

ACS POLICY DOCUMENT

CLINICAL FLOW CYTOMETRY IN VITRO DIAGNOSTIC TEST REQUIREMENTS

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Paper-based publications

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The Australasian Cytometry Society (ACS) was established in 1979 and incorporated in 1992 with the aim of promoting research, development and applications in, and to disseminate knowledge of flow cytometry.

A function of the ACS is to assist with development and application of clinical flow cytometry applications for hospitals and laboratories in the diagnosis and treatment of disease. This includes the preparation of policy documents, guidelines and education programs.

Policy documents produced by the ACS are issued to describe consensus agreement among its members and associates about methods and behaviors it follows in conducting its affairs activities both general and in specific circumstances. These policy documents while not binding are provided as a guide and to assist laboratories with conforming to legislative requirements for testing considered acceptable for good laboratory practice.

Failure to consider these policy documents may pose a risk to public health and patient safety.

SCOPE

The ‘*ACS Policy Document, In Vitro Diagnostic Test Notification*’ is an ACS policy document intended to assist ACS members and associates with understanding the process of clinical flow cytometry test notification for the Therapeutics and Goods Administration as In-Vitro Diagnostic Tests.

This document is to be read in conjunction with the TGA document ‘*Requirements for the Development and Use of In-House In Vitro Diagnostic Medical Devices (IVDs)*’, a Tier 3B National Pathology Accreditation Advisory Council (NPAAC) document, and the Tier 2 ‘*Requirements for Medical pathology Services*’ NPAAC document. The former 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”.

This policy statement aims for adherence to 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.

References to specific guidelines in the related NPAAC documents are provided for assistance under the headings in this document.

This document is for use in laboratories providing clinical flow cytometry services.

ABBREVIATIONS

ACS	Australasian Cytometry Society
ARTG	Australian Register of Therapeutic Goods
In-house IVD	In-house In Vitro Diagnostic Medical Device
MRD	Minimal residual disease testing
NATA	National Association of Testing Authorities
NPAAC	means National Pathology Accreditation Advisory Council
QC	Quality Control
RMPS	means Requirements for Medical Pathology Services, Tier 2, NPAAC Standard
RUO	Research Use Only
TGA	Therapeutic Goods Administration

DEFINITIONS

CD	Cluster definition number used to identify individual markers e.g. CD3 for the pan T cell antigen
Count	means to acquire data on a flow cytometer
Cocktail	means an antibody reagent test mixture pre-prepared for use over the period of time validated.
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
Guidelines for Clinical Flow Cytometry Laboratory Practice	means the overarching ACS document broadly outlining standards for good clinical flow cytometry laboratory 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.

In vitro diagnostic medical device (IVD)	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.
In-house IVD	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.
Modified IVD	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 (i.e., modifications that could affect the performance of the device and would require validation).
markers	means antigens on cells of interest used for diagnostic purposes
Requirements for Medical Pathology Services (RMPS)	means the overarching NPAAC 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.
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
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INTRODUCTION

This ACS policy document, together with ‘*Guidelines for Clinical Flow Cytometry Laboratory Practice*’, is intended to provide guidance and consensus for clinical flow cytometry laboratories in their notification and compliance with TGA requirements for Class 1-3 in-house IVD Testing.

This is a policy document only not a regulation or standard. The aim is that all in-house tests are produced to be safe and reliant following standards for design, production, verification and validation.

In each section of this document, points deemed important are identified as either ‘Policy’ or ‘Commentary’, as follows:

- A Policy is a consensus recommendation for acceptable methods or activity for organisation members, aiming for best medical laboratory practice for a procedure, method, staffing resource or facility. Policies are prefaced with a ‘P’ (e.g. P2.2).
- A Commentary may be provided to give clarification to the Policies 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.

This document should be read in conjunction with NPAAC documents:

- Tier 2 ‘*Requirements for Medical Pathology Services*’
- Tier 3B ‘*Requirements for the Development and Use of In-House In Vitro Diagnostic Medical Devices (IVDs)*’

Class 1-3 In-house IVDs are exempt from inclusion on the Australian Register of Therapeutic Goods (ARTG) provided the laboratory is NATA accredited (i.e., to ISO 15189), complies with the NPAAC standard ‘*Requirements for the development and use of in-house IVDs*’ and notifies the TGA of the Class 1-3 in-house IVDs that they hold by 1 July 2017. Class 1-3 In-house IVDs are therefore not ‘registered’ or ‘included’ on the ARTG.

This is a notification process only, where information provided to the TGA cannot be accessed by other laboratories or the public, but may be provided by the TGA to NATA to assist in assessments of individual laboratories. The Class 1-3 in-house IVD notification database will also be used by the TGA to assist in the investigation of any reported adverse event associated with the use or performance of a Class 1-3 in-house IVD.

BACKGROUND

In Australia, the IVD regulatory framework was introduced in July 2010. All in vitro diagnostic medical devices (IVDs) are regulated as a subset of medical devices in the *Therapeutic Goods (Medical Devices) Regulations 2002* (the Regulations). The framework applies to both commercially supplied IVDs and in-house IVDs and is designed to ensure that all IVDs undergo a level of scrutiny that is relevant to the risk classification for the device. All IVDs are required to meet minimum requirements for quality, safety and performance.

The transition period for laboratories to notify TGA of Class 1-3 in-house IVD tests ends 1st July 2017. The predominance of in-house testing in clinical flow cytometry laboratories has made this notification process of great interest. As a result this document has been produced to assist with laboratories seeking clarification and consensus on the process involved. The primary referring authority for this document remains the TGA and NATA organisational staff from whose assistance for commentary throughout this document is acknowledged.

1. CLASS 1-3 IN-HOUSE IVD TEST NOTIFICATION

To be read in accordance with the NPAAC standard, *‘Requirements for the Development and Use of In-House In Vitro Diagnostic Medical Devices (IVDs)’*.

P1.1 All flow cytometry assays which are in-house IVDs need to be notified to the TGA. This includes flow cytometry assays developed from Research Use Only (RUO) products and any modification of a commercial IVD, including deviation from the manufacturer’s described methodology or analysis that would require validation.

C 1.1(i) This includes modification of analysis, gating and analyser setup, reagent dilution, use of antibodies beyond manufacturer’s expiry date, use of a commercially supplied IVD for an application that is not intended by the manufacturer of the IVD.

C1.1(ii) Tests to be notified include those billable by Medicare and those that are not.

P1.2 Notification process prior to 1st July 2017 involves providing a list of Class 1-3 in-house IVDs and their associated risk classification (i.e., Class 1, 2 or 3 in-house IVD) to the TGA.

C1.2(i) At the time of notification to the TGA, laboratories must be NATA accredited for all the Class 1-3 in-house IVDs being used in their laboratory.

C1.2(ii) TGA does not require validation documentation to be submitted in the notification

C1.2(iii) All TGA requires in the notification is the attachment of a document that lists the Class 1-3 in-house IVDs and the classification (e.g., in excel spreadsheet format). If preferred, laboratories can attach a copy of their NATA test list identifying their Class 1-3 in-house IVDs.

C1.2(iv) The TGA will not reject a notification if a laboratory makes an error in classification but may contact the laboratory and provide assistance to correct any significant errors.

C1.2(v) Laboratories that introduce new Class 1-3 in-house IVDs after 1st July 2017 will need to obtain NATA accreditation for these tests by 1 July

of the following financial year and submit a new notification to the TGA by this date.

P1.3 Instruments, individual reagents etc that are used in an in-house test do not need to be identified in the notification.

P1.4 In-house developed quality control material is considered to be part of the overall in-house test procedure and does not need to be notified as an individual in-house IVD.

C1.4 Additional in-house developed QC material that is not part of an overall in-house test can be included in the notification by selecting a field that will be available in the notification form (e.g., ‘Haematology related quality control material’) but does not need to be individually identified in the in-house test list.

P1.5 Availability of a commercially supplied test kit/product does not mean it is automatically suitable for the clinical application required.

C1.5 For example guidelines for the diagnosis of HLA-B27 require two clones of HLA-B27 to be tested. This may require a combination of commercially supplied IVDs and/or in-house test methods that can then be validated and notified as a single in-house IVD test. Similarly for PNH testing, and malignancy testing where ‘back bone’ cocktails may be provided requiring modification by addition of supplementary markers.

2. TEST NOMENCLATURE

P2.1 Tests can be notified as in-house IVDs for the identification of diagnostic immunophenotypes (i.e., notified as a single test), not individual CD components (e.g. CD3, CD4).

P2.2 Tests can be notified according to their intended use.

C2.2(i) Tests for minimal residual disease, myelodysplasia, relapse, disease monitoring, surface markers, may share the test name for malignancy diagnosis e.g. *Haematology Oncology Immunophenotyping*

- C2.2(ii) Individual panels of a test need not be notified individually e.g. ‘*Haematology Oncology Immunophenotyping*’ for a complex of test panels.
- C2.2(iii) Immune status testing, lymphocyte subsets, T cell subsets though used to determine immune status, or monitor CD4 or CD19 therapy may share the same test name e.g. *Lymphocyte Subset Immunophenotyping*
- C2.2(iv) Use of the descriptive ‘*Immunophenotyping*’, ‘*by Flow Cytometry*’ identify the test as flow cytometry fluorescent marker based, and not alternative test modalities e.g. “HbF Test” may mean blood morphology Kleihauer Test.

P2.3 It is recommended consensus notification names be used for common flow cytometry tests.

Common test names may include:

- *Haematology Oncology Immunophenotyping*
- for leukaemia, lymphoma, myeloma, MRD etc:
- *Lymphocyte Subset Immunophenotyping*
- for immune status and HIV therapy (CD4)
- *CD34 Haematopoietic Progenitor Cell Enumeration*
- *Paroxysmal Nocturnal Haemoglobinuria Immunophenotyping*
- *Haemoglobin F Immunophenotyping*
- *HLA-B27 Immunophenotyping*
- *Hereditary Spherocytosis Screening by Flow Cytometry*
- *Flow Cytometric Assessment of HLA Alloantibodies*

3. TEST CLASSIFICATION

TGA tests are classed into 4 groups according to risk of the disease diagnosed to individual patients and the public in general:

- 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

Further information can be found in the IVD classification guidance document on TGA's website, <https://www.tga.gov.au/publication/classification-ivd-medical-devices>

P3 Most clinical flow cytometry tests fall into Class 2 or 3 IVDs.

Recommended consensus classifications for common flow cytometry tests are:

Class 2: *HLA-B27 Immunophenotyping; Haemoglobin F Immunophenotyping; Hereditary Spherocytosis Screening by Flow Cytometry*

Class 3: *Haematology Oncology Immunophenotyping; Lymphocyte Subset Immunophenotyping; CD34 Haematopoietic Progenitor Cell Enumeration; Paroxysmal Nocturnal Haemoglobinuria Immunophenotyping; Flow Cytometric Assessment of HLA Alloantibodies*

4. VALIDATION

P4.1 Flow cytometry assays validated and audited during NATA assessments should be suitable for Class 1-3 in-house IVD notification.

C4.1(i) Design of validation, documentation required is described in the NPAAC Standard. Selection of test samples and numbers is considered test dependent and general comment is made only.

C4.1(ii) Documentation of validation should be reviewed to meet the NPAAC Standard. Validation documentation for any new Class 1-3 in-house test not previously reviewed by NATA will be assessed during the next accreditation assessment activity.

C4.1(iii) In-house assays validated before the 2007 2nd Edition, NPAAC *Requirements for the Development and use of In-House IVDs (2007)*, may use QAP data, QC reports, clinical correlation, as evidence of validation and ongoing test performance. It is expected that most of these in-house tests would already be included under the scope of a laboratory's NATA accreditation and therefore would not require any further evaluation of the validation data by NATA.

C4.1(iv) Performance of individual components of a test or cocktail e.g. CD markers should be reported and not the final immunophenotype alone.

P4.2 If not able to validate an in-house IVD for the reasons stated in Clause S1.3 of the NPAAC Standard (e.g. no suitable alternative assay and it is for a new or uncommon condition where its rarity precludes the laboratory from fulfilling all the validation requirements) a comment needs to be made on reports:

“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.”

5. ADVERSE EVENT REPORTING

P5 Reporting of adverse events to the TGA is required for all in-house IVDs

- C5(i) Adverse events are unintended events that have, or might have, led to a death or serious injury. For IVDs, an adverse event can be a problem associated with the use or performance of an IVD that has caused, or could cause, harm to the user of the device, patients, caregivers, health professionals or others. Post market requirements, including adverse event reporting are described in Section 10 of the NPAAC Standard.
- C5(ii) Adverse events associated with the use or performance of a commercially supplied IVD should also be reported to the TGA.
- C5(iii) More information on adverse event reporting and how to report an adverse event can be found on the TGA website, <https://www.tga.gov.au/reporting-adverse-events> .
- C5(iv) For any problems with Class 1-3 in-house IVDs that are not associated with an adverse event it is expected that the laboratory will take appropriate corrective action as required under their NATA accreditation (see Section 9 of the NPAAC Standard).

REFERENCES

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Regulatory Requirements for In-house IVDs, Version 2.0, March 2016, Australian Government, Department of Health, Therapeutic Goods Administration

Requirements for the Development and Use of In-house In Vitro Diagnostic Devices (IVDs), Third Edition 2014

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ACS policy and guideline documents are available on the website: www.cytometry.org.au

Correspondences

For further information on the regulatory requirements for Class 1-3 in-house IVDs contact the Therapeutic Goods Administration email: devicereforms@tga.gov.au

For further information on ACS policy documents contact email: clinicalguidelines@cytometry.org.au