be taken into consideration when assessing IVD performance. An example of this would be use of the recent Public Health Laboratory Network (PHLN) guidelines for gonococcal polymerase chain reaction (PCR).
C4.5(ii) Consideration should be given to seeking statistical advice if required.

S4.6 The source and number of Specimens tested during the validation phase must be documented.

C4.6 Relevant legislative and organisational policies on the use of clinical samples for validation purposes must be followed. 1

S4.7 An estimate of measurement uncertainty of the in-house IVD must be determined where relevant and possible.

S4.8 The detectable and measurable range and limit of detection of the IVD must be determined where it yields a quantitative or, where appropriate, a semi-quantitative result.

C4.8(i) In general, validation of quantitative, semi-quantitative and qualitative IVD procedures should include a comparative evaluation of the IVD against the definitive method, a reference method, or an established procedure with known analytical performance and clinical utility. Where there are discrepancies between the new in-house IVD and its comparator, then an analysis of discrepant results should be performed using other test modalities, review of clinical and other information, and/or referral to another laboratory for testing.

C4.8(ii) Cut-off values for determination of positivity and/or negativity should be derived for an IVD where it yields a semi-quantitative or qualitative result.

C4.8(iii) Where appropriate, it should be demonstrated that IVDs for genetic tests are capable of distinguishing between homozygotes, heterozygotes and hemizygotes for the alleles in question.

S4.9 There must be an investigation to detect possible interference of performance of the IVD, where applicable. The Laboratory must be able to show that at least the most likely interfering substances have been eliminated as a source of error.

C4.9 It is important to know whether the IVD responds uniquely to the analyte that it was designed to measure or detect, or whether there are any other analytes that may also react with the test system to give unexpected or invalid results. This is particularly important in nucleic acid amplification for viral or bacterial markers, where highly conserved areas of DNA may cross many species boundaries.

S4.10 Measurement of robustness must be performed by determining the impact of expected changes in conditions.

C4.10 Expected changes may include operator, equipment (where more than one instrument may be used), different source of reagent, or changes in parameters such as pH, temperature and/or humidity. This is particularly important where the in-house IVD is distributed within a Laboratory network. Measurement can be done by use of controls and an evaluation panel that best tests the critical components of technical performance, particularly the sensitivity and specificity of the test.
S4.11  Reagent stability must be monitored and recorded over time, and comparable performance of the IVD from batch to batch must be demonstrated. Expiry dates, if relevant, must be documented.

C4.11 The internal QC and/or external proficiency testing programs will assist with this process.

S4.12  Equipment should be used in its intended manner or, if not, then the performance of the equipment must be verified as part of the in-house IVD validation.

S4.13  Laboratories must verify the performance of their in-house IVDs for the intended Specimen types and conditions.

C4.13(i) Types of Specimens used for validation should be as similar as possible to the Specimens expected to be routinely received for testing.

C4.13(ii) Specimens should also be chosen to yield results that cover at least the range of possible results expected from patient samples.

S4.14  Laboratories must determine appropriate Specimen handling, storage conditions, and Specimen types, where applicable, and inform collection staff and staff performing the medical testing with the in-house IVD of these limitations.
5 Particular requirements - Scientific Validity
(Refer to Standard 3, Standard 6B and Standard 7 in Requirements for Medical Pathology Services)

The scientific validity of an analyte is the association of that analyte with a clinical condition or physiological state.

Scientific validity is often identified from academic research, and is supported by studies evaluating the analyte for potential clinical applications. The generation and assessment of clinical evidence is an ongoing process. Information related to clinical evidence should be monitored routinely once the in-house IVD is being used for patient testing by the Laboratory.

S5.1 A clinically useful association between the clinical condition and the interpretation of the in-house IVD must be demonstrated. Level 1 or Level 2 published evidence must be cited based on either NHMRC\(^1\), EGAPP\(^2\), Eurogentest Gene cards\(^3\) or other guidelines for the evaluation of such evidence.

C5.1 A single retrospective study or a case-control study (evidence Level 3), whilst important in establishing proof of concept should not necessarily be considered sufficient to clinically validate a new biomarker assay.

S5.2 Requirements of clinicians and other relevant parties, including their expectations relating to the level of service and the type and extent of interpretation, must be considered when designing an in-house IVD.

C5.2 Some of these issues may be the prevalence of the clinical condition, the expected number and frequency of referrals, the need for out-of-hours testing, whether a reference laboratory service is required or whether a lower level of service is sufficient to fulfill the clinical requirements. For example, a qualitative assay for BCR–ABL mRNA may be acceptable for diagnostic purposes in chronic myeloid leukaemia, whereas a quantitative assay will be required for the monitoring of residual disease.
6 Particular requirements - Clinical Performance
(Refer to Standard 3, Standard 6B and Standard 7 in Requirements for Medical Pathology Services)

The clinical performance of an in-house IVD medical device is its ability to yield results that are correlated with a particular clinical condition/physiological state in accordance with target population and intended user.

S6.1 Clinical sensitivity and specificity must be determined by the predictive values of both positive and negative test results relevant to the prevalence of the disorder, and the predicting of future and inherited disease, in the defined test setting.

C6.1 Such data can be derived from multiple sources such as clinical performance studies or experience gained by routine diagnostic testing.

Further information on clinical performance study design may be found in the GHTF document GHTF/SG5/N8:2012 entitled Clinical Evidence for IVD medical Devices – Clinical Performance Studies for In Vitro Diagnostic Medical Devices. (Please note that GHTF documents are now published through the International Medical device Regulators Forum which can be found on the International Medical Device Regulators Forum Website.)
7 Particular requirements - Clinical Utility

(Refer to Standard 3, Standard 6B and Standard 7 in Requirements for Medical Pathology Services)

The clinical utility of any new in-house IVD medical device is the usefulness of results obtained from testing with the IVD and the value of the information to the individual being tested and/or to the broader population.

S7.1 New in-house IVDs for novel tests, or established IVDs for a novel use, must only be offered in the clinical setting (as opposed to the research setting) where there is sufficient evidence of clinical utility for the specific population of patients in which the assay is intended for use.

C7.1(i) Levels of evidence must be assessed based on either NHMRC\(^1\), EGAPP\(^2\) Eurogentest Clinical Utility Gene Cards\(^3\), or other guidelines for the evaluation of such evidence.

C7.1(ii) The pre-test probability of a positive or negative result, and therefore the risks associated with false positive or negative results, can change dramatically from one population to another (e.g. symptomatic vs asymptomatic patients).

C7.1(iii) Assessment of evidence of clinical utility should focus upon the following

a) supporting data from clinicians on why the test is needed and how it is intended to be used for clinical decision making
b) the quality of individual studies, the overall body of evidence, and the quantity of relevant data
c) the consistency and generalisability of findings.

S7.2 The introduction of an in-house IVD must be a planned activity designed to produce a test fit for purpose with regard to clinical performance and clinical utility. The laboratory must be able to demonstrate that the product design and development process is directed towards fulfilling these criteria.

C7.2(i) Some of these issues may be the prevalence of the clinical condition, the expected number and frequency of referrals, the need for out-of-hours testing, whether a reference Laboratory service is required or whether a lower level of service is sufficient to fulfill the clinical requirements. For example, a qualitative assay for BCR–ABL mRNA may be acceptable for diagnostic purposes in chronic myeloid leukaemia, whereas a quantitative assay will be required for the monitoring of residual disease.
8 Particular requirements – Multivariate Index Assays

A Multivariate Index Assay (MIA) means an IVD medical device that -

(c) combines the values of multiple variables using an interpretation function to yield a final, patient-specific result (such as a score or an index etc.) that is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease, and

(d) provides a result whose derivation is non-transparent and cannot be independently derived or verified by the end user.

In other words, the requesting clinician requires information from the test developer, rather than generally accepted information from the clinical community, in order to interpret the MIA result for use in patient management.

Due to the lack of commercially supplied MIAs approved by the TGA, any MIA in use in Australia would by necessity be regarded as an in-house IVD. This may be problematic given that, for proprietary and commercial reasons, the interpretation patterns used to derive a score or index may not have been published. The obligation for clinical validation and utility assessment prior to diagnostic use are, however, not obviated or lessened by the proprietary or commercial nature of such assays.

S8.1 Multivariate Index Assays that have not been approved for diagnostic use by the TGA (or are sold as RUO) must be considered an in-house IVD and evaluated in accordance with this document before being used for diagnostic or therapeutic purposes.

C8.1 In particular, validation, verification and documentation of the algorithm in relation to clinical utility of the assay must be subject to the same level of rigour as other analytical aspects of the assay.
9  Particular requirements - Monitoring, Analysis and Improvement

(Refer to Standard 7 in Requirements for Medical Pathology Services)

The purpose of monitoring the performance of in-house IVDs and the analysis of such monitoring is to ensure that there are processes in place to demonstrate the conformity of the IVD (i.e. its suitability for purpose). The Laboratory should be able to identify and implement any changes necessary to maintain the quality and suitability of the IVD for its intended purpose, and to ensure continued suitability and effectiveness.

S9.1  Previously defined and documented performance characteristics of the IVD must be monitored and measured to verify that product requirements have been met.

C9.1(i) Where Laboratories generate their own in-house quality control material then such material is also an in-house IVD and must be validated as such, and must also be included on the TGA in-house IVD notification database.

C9.1(ii) Where available, Laboratories should use well-characterised and standardised control material that is available to a range of Laboratories. However, if necessary, Laboratories may generate their own quality control material. If so, they must verify stability of such material under the storage and any inter-Laboratory transport conditions used.

C9.1(iii) Where possible, preventive action should be taken to eliminate causes of potential non-conformities in order to prevent their occurrence, as identified through the risk analysis undertaken during the design phase of the IVD.

S9.2  The organisation must establish documented procedures to analyse appropriate data, in order to demonstrate the conformity of the in-house IVD to product specifications.

C9.2  Data should be sourced from multiple sources such as internal audits, user feedback, nonconformity to internal QC or external quality assurance, and feedback from suppliers on specific reagents or products incorporated into the in-house IVD.
10 Particular requirements - Adverse Event Reporting and Recalls

(Refer to Standard 3, Standard 6B and Standard 7 in Requirements for Medical Pathology Services)

Adverse event reporting

The act of reporting information about an adverse event is not an admission of liability for the event or its consequences.

S10.1 Information about an adverse event resulting from the use of an IVD, including an in-house IVD, must be reported to the Laboratory’s senior management and to the Therapeutic Goods Administration (TGA) as soon as practicable but within the timeframes specified

C10.1(i) Information about an adverse event that presents a serious public health threat or concern must be reported to the TGA within 48 hours of the Laboratory becoming aware of the event.

C10.1(ii) Information about an adverse event that led to the death or serious deterioration in the state of health of a patient, a user of the IVD or another person must be reported to the TGA within 10 days of the Laboratory becoming aware of the event.

C10.1(iii) Information about an adverse event which might lead to the death or serious deterioration in the state of health of a patient, a user of the IVD or another person must be reported to the TGA within 30 days of the Laboratory becoming aware of the event.

C10.1(iv) Adverse events may arise from malfunction or deterioration in the characteristics or performance of the IVD, inadequacy in the design, production, labelling or instructions for use of the IVD, or use of the IVD that is contrary to the intended use.

C10.1(v) Adverse events that lead to a serious deterioration in the state of health of a patient, a user of the IVD or another person include:
(a) a life threatening illness or injury
(b) permanent impairment of a body function
(c) permanent damage to a body structure; or
(d) a condition necessitating medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure.

C10.1(vi) Adverse events include ‘near misses’ that did not result in any harm but might have led to the death or serious deterioration in the health of a patient or user of an IVD on another occasion.
C10.1(vii) Reporting of information about adverse events to the TGA should occur through the Medical Device Incident Report Investigation Scheme (IRIS). Forms for reporting can be found on the TGA website and can be submitted to IRIS by mail, fax or email.

C10.1(viii) Reporting of information about adverse patient outcomes to the TGA is not required where the adverse outcome resulted from known limitations in the design of the IVD and the IVD performed within its accepted design parameters e.g. A false negative result leads to a patient not being treated. The analytical sensitivity of the IVD is known to be 95% and is clearly stated in the instructions for use. The IVD was performing within its design parameters, as evidence by results of positive controls performed with the patient’s sample.

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<thead>
<tr>
<th>Examples or causes of adverse events</th>
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<tr>
<td>Malfunction or deterioration in the characteristics or performance of an IVD</td>
<td>False negatives</td>
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<tr>
<td>Inadequacy in the design or manufacture of an IVD</td>
<td>Poor sensitivity/ specificity/change in demographics</td>
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<tr>
<td>Inadequacy in the labelling or instructions for use for an IVD</td>
<td>incorrect use of kit e.g. incubation time</td>
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Recalls

S10.2 A Laboratory must report to its senior management and the TGA, information relating to any malfunction or deterioration in a Class 4 in-house IVD, or inadequacy in its design, production, labelling or instructions for use, that has led the Laboratory to take steps to recover devices of that kind that have been distributed for use in that laboratory or other laboratories within that laboratory network.

C10.2(i) Reporting of recalls to the TGA Recalls Unit can be made by mail, fax or email and should be done in accordance with the requirements of Uniform Recall Procedure for Therapeutic Goods (URPTG). Contact information for the Recalls Unit can be found on the TGA website or by telephoning 1800 020 512.
11 Particular requirements - Documentation

(Refer to Standard 3 in Requirements for Medical Pathology Services)

S11.1 The Laboratory must establish documented procedures for the design, development, production, validation and monitoring of an in-house IVD.

C11.1(i) This documentation on method establishment must include where relevant:

(a) description of the analytical method
(b) selection criteria for reagents and their source(s)
(c) quality and identity of standards used
(d) description of experiments to determine accuracy, imprecision and any other performance characteristics
(e) an estimate of measurement uncertainty
(f) description of stability studies
(g) information on sample processing and storage
(h) summary tables of analytical runs, including any method deviations
(i) any calculations applied to results
(j) summary information on QC samples
(k) post-implementation monitoring and improvement
(l) the use of assays for non-validated criteria
(m) any other relevant information relating to the assay.

Other relevant information may include:

(a) criteria for acceptance or rejection of the standard or calibration curve
(b) criteria for acceptance or rejection of QC
(c) criteria for variability of duplicate assays.

C11.1(ii) The Laboratory must produce a report on method validation that shows the successful completion of appropriate validation studies for the in-house IVD in question.

The method-validation report should include:

(a) summary information
(b) method development and establishment
(c) risk analysis
(d) application of the method to routine sample analysis
(e) management approval for implementation
(f) references
(g) other relevant information.

C11.1(iii) Documentation relating to design, development and validation must be retained for a period of not less than 3 years after cessation of use of the in-house IVD.

C11.1(iv) The summary should list all method-validation studies, verification and revalidation signed by a Laboratory Director or delegate. Any changes to the method over time, including subsequent revalidation and/or verification, should be added to the summary report.

C11.1(v) Where full validation data is not readily accessible for in-house IVDs produced prior to the 2nd Edition of the NPAAC Requirements for the Development and use of In-House IVDs (2007), evidence to support the analytical and of clinical performance of an in-house IVD may be provided in the form of ongoing monitoring and surveillance, which may include historical QAP data, QC reports, clinical correlation.

**Ongoing addition of validation data from routine use**

It is recommended that the following data should be added to the validation file over time-

(a) QC monitoring of sensitivity and specificity
(b) Uncharacteristic changes to detection limits.
Appendix A  Essential Principles (Normative)

Note: The following Essential Principles for safety and performance are taken directly from legislation and provide information about the performance levels required, hazards to be addressed, or issues to be considered when manufacturing medical devices. Readers are encouraged to review the current Regulations from ComLaw (ComLaw Website) noting that legislation may be subject to amendment from time to time.

Therapeutic Goods (Medical Devices) Regulations 2002 Schedule 1

Part 1  General principles

1  Use of medical devices not to compromise health and safety

A medical device is to be designed and produced in a way that ensures that:

(a) the device will not compromise the clinical condition or safety of a patient, or the safety and health of the user or any other person, when the device is used on a patient under the conditions and for the purposes for which the device was intended and, if applicable, by a user with appropriate technical knowledge, experience, education or training; and

(b) any risks associated with the use of the device are:

(i) acceptable risks when weighed against the intended benefit to the patient; and
(ii) compatible with a high level of protection of health and safety.

2  Design and construction of medical devices to conform with safety principles

(1) The solutions adopted by the manufacturer for the design and construction of a medical device must conform with safety principles, having regard to the generally acknowledged state of the art.

(2) Without limiting subclause (1), in selecting appropriate solutions for the design and construction of a medical device so as to minimise any risks associated with the use of the device, the manufacturer must:

(a) first, identify hazards and associated risks arising from the use of the device for its intended purpose, and foreseeable misuse of the device; and

(b) second, eliminate, or reduce, these risks as far as possible by adopting a policy of inherently safe design and construction; and

(c) third, if appropriate, ensure that adequate protection measures are taken, including alarms if necessary, in relation to any risks that cannot be eliminated; and

(d) fourth, inform users of any residual risks that may arise due to any shortcomings of the protection measures adopted.

(3) In paragraph 2 (d):

residual risk, for a medical device, means the risk remaining after the measures described in paragraphs (2) (a), (b) and (c) have been applied.
3 Medical devices to be suitable for intended purpose

A medical device must:

(a) perform in the way intended by the manufacturer; and
(b) be designed, produced and packaged in a way that ensures that it is suitable for one or more of the purposes mentioned in the definition of *medical device* in subsection 41BD (1) of the Act.

4 Long-term safety

A medical device must be designed and produced in a way that ensures that if:

(a) the device is used within the period, indicated by the manufacturer, in which the device can be safely used; and
(b) the device is not subjected to stresses that are outside the stresses that can occur during normal conditions of use; and
(c) the device is regularly maintained and calibrated in accordance with the manufacturer’s instructions;

the characteristics and performances mentioned in clauses 1, 2 and 3 are not adversely affected.

5 Medical devices not to be adversely affected by transport or storage

A medical device must be designed, produced and packed in a way that ensures that the characteristics and performance of the device when it is being used for its intended purpose will not be adversely affected during transport and storage that is carried out taking account of the instructions and information provided by the manufacturer.

6 Benefits of medical devices to outweigh any undesirable effects

The benefits to be gained from the use of a medical device for the performance intended by the manufacturer must outweigh any undesirable effects arising from its use.

Part 2 Principles about design and construction

7 Chemical, physical and biological properties

7.1 Choice of materials

In ensuring that the requirements of Part 1 are met in relation to a medical device, particular attention must be given to:

(a) the chemical and physical properties of the materials used in the device; and
(b) the compatibility between the materials used and biological tissues, cells, body fluids and specimens;

having regard to the intended purpose of the device.
7.2 Minimisation of risks associated with contaminants and residues

(1) A medical device must be designed, produced and packed in a way that ensures that any risks associated with contaminants and residues that may affect a person who is involved in transporting, storing or using the device, or a patient, are minimised, having regard to the intended purpose of the device.

(2) In minimising risks, particular consideration must be given to the likely duration and frequency of any tissue exposure associated with the transportation, storage or use of the device.

7.3 Ability to be used safely with materials etc

(1) A medical device must be designed and produced in a way that ensures that the device can be used safely with any material, substance or gas with which the device may come into contact during normal use or use in routine procedures.

(2) If the device is intended to be used to administer medicine, it must be designed and produced in a way that ensures that the device:

(a) is compatible with the provisions and restrictions applying to the medicine to be administered; and
(b) allows the medicine to perform as intended.

7.4 Verification of incorporated substance

(1) If a medical device incorporates, or is intended to incorporate, as an integral part, a substance that, if used separately, might be considered to be a medicine that is intended to act on a patient in a way that is ancillary to the device:

(a) the safety and quality of the substance must be verified in accordance with the requirements for medicines; and
(b) the ancillary action of the substance must be verified having regard to the intended purpose of the device.

(2) For the purposes of this clause, any stable derivative of human blood or human plasma is considered to be a medicine.

7.5 Minimisation of risks associated with leaching substances

A medical device must be designed and produced in a way that ensures that any risks associated with substances that may leach from the device are minimised.

7.6 Minimisation of risks associated with ingress or egress of substances

A medical device must be designed and produced in a way that ensures that any risks associated with unintentional ingress of substances into, or unintentional egress of substances out of, the device are minimised, having regard to the nature of the environment in which the device is intended to be used.
8 Infection and microbial contamination

8.1 Minimisation of risk of infection and contamination

(1) A medical device must be designed and produced in a way that ensures that the risk of infection to a patient, a user, or any other person, is eliminated or minimised.

(2) The device must be designed in a way that:

(a) allows it to be easily handled; and
(b) if appropriate, minimises contamination of the device or specimen by the patient, user or other person; and
(c) if appropriate, minimises contamination of the patient, user or other person by the device or specimen.

8.2 Control of animal, microbial or recombinant tissues, tissue derivatives, cells and other substances

(1) This clause applies in relation to a medical device that contains:

(a) tissues, tissue derivatives, cells or substances of animal origin that have been rendered non-viable; and
(b) tissues, tissue derivatives, cells or substances of microbial or recombinant origin.

(2) If the tissues, tissue derivatives, cells or substances originated from animals, the animals must have been subjected to appropriate veterinary controls and supervision, having regard to the intended use of the tissues, tissue derivatives, cells or substances.

(3) If the medical device contains tissues, tissue derivatives, cells or substances of animal origin, a record must be kept of the country of origin of each animal from which the tissues, tissue derivatives, cells or substances originated.

(4) The processing, preservation, testing and handling of tissues, tissue derivatives, cells or substances of animal, microbial or recombinant origin must be carried out in a way that ensures the highest standards of safety for a patient, the user of the device, and any other person.

(5) In particular, the production process must implement validated methods of elimination, or inactivation, in relation to viruses and other transmissible agents.

Note: This may not apply to certain IVD medical devices if the characteristics mentioned in subclause 8.2 (5) are integral to the intended purpose of the IVD medical device.

8.3 Medical devices to be supplied in a sterile state

(1) This clause applies in relation to a medical device that is intended by the manufacturer to be supplied in a sterile state.

(2) The device must be designed, produced and packed in a way that ensures that the device is sterile when it is supplied, and will remain sterile, if stored and transported in accordance with the directions of the manufacturer, until the protective packaging is opened or damaged.
(3) The device must be produced and sterilised using an appropriate validated method.
(4) The device must be produced in appropriately controlled conditions.

8.4 Medical devices to be supplied in a non-sterile state

(1) A medical device that is intended by the manufacturer to be supplied in a non-sterile state must be packed in a way that ensures that the device maintains the level of cleanliness stipulated by the manufacturer.

(2) If the device is intended to be sterilised before it is used, the device must be packed in a way that:

   (a) ensures that the risk of microbial contamination is minimised; and
   (b) is suitable, having regard to the method of sterilisation that the manufacturer indicates is to be used for the device.

(3) The device must be produced in appropriately controlled conditions.

8.5 Distinction between medical devices supplied in sterile and non-sterile state

If a medical device is supplied in both a sterile state and a non-sterile state, the information provided with the device must clearly indicate whether the device is in a sterile state or a non-sterile state.

9 Construction and environmental properties

9.1 Medical devices intended to be used in combination with other devices or equipment

A medical device that is intended by the manufacturer to be used in combination with another medical device or other equipment (including a connection system) must be designed and produced in a way that ensures that:

   (a) the medical device, and any other device or equipment with which it is used, operate in a safe way; and
   (b) the intended performance of the device, and any other device or equipment with which it is used, is not impaired.

9.2 Minimisation of risks associated with use of medical devices

A medical device must be designed and produced in a way that ensures that, as far as practicable, the following risks are removed or minimised:

   (a) the risk of injury arising from the physical features of the device;
   (b) any risks associated with reasonably foreseeable environmental conditions;
   (c) the risk of reciprocal interference involving other devices that are normally used in an investigation or treatment of the kind for which the device is intended to be used;
   (d) any risks arising if maintenance or calibration of the device is not possible;
   (e) any risks associated with the ageing of materials used in the device;
(f) any risks associated with loss of accuracy of any measuring or control mechanism of the device;
(g) the risk of fire or explosion occurring during normal use of the device, and in the event of a single fault condition, especially if the device is intended to be exposed to flammable substances or substances that can cause combustion;
(h) the risks associated with disposal of any waste substances.

10 Medical devices with a measuring function

(1) A medical device that has a measuring function must be designed and produced in a way that ensures that the device provides accurate, precise and stable measurements within the limits indicated by the manufacturer and having regard to the intended purpose of the device.

(2) The measurement, monitoring and display scale of the device must be designed and produced in accordance with ergonomic principles, having regard to the intended purpose of the device.

(3) The measurements made by the device must be expressed:

(a) in Australian legal units of measurement; or
(b) if the device measures a physical quantity for which no Australian legal unit of measurement has been prescribed under the National Measurement Act 1960, in units approved by the Secretary for the particular device.

11 Protection against radiation

11.1 Minimisation of exposure to radiation

A medical device must be designed and produced in a way that ensures that the exposure of a patient, the user, or any other person, to radiation is minimised, having regard to the levels of radiation required to enable the device to perform its therapeutic and diagnostic functions and the intended purpose of the device.

11.2 Medical devices intended to emit radiation

(1) This clause applies in relation to a medical device that is intended by the manufacturer to emit hazardous levels of visible or invisible radiation because the emission is necessary for a specific medical purpose, the benefit of which is considered to outweigh the risks inherent in the emission.

(2) The device must be designed and produced in a way that ensures that the user can control the level of the emission.

(3) The device must be designed and produced in a way that ensures the reproducibility and tolerance of relevant variable parameters.

(4) If practicable, the device must be fitted with a visual indicator or an audible warning, or both, that operates if potentially hazardous levels of radiation are emitted.
11.3 Minimisation of exposure to unintended radiation

A medical device must be designed and produced in a way that ensures that the exposure of a patient, the user, or any other person, to the emission of unintended, stray or scattered radiation is minimised.

11.4 Operating instructions

The operating instructions for a medical device that emits radiation must include detailed information about the following matters:

(a) the nature of the radiation emitted;
(b) the means by which patients and users can be protected from the radiation;
(c) ways to avoid misusing the device;
(d) ways to eliminate any risks inherent in the installation of the device.

11.5 Medical devices intended to emit ionising radiation — additional requirements

(1) This clause applies, in addition to clauses 11.1 to 11.4, in relation to a medical device that is intended by the manufacturer to emit ionising radiation.

(2) The device must be designed and produced in a way that ensures that, if practicable, the quantity, geometry and energy distribution (or quality) of radiation emitted can be controlled and varied, having regard to the intended purpose of the device.

(3) If the device is intended to be used for diagnostic radiology, the device must be designed and produced in a way that ensures that, when used in relation to a patient for a purpose intended by the manufacturer:

(a) the device achieves an appropriate image or output quality for that purpose; and
(b) the exposure of the patient, or the user, to radiation is minimised.

(4) If the device is intended to be used for therapeutic radiology, the device must be designed and produced in a way that ensures that the delivered dose of radiation, the type and energy of the radiation beam and, if appropriate, the energy distribution of the radiation beam, can be reliably controlled and monitored.

12 Medical devices connected to or equipped with an energy source

12.1 Medical devices incorporating electronic programmable systems

A medical device that incorporates an electronic programmable system must be designed and produced in a way that ensures that:

(a) the performance, reliability, and repeatability of the system are appropriate for the intended purpose of the device; and
(b) any consequent risks associated with a single fault condition in the system are minimised.
12.2 Safety dependent on internal power supply

(1) This clause applies in relation to a medical device if the safety of a patient on whom the device is to be used will depend on an internal power supply for the device.

(2) The device must be fitted with a means of determining the state of the power supply.

12.3 Safety dependent on external power supply

(1) This clause applies in relation to a medical device if the safety of a patient on whom the device is to be used will depend on an external power supply for the device.

(2) The device must be fitted with an alarm system that indicates whether a power failure has occurred.

12.4 Medical devices intended to monitor clinical parameters

A medical device that is intended by the manufacturer to be used to monitor one or more clinical parameters of a patient must be fitted with an appropriate alarm system to warn the user if a situation has developed that could lead to the death of the patient or a severe deterioration in the state of the patient’s health.

12.5 Minimisation of risk of electromagnetic fields

A medical device must be designed and produced in a way that ensures that the risk of an electromagnetic field being created that could impair the operation of other devices or equipment being used in the vicinity of the medical device is minimised.

12.6 Protection against electrical risks

A medical device must be designed and produced in a way that ensures that, as far as possible, when the device is installed correctly, and the device is being used for an intended purpose under normal conditions of use and in the event of a single fault condition, patients, users, and any other persons, are protected against the risk of accidental electric shock.

12.7 Protection against mechanical risks

A medical device must be designed and produced in a way that ensures that a patient, the user, and any other person, is protected against any mechanical risks associated with the use of the device.

12.8 Protection against risks associated with vibration

(1) A medical device must be designed and produced in a way that ensures that any risks associated with vibrations generated by the device are minimised.

(2) If vibrations are not part of the intended performance of the device, particular attention must be given to relevant technical progress, and the available means, for limiting vibrations, particularly at source.
12.9 Protection against risks associated with noise

(1) A medical device must be designed and produced in a way that ensures that any risks associated with noise emitted by the device are minimised.

(2) If noise is not part of the intended performance of the device, particular attention must be given to relevant technical progress, and the available means, for reducing the emission of noise, particularly at source.

12.10 Protection against risks associated with terminals and connectors

A medical device that is intended by the manufacturer to be connected to an electric, gas, hydraulic, pneumatic or other energy supply must be designed and produced in a way that ensures that any risks to the user associated with the handling of a terminal or connector on the device, in relation to the energy supply, are minimised.

12.11 Protection against risks associated with heat

A medical device must be designed and produced in a way that ensures that, during normal use, any accessible part of the device (other than any part intended by the manufacturer to supply heat or reach a given temperature), and any area surrounding an accessible part of the device, does not reach a potentially dangerous temperature.

12.12 Protection against risks associated with administration of energy or substances

(1) This clause applies in relation to a medical device that is intended by the manufacturer to be used to administer energy or a substance to a patient.

(2) The device must be designed and produced in a way that ensures that:

(a) the delivered rate and amount of energy, or of the substance, can be set and maintained accurately to ensure the safety of the patient and the user; and

(b) as far as possible, the accidental release of dangerous levels of energy or of the substance is prevented.

(3) The device must be fitted with a means of indicating or, if appropriate, preventing inadequacies in the rate and amount of energy, or of the substance, administered that might cause danger to the patient, the user or any other person.

(4) The functions of each control and indicator on the device must be clearly specified on the device.

(5) If the instructions for the operation of the device, or the operating or adjustment parameters for the device, are displayed by means of a visual system incorporated into the device, the instructions or parameters must be able to be understood by the user and, if appropriate, the patient.
12.13 Active implantable medical devices

(1) An active implantable medical device must incorporate, display, emit or exhibit a code or unique characteristic that can be used to identify:

   (a) the type of device; and
   (b) the manufacturer of the device; and
   (c) the year of manufacture of the device.

(2) The code or unique characteristic must be able to be read without the need for surgery to the person in whom the device is implanted.

13 Information to be provided with medical devices

13.1 Information to be provided with medical devices — general

(1) The following information must be provided with a medical device:

   (a) information identifying the device;
   (b) information identifying the manufacturer of the device;
   (c) information explaining how to use the device safely;

having regard to the training and knowledge of potential users of the device.

(2) In particular:

   (a) the information required by clause 13.3 must be provided with a medical device; and
   (b) if instructions for use of the device are required under subclause 13.4, the information mentioned in subclause 13.4 (3) must be provided in those instructions.

(3) The information:

   (a) must be provided in English; and
   (b) may also be provided in any other language.

Note The information may also include diagrams or drawings.

(4) The format, content and location of the information must be appropriate for the device and its intended purpose.

(5) Any number, letter, symbol, or letter or number in a symbol, used in the information must be legible and at least 1 millimetre high.

(6) If a symbol or identification colour that is not included in a medical device standard is used in the information provided with the device, or in the instructions for use of the device, the meaning of the symbol or identification colour must be explained in the information provided with the device or the instructions for use of the device.
13.2 Information to be provided with medical devices — location

(1) Unless it is impracticable or inappropriate to do so, the information required to be provided with a medical device must be provided on the device itself.

(2) If it is not practicable to comply with subclause (1) in relation to the provision of the information, the information must be provided:

(a) on the packaging used for the device; or
(b) in the case of devices that are packaged together because individual packaging of the devices for supply is not practicable — on the outer packaging used for the devices.

(3) If it is not practicable to comply with subclause (1) or (2) in relation to the provision of the information required under subregulation 10.2 (1) or clause 13.3, the information must be provided on a leaflet supplied with the device.

(4) If it is not practicable to comply with subclause (1) or (2) in relation to the provision of the information required under clause 13.4, the information must be provided in a printed document or using other appropriate media.

13.3 Information to be provided with medical devices — particular requirements

The information mentioned in the following table must be provided with a medical device.

<table>
<thead>
<tr>
<th>Item</th>
<th>Information to be provided</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The manufacturer’s name, or trading name, and address</td>
</tr>
<tr>
<td>2</td>
<td>The intended purpose of the device, the intended user of the device, and the kind of patient on whom the device is intended to be used (if this information is not obvious)</td>
</tr>
<tr>
<td>3</td>
<td>Sufficient information to enable a user to identify the device, or if relevant, the contents of packaging</td>
</tr>
<tr>
<td>4</td>
<td>Any particular handling or storage requirements applying to the device</td>
</tr>
<tr>
<td>5</td>
<td>Any warnings, restrictions, or precautions that should be taken, in relation to use of the device</td>
</tr>
<tr>
<td>6</td>
<td>Any special operating instructions for the use of the device</td>
</tr>
<tr>
<td>7</td>
<td>If applicable, an indication that the device is intended for a single use only</td>
</tr>
<tr>
<td>8</td>
<td>If applicable, an indication that the device has been custom-made for a particular individual or health professional and is intended for use only by that individual or health professional</td>
</tr>
</tbody>
</table>
| 9    | If applicable, an indication that:  
(a) if the device is a medical device other than an IVD medical device — the device is intended for pre-market clinical investigation; or  
(b) if the device is an IVD medical device — the device is intended for performance evaluation only |
### Item Information to be provided

<table>
<thead>
<tr>
<th>Item</th>
<th>Information to be provided</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>For a sterile device, the word ‘STERILE’ and information about the method that was used to sterilise the device</td>
</tr>
<tr>
<td>11</td>
<td>The batch code, lot number or serial number of the device</td>
</tr>
<tr>
<td>12</td>
<td>If applicable, a statement of the date (expressed in a way that clearly identifies the month and year) up to when the device can be safely used</td>
</tr>
<tr>
<td>13</td>
<td>If the information provided with the device does not include the information mentioned in item 12 — a statement of the date of manufacture of the device (this may be included in the batch code, lot number or serial number of the device, provided the date is clearly identifiable)</td>
</tr>
<tr>
<td>14</td>
<td>If applicable, the words ‘for export only’</td>
</tr>
</tbody>
</table>

*Note* In addition to the information mentioned in the above table, regulation 10.2 requires certain information to be provided with a medical device.

### 13.4 Instructions for use

1. Instructions for the use of a medical device must be provided with the device.
2. However, instructions for the use of a medical device need not be provided with the device, or may be abbreviated, if:
   
   a. the device is a Class I medical device, a Class Iia medical device or a Class 1 IVD medical device; and
   b. the device can be used safely for its intended purpose without instructions.

3. Instructions for the use of a medical device must include information mentioned in the following table that is applicable to the device.

<table>
<thead>
<tr>
<th>Item</th>
<th>Information to be provided</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The manufacturer’s name, or trading name, and address</td>
</tr>
<tr>
<td>2</td>
<td>The intended purpose of the device, the intended user of the device, and the kind of patient on whom the device is intended to be used</td>
</tr>
<tr>
<td>3</td>
<td>Information about any risk arising because of other equipment likely to be present when the device is being used for its intended purpose (for example, electrical interference from electro-surgical devices or magnetic field interference from magnetic resonance imaging devices)</td>
</tr>
<tr>
<td>4</td>
<td>Information about the intended performance of the device and any undesirable side effects caused by use of the device</td>
</tr>
<tr>
<td>5</td>
<td>Any contra-indications, warnings, restrictions, or precautions that may apply in relation to use of the device</td>
</tr>
<tr>
<td>6</td>
<td>Sufficient information to enable a user to identify the device, or if relevant, the contents of packaging</td>
</tr>
<tr>
<td>Item</td>
<td>Information to be provided</td>
</tr>
<tr>
<td>------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>7</td>
<td>Any particular handling or storage requirements applying to the device</td>
</tr>
<tr>
<td>8</td>
<td>If applicable, an indication that the device is intended for a single use only</td>
</tr>
<tr>
<td>9</td>
<td>If applicable, an indication that the device has been custom-made for a particular individual or health professional and is intended for use only by that individual or health professional</td>
</tr>
</tbody>
</table>
| 10   | If applicable, an indication that:  
|      | (a) if the device is a medical device other than an IVD medical device — the device is intended for pre-market clinical investigation; or  
|      | (b) if the device is an IVD medical device — the device is intended for performance evaluation only |
| 11   | For a sterile device, the word ‘STERILE’ and information about the method that was used to sterilise the device |
| 12   | For a device that is intended by the manufacturer to be supplied in a sterile state:  
|      | (a) an indication that the device is sterile; and  
|      | (b) information about what to do if sterile packaging is damaged; and  
<p>|      | (c) if appropriate, instructions for resterilisation of the device |
| 13   | For a medical device that is intended by the manufacturer to be sterilised before use — instructions for cleaning and sterilising the device which, if followed, will ensure that the device continues to comply with the applicable provisions of the essential principles |
| 14   | Any special operating instructions for the use of the device |
| 15   | Information to enable the user to verify whether the device is properly installed and whether it can be operated safely and correctly, including details of calibration (if any) needed to ensure that the device operates properly and safely during its intended life |
| 16   | Information about the nature and frequency of regular and preventative maintenance of the device, including information about the replacement of consumable components of the device during its intended life |
| 17   | Information about any treatment or handling needed before the device can be used |
| 18   | For a device that is intended by the manufacturer to be installed with, or connected to, another medical device or other equipment so that the device can operate as required for its intended purpose — sufficient information about the device to enable the user to identify the appropriate other medical device or equipment that will ensure a safe combination |
| 19   | For an implantable medical device — information about any risks associated with its implantation |</p>
<table>
<thead>
<tr>
<th>Item</th>
<th>Information to be provided</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>For a reusable device:</td>
</tr>
<tr>
<td></td>
<td>(a) information about the appropriate processes to allow reuse of the device (including information about cleaning, disinfection, packaging and, if appropriate, resterilisation of the device); and</td>
</tr>
<tr>
<td></td>
<td>(b) an indication of the number of times the device may be safely reused</td>
</tr>
<tr>
<td>21</td>
<td>For a medical device that is intended by the manufacturer to emit radiation for medical purposes — details of the nature, type, intensity and distribution of the radiation emitted</td>
</tr>
<tr>
<td>22</td>
<td>Information about precautions that should be taken by a patient and the user if the performance of the device changes</td>
</tr>
<tr>
<td>23</td>
<td>Information about precautions that should be taken by a patient and the user if it is reasonably foreseeable that use of the device will result in the patient or user being exposed to adverse environmental conditions</td>
</tr>
<tr>
<td>24</td>
<td>Adequate information about any medicinal product that the device is designed to administer, including any limitations on the substances that may be administered using the device</td>
</tr>
<tr>
<td>25</td>
<td>Information about any medicine (including any stable derivative of human blood or blood plasma) that is incorporated, or is intended to be incorporated, into the device as an integral part of the device</td>
</tr>
<tr>
<td>25A</td>
<td>For a medical device, other than an IVD medical device, information about any tissues, tissue derivatives, cells or substances of animal origin that have been rendered non-viable, or tissues, cells or substances of microbial or recombinant origin that are included in the device</td>
</tr>
<tr>
<td>26</td>
<td>Information about precautions that should be taken by a patient and the user if there are special or unusual risks associated with the disposal of the device</td>
</tr>
<tr>
<td>27</td>
<td>Information about the degree of accuracy claimed if the device has a measuring function</td>
</tr>
<tr>
<td>28</td>
<td>Information about any particular facilities required for use of the device or any particular training or qualifications required by the user of the device</td>
</tr>
<tr>
<td>29</td>
<td>For an IVD medical device, information (including, to the extent practicable, drawings and diagrams) about the following:</td>
</tr>
<tr>
<td></td>
<td>(a) the scientific principle (the ‘test principle’) on which the performance of the IVD medical device relies;</td>
</tr>
<tr>
<td></td>
<td>(b) specimen type, collection, handling and preparation;</td>
</tr>
<tr>
<td></td>
<td>(c) reagent description and any limitations (for example, use with a dedicated instrument only);</td>
</tr>
</tbody>
</table>
### Item Information to be provided

- **(d)** assay procedure including calculations and interpretation of results;
- **(e)** interfering substances and their effect on the performance of the assay;
- **(f)** analytical performance characteristics, such as sensitivity, specificity, accuracy and precision;
- **(g)** clinical performance characteristics, such as sensitivity and specificity;
- **(h)** reference intervals, if appropriate;
- **(i)** any precautions to be taken in relation to substances or materials that present a risk of infection.

### 14 Clinical evidence

Every medical device requires clinical evidence, appropriate for the use and classification of the device, demonstrating that the device complies with the applicable provisions of the essential principles.

Note   See regulation 3.11 and the clinical evaluation procedures.

### 15 Principles applying to IVD medical devices only

1. An IVD medical device must be designed and manufactured in a way in which the analytical and clinical characteristics support the intended use, based on appropriate scientific and technical methods.
2. An IVD medical device must be designed in a way that addresses accuracy, precision, sensitivity, specificity, stability, control of known relevant interference and measurement of uncertainty, as appropriate.
3. If performance of an IVD medical device depends in whole or part on the use of calibrators or control materials, the traceability of values assigned to the calibrators or control material must be assured through a quality management system.
4. An IVD medical device must, to the extent reasonably practicable, include provision for the user to verify, at the time of use, that the device will perform as intended by the manufacturer.
5. An IVD medical device for self-testing must be designed and manufactured so that it performs appropriately for its intended purpose, taking into account the skills and the means available to users and the influence resulting from variation that can reasonably be anticipated in the user’s technique and environment.
6. The information and instructions provided by the manufacturer of an IVD medical device for self-testing must be easy for the user to understand and apply.
7. An IVD medical device for self-testing must be designed and manufactured in a way that reduces, to the extent practicable, the risk of error in the use of the device, the handling of the sample and the interpretation of results.
Appendix B  Classification rules for IVDs (Normative)

Note: The following classification rules for IVDs are taken directly from legislation and present the criteria used for assigning the risk classification to an IVD medical device. Readers are encouraged to review the current Regulations from ComLaw (ComLaw Website) noting that legislation may be subject to amendment from time to time.

Therapeutic Goods (Medical Devices) Regulations 2002, Schedule 2A

1.1 Detection of transmissible agents posing high public health risk

An IVD medical device intended to be used for any of the following purposes is classified as a Class 4 IVD medical device or a Class 4 in-house IVD medical device:

(a) to detect the presence of, or exposure to, transmissible agents in blood, blood components, blood products, cells, tissues or organs or any derivatives of these products of human or animal origin, in order to assess their suitability for transfusion or transplantation;

(b) to detect the presence of, or exposure to, a transmissible agent that causes a serious disease with a high risk of propagation in Australia.

1.2 Detection of red blood cell antigens and antibodies and non-red cell typing

(1) An IVD medical device is classified as a Class 3 IVD medical device or a Class 3 in-house IVD medical device if:

(a) the device is intended to be used for detection of biological markers in order to assess the immunological compatibility of blood, blood components, blood products, cells, tissues or organs that are intended for transfusion or transplantation; and

(b) the device is not a device mentioned in subclause (2).

(2) An IVD medical device intended to detect any of the following markers mentioned for the following blood group systems is classified as a Class 4 IVD medical device or a Class 4 in-house IVD medical device:

(a) ABO system — ABO1 (A), ABO2 (B), ABO3 (AB);
(b) Rhesus system — RH1 (D), RH2 (C), RH3 (E), RH4 (c), RH5 (e);
(c) Kell system — KEL1 (K);
(d) Kidd system — JK1 (Jka), JK2 (Jkb);
(e) Duffy system — FY1 (Fya), FY2 (Fyb).
1.3 Detection of transmissible agents or biological characteristics posing moderate public health risk or high personal risk

(1) An IVD medical device is classified as a Class 3 IVD medical device or a Class 3 in-house IVD medical device if it is intended for any of the following uses:

(a) detecting the presence of, or exposure to, a sexually transmitted agent;
(b) detecting the presence in cerebrospinal fluid or blood of an infectious agent with a risk of limited propagation;
(c) detecting the presence of an infectious agent, if there is a significant risk that an erroneous result would cause death or severe disability to the individual or foetus being tested;
(d) pre-natal screening of women in order to determine their immune status towards transmissible agents;
(e) determining infective disease status or immune status, if there is a risk that an erroneous result will lead to a patient management decision resulting in an imminent life-threatening situation for the patient;
(f) the selection of patients:
   (i) for selective therapy and management; or
   (ii) for disease staging; or
   (iii) in the diagnosis of cancer;
(g) human genetic testing;
(h) to monitor levels of medicines, substances or biological components, when there is a risk that an erroneous result will lead to a patient management decision resulting in an immediate life-threatening situation for the patient;
(i) the management of patients suffering from a life-threatening infectious disease;
(j) screening for congenital disorders in a foetus.

Note for paragraph (f) An IVD medical device would fall into Class 2 under clause 1.7 if:

(a) a therapy decision would usually be made only after further investigation; or
(b) the device is used for monitoring.

(2) Despite subclause (1), an IVD medical device is classified as a Class 3 IVD medical device or a Class 3 in-house IVD medical device if it is used to test for transmissible agents included in the Australian National Notifiable Diseases Surveillance System (NNDSS) list as published from time to time by the Australian government.

1.4 IVD medical devices for self-testing

An IVD medical device for self-testing is classified as a Class 3 IVD medical device unless:

(a) the result of the examination is not determining a serious condition, ailment or defect; or
(b) the examination is preliminary and follow-up additional testing is required.

1.5 Non assay-specific quality control material

Despite clauses 1.1 to 1.4, an IVD medical device that is intended to be used as non assay-specific quality control material is classified as a Class 2 IVD medical device or a Class 2 in-house IVD medical device.
1.6 Reagents, instruments etc

(1) A reagent or other article that possesses specific characteristics, intended by the manufacturer, to make it suitable for in vitro diagnostic procedures related to a specific examination is classified as a Class 1 IVD medical device or a Class 1 in-house IVD medical device.

(2) Despite clauses 1.1 to 1.5, the following IVD medical devices are classified as Class 1 IVD medical devices or Class 1 in-house IVD medical devices:

(a) an instrument, intended by the manufacturer, to be specifically used for in vitro diagnostic procedures;
(b) a specimen receptacle, other than a specimen receptacle that is intended for use in self-testing;
(c) a microbiological culture medium.

(3) In this clause:

examination means a set of operations having the object of determining the value or characteristics of a property.

Note In some disciplines (for example, microbiology) an examination is the combination of a number of tests, observations or measurements.

specimen receptacle means a device, whether vacuum-type or not, specifically intended by its manufacturer for the primary containment and preservation of a specimen derived from the human body for the purpose of in vitro diagnostic examination.

Note 1 A specimen receptacle is considered to be an IVD medical device.

Note 2 A product for general laboratory use is not an IVD medical device unless the product is specifically intended by its manufacturer to be used for in vitro diagnostic examination.

1.7 Other IVD medical devices are Class 2 IVD medical devices

An IVD medical device not mentioned in this Schedule is classified as a Class 2 IVD medical device or a Class 2 in-house IVD medical device.

1.8 IVD medical devices intended for export only

Despite clauses 1.1 to 1.7, an IVD medical device is classified as a Class 1 IVD medical device if it is intended by the manufacturer for export only.
Appendix C  Procedures applying only to certain classes of in-house IVD medical devices (Normative)

Therapeutic Goods (Medical Devices) Regulations 2002 Schedule 3, Part 6A

The following conformity assessment procedures are taken directly from legislation and outline the minimum requirements to be met by laboratories producing Class 1-3 in-house IVDs. Readers are encouraged to review the current Regulations from ComLaw ([CamLaw Website](http://www.camlaw.gov.au)) noting that legislation may be subject to amendment from time to time.

1.1 Overview

The conformity assessment procedures set out in this Part apply to the manufacturer of a Class 3 in-house IVD medical device, Class 2 in-house IVD medical device or Class 1 in-house IVD medical device.

1.2 Procedures

(1) The manufacturer must, using a form approved by the Secretary, notify the Secretary, on a day (the notification day) no later than 1 July 2014 and then annually on a day no later than the notification day, of the following matters:

(a) contact details of the laboratory;
(b) in-house IVD medical devices manufactured.

Penalty: 10 penalty units.

(2) A laboratory that manufactures an in-house IVD medical device must meet the National Pathology Accreditation Advisory Council performance standard Requirements for the Development and Use of In-house In Vitro Diagnostic Devices (IVDs) as amended from time to time.

(3) A laboratory that manufactures an in-house IVD medical device must be accredited as a medical testing laboratory by the National Association of Testing Authorities (NATA) or by a conformity assessment body determined by the Secretary.

(4) A laboratory that manufactures an in-house IVD medical device must meet the standard published by the International Organization for Standardization known as ISO 15189, Medical laboratories — Particular requirements for quality and competence as amended from time to time.

1.3 Information to be given to authorised person

(1) If asked to do so by an authorised person, the manufacturer of a device must:

(a) give to the Secretary the following information in relation to the quality management system or the kinds of medical device to which the system is applied:
(i) a copy of the documentation mentioned in subclause (2);
(ii) data for the design of the kinds of medical device (for example, the results of any analysis of the device, calculations or tests);
(iii) data for the manufacture of the kinds of medical device (for example, inspection reports, test data, calibration data, information about the qualifications of staff); and

(b) arrange for tests specified by the authorised person to be carried out for the purpose of checking whether the quality management system is operating effectively.

(2) The documentation must include the following information:

(a) the manufacturer’s quality objectives;
(b) the organisation of the manufacturer’s business, including a description of the following:

(i) the organisational structure of the business;
(ii) the responsibilities of managerial staff and their authority in relation to the quality of the design and production of medical devices manufactured by the manufacturer;
(iii) the methods of monitoring whether the system is operating effectively, including whether the desired quality of design and product is being achieved and how products that fail to meet the desired quality are controlled;

(c) the design of the kind of medical device to which the system is to be applied, including the following:

(i) details of the processes, systems and measures used for controlling, monitoring and verifying that, at each stage of the design process, the device complies with the applicable provisions of the essential principles;
(ii) a general description of the kind of device, and of any variants of the kind of device, that the manufacturer plans to manufacture;
(iii) details of the design specifications for the kind of device, including:

(A) any medical device standard or conformity assessment standard that has been applied to the device; and
(B) the results of the risk analysis carried out; and
(C) if no medical device standard or conformity assessment standard, or part of it, has been applied to the device — the solutions adopted to ensure that each device complies with the applicable provisions of the essential principles;

(iv) for a kind of device that is intended by the manufacturer to be connected to another device — evidence demonstrating that the device will comply with the applicable provisions of the essential principles when it is connected to the other device and both devices are being used for their intended purposes;

(v) a statement indicating whether or not the device contains viable tissues, cells or substances of human or animal origin;

(vi) a copy of the clinical evidence, in relation to the kind of device, required by the clinical evaluation procedures;
(vii) a copy of the information to be provided with the kind of device, when relevant;

(d) the inspection and quality assurance techniques to be applied in the production of the kind of medical device to which the system is to be applied, including information about the following:

(i) the processes and procedures to be used and the documents relating to those processes and procedures;
(ii) the procedures to be used for purchasing goods or services in relation to the production of the kind of device and the documents relating to those procedures;
(iii) product identification procedures to be prepared and kept up-to-date from drawings, specifications or other documents at each stage of production;

(e) the tests or trials to be carried out before, during and after production of the kind of medical device to which the system is to be applied, including information about:

(i) the frequency with which the tests or trials are to be carried out; and
(ii) the equipment (including the traceability of the calibration of the equipment) used, or to be used, to carry out the tests or trials;

(f) the system for reviewing experience gained in the post-production phase for the kind of medical device to which the quality management system has been applied, and the means by which any necessary corrective action will be applied to the design or production of such devices;

(g) whether:

(i) a conformity assessment standard, or part of a conformity assessment standard, has been applied to the system; or
(ii) the solutions adopted to ensure that the system is of a kind that its application will ensure that each medical device to which the system is applied complies with the applicable provisions of the essential principles, the classification rules and these conformity assessment procedures, at each stage, from the design of the device until its final inspection before being supplied.

(3) If any inspections or tests are carried out by an authorised person in relation to the manufacturer’s premises, or medical devices produced by the manufacturer, the manufacturer may ask the authorised person to give to the manufacturer a report stating the findings of the inspections or tests.

1.4 Post-marketing system

(1) The manufacturer of an in-house IVD medical device must establish, and keep up-to-date, a post-marketing system that complies with subclause (2) for use for a device of that kind.
(2) A post-marketing system complies with this subclause in relation to an in-house IVD medical device if the system requires the manufacturer of the device to:

(a) systematically review experience gained in the post-production phase for medical devices of that kind; and

(b) implement appropriate means to apply any necessary corrective action for the design or production of those devices; and

(c) notify the Secretary as soon as practicable after becoming aware of:

(i) information relating to:

(A) any malfunction or deterioration in the characteristics or performance of the kind of device; or

(B) any inadequacy in the design, production, labelling, instructions for use or advertising materials of the kind of device; or

(C) any use in accordance with, or contrary to, the use intended by the manufacturer of the kind of device;

that might lead, or might have led, to the death of a patient or a user of the device, or to a serious deterioration in his or her state of health; or

(ii) information relating to any technical or medical reason for a malfunction or deterioration of a kind mentioned in subparagraph (i) that has led the manufacturer to take steps to recover devices of that kind that have been distributed.
Appendix D  FAQs and Examples – for guidance (Informative)

The following guidance is provided in response to frequently asked questions relating to in-house IVDs.

If a Laboratory makes up its own culture media, are these in-house IVDs?

If a Laboratory utilises their own formulation to make microbiological culture media from general Laboratory reagents (e.g. dehydrated powders and agar bases) with the intention of using them for a diagnostic purpose, then they are considered Class 1 in-house IVDs.

If a Laboratory makes up its own stains, are these in-house IVDs?

If a laboratory utilises their own formulation to make stains, dyes or other staining solutions (e.g. fixatives, decolorising agents) with the intention of using them for a diagnostic purpose, then those stains are considered in-house IVDs.

What are the requirements for validating stains that are prepared in-house?

The validation of staining solutions that have been prepared ‘in-house’ should consider the following aspects:

- Physical properties of the individual components used as well as the finished product (e.g. pH, ionic concentration, water quality – deionised/filtered).
- Testing of the finished stain using a range of specimens as appropriate to the stain type (tissue sections, organisms, control slides etc).
- The test slides should cover the range of features in tissue or cells that are expected to be seen under routine conditions of use.

When validating the performance of an in-house IVD, what constitutes statistically significance numbers?

Because circumstances can vary so much, even between similar IVDs, it is not possible to specify the minimum numbers of samples required to be tested in any situation, but ideally every effort should be made to make the evaluation of sensitivity and specificity of the assay statistically significant.

Each variable aspect of an assay which may have an impact on assay performance should be considered, including (but not limited to):

- The range and number of samples tested should be selected to cover the entire measuring range – i.e., the upper, middle lower concentrations of the target analyte, with particular consideration given to the upper and lower extremes for quantitative or semi-quantitative assays, or for qualitative assays the limit of detection (i.e., near cut off);
- Samples should be selected from a population range similar to the intended setting of use (adults, elderly, children, neonates, endemic persons (important for some infectious diseases);
- The recommended Specimen types (serum, plasma, urine, saliva etc), and storage stability;
Specimen characterisation should include enough samples to cover likely variants of the target analyte, including different serotypes, sub-types, weakly reacting specimens, or if there is more than one analyte, a number of mixed targets across the selection of specimens tested. If there is difficulty in availability of suitable Specimens, every effort should be made to obtain them from alternative sources (other Laboratories, commercially sourced Specimens, spiked).

A selection of samples representing similar or commonly cross-reacting clinical conditions or infectious diseases should be included.

What particular aspects of my in-house assay do I need to validate?

The classification and intended purpose of the in-house IVD will determine depth of validation required and the aspects to be validated,

- An in-house IVD developed from first principles or developed (or modified) from a published source would require more validation than an in-house IVD based on changes made to a commercially supplied IVD.
- Where a commercial IVD has been modified, validation should focus principally on the effects of that change.
- Factors to be considered include the target analyte of the IVD, whether it is a qualitative or quantitative assay, complexity of methodology, the availability and range of characterised samples, the availability of published (peer-reviewed) articles relating to that IVD or other similar IVDs. Each performance characteristic should be considered (as appropriate) and may include: sensitivity and specificity (both analytical and clinical); accuracy (trueness); precision (reproducibility and repeatability); measuring range; linearity; and assay cut-off.

How are assays that are labelled research use only (RUO), including components such as primers or probes to be treated?

- If a Laboratory is utilising primers and probes as components for use in an in-house IVD, or if they utilising a RUO marked kit which they intend to use for a diagnostic purpose (i.e. reporting of patient results) then the assay they have developed meets the definition of an in-house IVD and the Laboratory is required to validate in accordance with this document.
- The suppliers of kits marked RUO should be aware that under the Therapeutic Goods Act, the definition of a therapeutic good includes goods that are represented in any way to be, or that are, whether because of the way in which the goods are presented or for any other reason, likely to be taken to be for therapeutic use.
- Representation for therapeutic use includes verbal or written statements made in relation to products as part of their labelling, advertising or promotion (regardless of the RUO label).

We perform flow cytometry on blood, bone marrow and tissue samples for the diagnosis of haematological malignancies. There is considerable heterogeneity between these malignancies and therefore the number of permutations for each panel of antibodies is considerable and is sample dependent. Does each panel of antibodies need to be validated and considered to be an in-house IVD?

- The test should be considered to be an in-house IVD for the identification of the most appropriate immunophenotype to assist with the accurate diagnosis of the malignancy. The in-house IVD may therefore be registered as a single test “Immunophenotyping of haematological malignancy” and not as each component (eg CD3, CD19 etc). Validation
should include the performance of each individual component singly and when used in a cocktail as well as the ability to accurately determine the immunophenotype.
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3. Eurogentest – Health Professionals – Clinical utility gene cards: good practice information for disease-specific tests


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