NATIONAL PATHOLOGY ACCREDITATION ADVISORY COUNCIL

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

(Fourth Edition 2018)

NPAAC Tier 3B Document

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Contents

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 In Vitro Diagnostic Medical Devices (Fourth Edition 2018)* 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.

These Requirements 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 are in the TGA Class 1, 2, and 3 risk categories require assessment to this Standard for accreditation purposes 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 need to be assessed by TGA to the relevant conformity assessment procedures prescribed in the *Therapeutic Goods (Medical Devices) Regulations 2002*[*1] in order to be listed on the ARTG.

It is a basic principle of laboratory practice that test methods should be validated before use and that the level of validation should be commensurate with the risks associated with the IVD, with respect to the user, 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.

[*] Therapeutic Goods (Medical Devices) Regulations 2002[1]

Abbreviations

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

Definitions

Term	Definition
Accuracy	means closeness of the agreement between the result of a measurement and a true value of the measurement.[†] If the true value cannot be determined, then an accepted value may be used as a substitute.
Adverse event	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.
Analytical performance	means the ability of an IVD medical device to detect or measure a particular analyte.
Clinical evidence for an IVD medical device	means all the information that supports the scientific validity and performance for its use as intended by the manufacturer.
Clinical utility	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.
Clinical performance	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.
Conformity assessment	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.[‡]
In vitro diagnostic medical device (IVD)	means the same as the definition in the *Therapeutic Goods (Medical Devices) Regulations 2002*[§1]. This is 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

[†] International vocabulary of basic and general terms in Metrology (VIM) draft 2004 revision, definition 3.5
[‡] Derived from ISO/IEC 17011:2004 – *Conformity assessment - General requirements for accreditation bodies accrediting conformity assessment bodies*
[§] Therapeutic Goods (Medical Devices) Regulations 2002[1]

Term	Definition
	medical device.
In-house IVD	means the same as the definition in the *Therapeutic Goods (Medical Devices) Regulations 2002*.[§1] This an IVD medical device that is: (a) within the confines or scope of an Australian laboratory or Australian laboratory network: (i) developed from first principles; or (ii) developed or modified from a published source; or (iii) developed or modified from any other source; or (iv) used for a purpose, other than the intended purpose assigned by the manufacturer; and (b) not supplied for use outside that laboratory or laboratory network.
Imprecision	means the dispersion of independent results of measurements obtained under specified conditions. Imprecision is expressed numerically as standard deviation or coefficient of variation.[**] *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.*
Intended purpose	means the same as the definition in the *Therapeutic Goods (Medical Devices) Regulations 2002*[§1] and is 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; and (d) technical documentation describing the mechanism of action of the device.
Medical Laboratory Network	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 and programs.
Method validation	means the process of defining an analytical requirement, and confirming that the method under consideration has performance capabilities consistent with that requirement.
Method verification	means procedures to test to what extent the performance data obtained by manufacturers during method validation can be reproduced in the environments of end-users.
Modified IVD	means any IVD medical device that is: (a) used for a purpose other than that intended by the original manufacturer; or

[**] Harmonized Terminology Database of the Clinical and Laboratory Sciences Institute

Term	Definition
	(b) not used in accordance with the manufacturer's instructions for use or the methodology prescribed (i.e. modifications that could affect the performance of the device and would require validation).
A Multivariate Index Assay (MIA)	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.
Requirements for Medical Pathology Services (RMPS)	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.
Scientific validity	means the association of an analyte to a clinical condition / physiological state.

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Introduction

The *Requirements for the Development and Use of In-house In Vitro Diagnostic Medical Devices (IVDs) (Fourth Edition 2018)* is an NPAAC Tier 3B document and 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.

The document has been reviewed to reflect the current regulatory requirements for 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*

ISO 13485 *Medical devices – Quality Management Systems – Requirements for Regulatory Purposes*

ISO 14971 *Medical devices – Application of Risk Management to Medical Devices*

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

All Tier 2 and Tier 3 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*

In addition to these Standards, laboratories must also comply with the relevant state and territory legislation (including any reporting requirements).

In each section of this 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 Department of Health.

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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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 to the *Therapeutic Goods (Medical Devices) Regulations 2002*[††1] (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 EP for safety and performance form the basis of the IVD regulatory framework and are set out in Schedule 1 of the Regulations.[††1]

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 consider the likelihood of harm and the severity of that harm, products are assigned to one of four risk categories:

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.[††1] 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 EP. The appropriate conformity assessment procedure is further established based on either commercial or in-house manufacture. More detailed information relating to classification of IVDs is available in the guidance document *Classification of IVD Medical Devices* available on the TGA website.[‡‡2]

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.

[††] Therapeutic Goods (Medical Devices) Regulations 2002[1]
[‡‡] TGA Classification of IVD medical devices[2]

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 guidance document *The Regulatory Requirements for In-House IVDs in Australia*.[§§3]

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.

Class 1-3 in-house IVDs are exempt from inclusion in the ARTG subject to certain conditions:

- Laboratories manufacturing in-house IVDs are required to notify the TGA by 1 July 2017 of all in-house IVDs manufactured. After 1 July 2017 laboratories are required to re-notify the TGA only when new in-house IVDs are introduced (by 1 July of the next financial year). The details will be maintained by the TGA in a repository.
- Laboratories manufacturing in-house IVDs must be accredited as a medical testing laboratory and must meet *AS ISO 15189 Medical laboratories – Requirements for quality and competence.* NATA/RCPA may be able to assess certain laboratories (that are outside the scope of ISO 15189) that manufacture Class 1-3 in-house IVDs against ISO/IEC 17025, *General requirement for the competence of testing and calibration laboratories.* Requests for assessment against ISO/IEC 17025 will be considered by NATA/RCPA on a case by case basis and only in exceptional circumstances (e.g. veterinary laboratories that primarily perform testing on animals but may also perform testing on human samples on request).
- A laboratory that manufactures (or develops) in-house IVDs must meet the NPAAC *Requirements for the Development and Use of In-house In Vitro Diagnostic Medical Devices (IVDs)*.
- Laboratories must maintain suitable documentation that can be used to demonstrate that each in-house IVD complies with the applicable provisions of the NPAAC Standards, including the *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.

Laboratories that manufacture Class 4 in-house IVDs need to include these in the ARTG, unless otherwise exempt. To do this, laboratories have a choice of two pathways:

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

Further information about conformity assessment procedures for Class 4 in-house IVDs is available on the TGA website.

[§§] The Regulatory Requirements for In-House IVDs in Australia[3]

Criteria for assessment of in-house IVDs

Standards outlined in this document, used for the assessment of in-house IVDs, have been separated into 11 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 of tests
11. Particular requirements – documentation.

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 to Section 11.

1. General Requirements

(Refer to Standard 2, Standard 4, Standard 5, Standard 7 and Standard 8 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 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 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 **must** 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 fulfil 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**, validation records **must** be available to the fullest possible extent.

C1.3(iv) Where an in-house IVD has been used in the circumstances described in C1.3(i), validation **must** be completed as soon as possible.

S1.4 If any modification is made to a commercially supplied 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 these Requirements.

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 commercially supplied IVD, and as such, **must** meet the requirements for commercially supplied IVDs as set out in the *Therapeutic Goods (Medical Devices) Regulations 2002*.[***1]

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.

[***] Therapeutic Goods (Medical Devices) Regulations 2002[1]

2. Particular Requirements – Design

(Refer to Standard 5 and Standard 7 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 produced is suitable for purpose.

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,[†††1] (refer to *Appendix A*) and consider 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, production, or the use of the validated IVD, through compliance with all state and territory occupational health and safety requirements.

C2.3(ii) ISO 14971 Medical Devices - *Application of Risk Management to Medical Devices*. Annex H: Guidance on risk management for in vitro diagnostic devices provides useful information on identification, evaluation and control of risk.

S2.4 The IVD must be designed and produced in a way that ensures it is safe to use for the entire 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.

[†††] refer to Schedule 1 of the Regulations available on Federal Register of Legislation[1]

3. Particular Requirements – Production and Contracted Services

(Refer to Standard 5, Standard 6 and Standard 7 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

vii) 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 before product use

viii) planned and documented specifications and processes for any packaging and labelling of the final product, accessories or components

ix) planned and documented specifications, processes and records if cleanliness of the environment is critical (e.g. 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 4 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 documented procedures to ensure that conditions preserving the effectiveness of an in-house IVD are not compromised.

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 5, 8 and Standard 9B 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 used.

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 cut-off of sensitivity for the IVDs.

S4.5 Sufficient numbers of specimens and appropriate statistical tools must be employed in the development phase 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 PHLN guidelines for gonococcal PCR.[‡‡‡4]

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.

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

[‡‡‡] PHLN guidelines for gonococcal PCR[4]

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 must be used in its intended manner or, 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 8B 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[5], EGAPP[6], Eurogentest Gene cards[7] 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.

6. Particular Requirements - Clinical Performance

(Refer to Standard 5 and Standard 8B 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 according to a target population and an intended user.

S6.1 The clinical sensitivity and specificity as well as positive and negative predictive values must be available for the relevant condition.

C6.1(i) Such data can be derived from multiple sources such as clinical performance studies, published studies from other groups, or experience gained by routine diagnostic testing.

C6.1(ii) 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 International Medical Device Regulators Forum

7. Particular Requirements - Clinical Utility

(Refer to Standard 5 and Standard 8B 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 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 in accordance with relevant criteria, such as NHMRC[5], EGAPP2[6], Eurogentest Clinical Utility Gene Cards[7], or other guidelines for the evaluation of such evidence. The criteria source **must** be cited.

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 on:

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 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 fulfil 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) is 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.

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

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 these Requirements 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 rigor as other analytical aspects of the assay.

9. Particular Requirements – Monitoring, Analysis and Improvement

(Refer to Standard 3 and Standard 8B in *Requirements for Medical Pathology Services*)

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 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 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 of Tests

(Refer to Standard 2, Standard 3, Standard 5 and Standard 7B 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 in-house IVD, must be reported to the laboratory's designated person and to the Therapeutic Goods Administration (TGA) as soon as practicable but within the timeframes specified.

C10.1(i) Laboratories **must** have documented procedures for reporting adverse events to the designated person and the TGA.

C10.1(ii) 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(iii) 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 in-house IVD or another person **must** be reported to the TGA within 10 days of the laboratory becoming aware of the event.

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

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

C10.1(vi) Adverse events that lead to a serious deterioration in the state of health of a patient, a user of the in-house 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(vii) 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 in-house IVD on another occasion.

C10.1(viii) Reporting of information about adverse events to the TGA should occur through the Medical Device Incident Report Investigation Scheme (IRIS).[****8]

C10.1(ix) 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 in-house IVD and the in-house 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 in-house IVD is known to be 95% and is clearly stated in the instructions for use/method. The in-house IVD was performing within its design parameters, as evidence by results of positive controls performed with the patient's sample. Although not initially considered an adverse event that requires reporting to TGA, such incidents must be recorded and monitored by the laboratory (as per **S9.2**) to ensure the in-house IVD is operating within expected limitations. Multiple incidences may identify a problem with an in-house IVD that subsequently could require reporting to the TGA as an adverse event.

C10.1(x) All Adverse event reporting procedures **must** be documented in the Quality Management System.

Table 1 Examples of adverse events and requirements

Adverse event	**Requirement**
A false negative result associated with the malfunction of an in-house IVD that presents a serious public health threat (e.g. false negative HIV donor screening result due to a malfunction of the in-house IVD).	Report to TGA within 48 hours of the laboratory becoming aware of the event.
A false negative result associated with the deterioration in the performance of an in-house IVD that has led to the death or serious deterioration in the state of health of a patient (e.g. false negative result for bacterial meningitis due to deterioration in the sensitivity of the in-house IVD).	Report to TGA within 10 days of the laboratory becoming aware of the event
A false negative or false positive result associated with an inadequacy in the design or manufacture of an in-house IVD which might lead to the death or serious deterioration in the health of a patient (e.g. incorrect genotype identification due to an inadequacy in the design of the in-house IVD that has resulted in inappropriate patient treatment).	Report to TGA within 30 days of the laboratory becoming aware of the event

**** Medical Device Incident Report Investigation Scheme (IRIS)[8]

Recalls

S10.2 A laboratory must report to its designated person and the TGA, information relating to any malfunction or deterioration of 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) Laboratories **must** have documented procedures in place for reporting any such recalls for Class 4 in-house IVDs to its designated person and the TGA.

C10.2(ii) 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 Recalls Unit.[††††]

[††††] TGA Recalls

11. Particular Requirements - Documentation

(Refer to Standard 5 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) a) 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.

b) 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 **must** 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 4 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 before the NPAAC *Requirements for the Development and Use of In-House IVDs* (Second Edition 2007), evidence to support the analytical and clinical performance of an in-house IVD may be provided in the form of ongoing monitoring and surveillance, which may include historical EQA data, QC reports or 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)

The Essential Principles are set out in Schedule 1 of the *Therapeutic Goods (Medical Devices) Regulations 2002* and provide information about the safety and 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 the Federal Register of Legislation noting that the legislation may be subject to amendment from time to time.

Appendix B Classification rules for IVDs (Normative)

The classification rules applicable for IVDs are located in Schedule 2A of the *Therapeutic Goods (Medical Devices) Regulations 2002*, and set out the assigned risk classification for an IVD medical device. Readers are encouraged to review the current Regulations on the Federal Register of Legislation noting that the legislation may be subject to amendment from time to time.

Appendix C Procedures applying to in-house IVD medical devices (Normative)

The conformity assessment procedures in Schedule 3, Part 6A of the *Therapeutic Goods (Medical Devices) Regulations 2002* set out the minimum requirements to be met by laboratories manufacturing Class 1-3 in-house IVDs.

The conformity assessment procedures in Schedule 3, Part 6B of the *Therapeutic Goods (Medical Devices) Regulations 2002* set out the minimum requirements to be met by laboratories manufacturing Class 4 in-house IVDs. Alternatively, if preferred, laboratories that manufacture Class 4 in-house IVD have the choice of applying the conformity assessment procedures set out in Schedule 3, Part 1 of the *Therapeutic Goods (Medical Devices) Regulations 2002* (i.e. same conformity assessment procedures as those for manufacturers of commercially supplied IVDs).

A copy of the current Regulations that may be subject to change from time to time can be accessed from Federal Register of Legislation.

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, decolourising 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 commercially supplied 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).

A laboratory performs 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 notified to the TGA as a single test "Immunophenotyping of haematological malignancy" and not as each component (e.g. 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.

References

1. Federal Register of Legislation 2018, *Therapeutic Goods (Medical Devices) Regulations 2002*, Therapeutic Goods Administration, Canberra, viewed 18 January 2018, <https://www.legislation.gov.au/Details/F2018C00049>
2. Therapeutic Goods Administration 2015, *Classification of IVD Medical Devices*, Therapeutic Goods Administration, Canberra, viewed 18 January 2018, <https://www.tga.gov.au/publication/classification-ivd-medical-devices>
3. Therapeutic Goods Administration 2017, *Regulatory Requirements for In-house IVDs*, Therapeutic Goods Administration, Canberra, viewed 18 January 2018, <https://www.tga.gov.au/publication/regulatory-requirements-house-ivds-australia>
4. Smith D W, Tapsall J W, Lum G 2005, *Guidelines for the use and interpretation of nucleic acid detection tests for Neisseria gonorrhoeae in Australia*, the Public Health Laboratory Network, Canberra, viewed 30 January 2018, <http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-phln-gono-guidelines.htm>
5. National Health and Medical Research Council 2007, Updated May 2015, *National Statement on Ethical Conduct on Research Involving Humans*, National Health and Medical Research Council, Canberra, viewed 18 January 2018, <https://www.nhmrc.gov.au/guidelines-publications/e72>
6. Teutsch S, Bradley L, Palomaki G, et al. *The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative: methods of the EGAPP Working Group*. Genetics in Medicine 2009;11(1):3-14.
7. Eurogentest 2011, *Harmonizing Genetic Testing Across Europe*, Eurogentest, Leuven, viewed 18 January 2018, <http://www.eurogentest.org/web/info/public/unit3/geneCards.xhtml>
8. Therapeutic Goods Administration 2018, *Reporting Adverse Events*, Therapeutic Goods Administration, Canberra, viewed 18 January 2018, <https://www.tga.gov.au/reporting-adverse-events>

Bibliography

British Standards Institute 2002, *Stability Testing for In Vitro Diagnostic Reagents* (EN 13640), British Standards Institute, London

Clinical and Laboratory Standards Institute 2012, *EP17-2A – Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline*, Clinical and Laboratory Standards Institute, Pennsylvania

Clinical and Laboratory Standards Institute 2012, *EP25 –A Evaluation of stability of In Vitro Diagnostic Reagents; Approved Guidelines*, Clinical and Laboratory Standards Institute, Pennsylvania

Clinical and Laboratory Standards Institute 2017, *Harmonized Terminology Database*, Clinical and Laboratory Sciences Institute, viewed 12 January 2018, < http://htd.clsi.org/>

Global Harmonization Task Force 2012, *GHTF/SG5/N6:2012 – Clinical evidence for IVD medical devices – Key Definitions and Concepts*, Global Harmonization Task Force

Global Harmonization Task Force 2012, *GHTF/SG5/N7:2012 – Clinical Evidence for IVD medical devices – Scientific Validity Determination and Performance evaluation*, Global Harmonization Task Force

Global Harmonization Task Force 2012, *GHTF/SG5/N8:2012 – Clinical evidence for IVD medical devices – Clinical Performance studies for In Vitro Diagnostic Medical Devices*, Global Harmonization Task Force

International Organization for Standardization 1993, *International Vocabulary of Basic and General Terms in Metrology (VIM)*, 2nd edition, International Organization for Standardization, Geneva

International Organization for Standardization 2003, *Medical Devices - Quality Management Systems - Requirements for Regulatory Purposes (ISO 13485)*, International Organization for Standardization, Geneva

International Organization for Standardization 2005, *Medical Devices - Application of Risk Management to Medical Devices (ISO/FDIS 14971)*, International Organization for Standardization, Geneva

International Organization for Standardization 2004, *ISO/IEC 17011:2004 – Conformity assessment - General requirements for accreditation bodies accrediting conformity assessment bodies*, International Organization for Standardization, Geneva

Joint Technical Committee CH-026, Safety in Laboratories 2005, *Australian and New Zealand Standard (AS/NZS) Safety in Laboratories (AS/NZS 2243)*, Standards Australia, Sydney

Merlin T, Weston A, Tooher R. *Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence'*. BMC Medical Research Methodology 2009;9:34-42

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