



The changing regulatory environment of *in vitro* diagnostics: implications for sponsors, manufacturers and laboratory users

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Abstract

Currently most *in vitro* diagnostic devices (IVDs, clinical pathology tests) are exempt from any form of pre-market assessment by the Australian Government Department of Health and Ageing Therapeutic Goods Administration (TGA). The TGA believes that current regulation is not in line with international best practice nor is it ensuring that public or personal health are appropriately protected by the current regulation applied to the introduction of a rapidly developing array of new tests. The TGA has therefore proposed a revised regulatory framework that will now see all IVDs undergo pre-market regulatory assessment in accordance with their level of risk. The new framework provides for four classes of IVDs ranging from Class 1 (lowest risk) to Class 4 (highest risk) and includes for the first time in-house manufactured laboratory tests. At the time of publication of this manuscript, it was anticipated that these changes would take effect from 1 July 2010 with a transition until 30 June 2014.

The purpose, scope and details of how the revised framework will function and effect laboratory scientists and sponsors/manufacturers are the subject of this review.

Keywords: Laboratory personnel, staff development, in-service training, medical science, scientist, pathology, professional status.

The author acknowledges that the information included in this review is current at the time of writing but is subject to change by the TGA prior to and during the implementation of the revised regulations. Any opinions expressed in this review are those of the author who is a regulatory consultant, and not necessarily those of Brandwood Biomedical or DevDx Clinical.

Introduction

Most diagnostic pathology tests are currently exempt from any form of pre-market regulatory scrutiny and are only subject to post market monitoring and vigilance by both the supplier and the Australian Government Department of Health and Ageing Therapeutic Goods Administration (TGA). In order to align with what the TGA believes is international best practice and ensure that public and personal health are adequately protected, the TGA has proposed a revised framework for the regulation of *in vitro* diagnostic devices (IVDs). Essentially, the new framework will see IVDs regulated as a subset of medical devices. This will require prior to its implementation, an amendment of the Therapeutic Goods Regulations (Therapeutic Goods Amendment (Medical Devices) Act 2002; Therapeutic Goods Act 1989). The new regulations

will see all IVDs classified and regulated according to risk categories ranging from Class 1 (lowest risk) to Class 4 (highest risk). Unlike the existing regulations, all in-house manufactured IVDs will now also be included under this umbrella. Existing IVDs, irrespective of their class, will need to transition to the new framework within four years of the introduction of the regulations (TGA 2009).

The TGA operates as a full cost recovery agency deriving its income from fees collected from sponsors and manufacturers in assessing safety, quality and efficacy claims for their products prior to inclusion on the Australian Register of Therapeutic Goods (ARTG). A major consequence of the new regulations will therefore be a substantial increase in regulatory processing costs for the Australian sponsor or manufacturer: 1) by virtue of the need to have all IVDs assessed and included on the ARTG; and 2) as a result of the TGA's policy to review its fees and charges annually.

What is an IVD?

As specified on the TGA website (2009) IVDs are, "in general, pathology tests and their related instrumentation used to carry out testing on human samples." Importantly,

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results from these tests must be intended to assist clinical diagnoses or make clinical management decisions. IVDs therefore include tests used in laboratories, at the point of care (e.g. in the Intensive Care Unit) and in the home (self testing). Under the proposed new Australian regulatory framework and as described on the TGA website (2009), IVDs will be specifically defined thus

- it is 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,
- it is intended by the manufacturer to be used *in vitro* for the examination of specimens derived from the human body, solely or principally for:
 - giving information about a physiological or pathological state or a congenital abnormality, or
 - determining safety and compatibility with a potential recipient; or
 - monitoring therapeutic measures.

The following tests are excluded from the scope of this definition:

- products intended for general laboratory use that are not manufactured, sold or presented for use as an IVD.
- products that are not intended to have a therapeutic indication such as tests for parentage; tests for alcohol and illicit drugs (including sports screening).

How are IVDs currently regulated in Australia?

Currently, in accordance with the Therapeutic Goods Regulation 1990, most IVDs are exempt from any form of TGA pre-market assessment, although manufacturers and sponsors are required to comply with post-market regulations and the Therapeutic Goods Advertising Code 2007. “Sponsors” are defined as a person or company who is legally responsible for the supply of a product in, or exported from Australia. Manufacturers may also be the sponsor but take responsibility for the design and development and manufacture of their products. In Australia there are few manufacturers so most IVDs supplied in Australia are manufactured overseas and sold and distributed by Australian sponsors.

IVDs for supply in Australia are classified according to Table 1 and are either registered or listed in the

Australian Register of Therapeutic Goods (ARTG) or exempt from entry in the ARTG.

Listed IVDs are routinely subjected to an administrative review by the TGA that includes evidence of Good Manufacturing Practice (GMP), instructions for use, details of any human or animal origin material, labeling and promotional material. Registrable IVDs, however, undergo an extensive pre-market review of the product’s Technical File including full safety and performance evaluation by the TGA’s sub-contracted reference laboratory in Victoria (NSRL).

Australian manufacturers must obtain a GMP licence issued by the TGA; whereas overseas manufacturers require an ISO 13485 certificate (for their quality management system) or a Conformité Européene (CE) certificate issued by a Notified Body designated in Europe for the purposes of the In Vitro Diagnostic Medical Devices Directive (98/79/EC).

Since most IVDs used in the Australian market fall within the exempt category, sponsors and manufacturers, largely, have not been exposed to the latter regulatory burden or cost associated with the TGA pre-market assessment process, thus enabling a wide range of tests and instrumentation to be made available. Under the proposed Australian regulatory framework this will change.

Table 1
Current legislative basis for regulation of IVDs (TGA 2008)

ARTG status	IVD “Type”
Registrable	Goods for diagnosis and monitoring of HIV, HCV
Listable	Diagnostic goods for <i>in vitro</i> use that are: <ul style="list-style-type: none"> • For home use • That incorporate material of human origin • That are sampling containers • Products on the Pharmaceutical Benefits Schedule
Exempt	All other IVDs

Why has the TGA proposed regulatory changes?

Like medicines, medical devices and IVDs are regulated to ensure that they are used as intended and do not harm patients or users. Like most regulatory agencies worldwide the TGA believes that the degree of regulatory pre-market assessment and post-market control should be commensurate with the degree of risk in using that particular device. The TGA has assessed their current model and in order to better align it with what they consider regulatory best practice and adhere to these principles, they feel that the current model is inadequate (TGA 2009). Certainly, only HIV and HCV tests are currently rigorously assessed for safety and performance

therefore most available tests on the market have not undergone any form of pre-market regulatory scrutiny at all. The TGA has therefore proposed that in order to provide a better level of protection of personal or public health, all IVDs should undergo a similar level of regulatory assessment and control. However, it is important to remember that Australian clinical laboratories are subject to strict laboratory accreditation requirements as set by the National Pathology Accreditation Advisory Council (NPAAC) and monitored by the National Association of Testing Authorities (NATA); this greatly minimises this inadequacy.

Since the speed, cost and regulatory control exerted over medical technology development continues to increase, according to the TGA, there is a real need for regulatory authorities to introduce a framework that not only consistently ensures public and personal protection, but allows manufacturers and sponsors to expeditiously bring new products to the market by applying uniformity of regulation across international jurisdictions.

Increasingly IVDs are also being developed for point of care testing and for home use and many of these are for serious diseases. Again, the TGA believes that current regulation does not provide assurance of public protection in this environment.

Finally, as indicated above, the current model is not aligned with international best practice that takes into consideration quality, safety and risk management practices and provides the degree of flexibility and capacity that is required to keep abreast of new testing platforms and technologies and emerging diseases.

The proposed new Australian IVD regulations are based on the GHTF (Global Harmonisation Task Force)

Under the auspices of the National Coordinating Committee on Therapeutic Goods (NCCTG), the TGA in close consultation with the IVD Industry in Australia has proposed a revised regulatory framework for all IVD products supplied in Australia. As for the medical devices framework, the upcoming IVD system is based largely on the Canadian classification system, some elements from the European system (Directive 98/79/EC) with the inclusion of certain Global Harmonisation Task Force (GHTF) recommendations (GHTF 2008; TGA 2009).

The new framework is modeled on the GHTF (2008) recommendations which are centred on a four-level public and personal risk-based classification scheme which is intended to overcome the shortcomings of the current Australian and European schemes.

Essentially the new framework will see IVDs regulated as a subset of medical devices. This will require,

prior to its implementation, an amendment of the Therapeutic Goods Regulations (Medical Devices) 2002. There will be no need to change the Therapeutic Goods Act itself.

The new regulatory framework as proposed will have the following major features (GHTF 2008; TGA 2009):

- all IVDs falling within the scope of the definition (for therapeutic use) will be included.
- legal supply will be contingent on inclusion of all IVDs onto the ARTG.
- all IVDs to comply with a set of Essential Principles (including those generic to all medical devices and a new set specific to IVDs) for quality, safety and performance of the IVD throughout the product life cycle
- two major elements intended to demonstrate objective evidence of safety and performance, benefits and risks:
 - pre-market: conformity assessment.
 - post-market: vigilance/surveillance, adverse event reporting and recalls.
- a four-tiered classification scheme based on different levels of risk for each class of device that determines the level of conformity assessment.
- the class is determined through a set of rules that determine risk, rather than being prescriptive (as it is the case with the European regulatory system).

Unlike the current regulatory environment, the new framework will see all commercial IVDs for therapeutic use included on the ARTG prior to being imported, supplied or exported from Australia. Provisions (under the current Special Access or Clinical Trial Notification Schemes) for access to unapproved IVDs, such as for use during clinical trials will remain.

Importantly, a major change in this framework is the intended regulation of “in-house” manufactured IVDs. In-house IVDs are developed and used within a laboratory or laboratory network and are widely used for clinical diagnosis and management.

The TGA (2007) regards as a laboratory network an organisation whose activities span more than one field of testing or program, or which operate at multiple sites within a field, or involve a combination of multiple sites and fields/programs under a single Approved Pathology Authority, with a single quality management system.

The proposed method for regulating in-house IVDs is discussed below.

The goal of GHTF is to provide a collaborative forum for representatives of member nations' regulatory authorities and industry representatives from the European Union, the United States of America, Japan, Canada and Australia to promote international convergence in regulatory requirements and practices; thereby presumably streamlining the regulatory process and promoting earlier access to medical devices.

On the surface, it appears reasonable that the TGA has sought guidance from the GHTF in the development of their new regulatory framework. However, to date, no other country has actually adopted the GHTF recommendations, so if the new regulations go ahead as planned, Australia will have a regulatory system for IVDs that is in fact unique. Some corners of the industry feel that the TGA may be pushing ahead too early.

The TGA has now targeted this implementation during 2010, although there is good reason to believe that this may not occur. The new IVD regulatory framework was originally intended to be implemented as part of the failed Australian and New Zealand combined regulatory agency project, the Australia New Zealand Therapeutic Products Authority (ANZTPA), since around 2002. There have been many delays to this project and likewise for the introduction of the IVD framework, partly as a result of the TGA experiencing difficulty with establishing a mechanism for dealing with the large bulk of IVDs used in Australia that are imported.

It will be interesting to observe when and how the implementation proceeds.

Once implemented, however, the TGA will provide for a four-year transition period that will assist sponsors and manufacturers develop and prepare the necessary regulatory technical documentation required.

Classification rules

IVDs will be classified in accordance with the level of risk posed to either the individual or public which arises directly through the use of the individual IVD (GHTF 2008; TGA 2009).

There are four risk classes:

- Class 4 IVD – high public health risk.
- Class 3 IVD – high personal risk or moderate public health risk.
- Class 2 IVD – low public health risk or moderate personal risk.
- Class 1 IVD – no public health risk or low personal risk.

The manufacturer is responsible for determining the classification of each of their products by applying the above classification rules. In doing so, they must consider

the intended use of the IVD and the significance of the final result to diagnosis or clinical management.

If more than one classification rule applies, the IVD will assume the highest classification level.

The lowest risk class, Class 1, includes items with low private and public risk, such as reagents, specimen containers and microbiological culture media – as well as IVDs intended for export only.

Class 2 IVDs include tests such as pregnancy tests and other tests that are not the sole determinant for diagnosis of a disease.

Class 3 IVDs include any tests for infectious diseases, tests that could put an individual in danger if it gives an erroneous reading is given and tests that represent the sole determinant for a diagnosis.

Class 4 includes high risk tests, including those that screen for transmissible agents in blood, such as HIV and hepatitis tests.

Further examples of IVDs falling within each classification can be found at: <http://www.tga.gov.au/ivd/overview.htm>

Essential Principles

The Essential Principles (EPs) set out the requirements relating to the safety and performance characteristics of the IVD that the manufacturer must be able to demonstrate through the application of appropriate standards and verification and validation processes.

Before registration of an IVD the manufacturer must satisfy themselves and the regulator that their product works as intended, that all hazards and risks to the patient or user have been addressed and that on balance the benefits derived from use of the IVD outweigh any risks.

The regulator does not mandate which EPs apply, it is up to the manufacturer to determine how to demonstrate their product's performance and safety by selecting the appropriate EPs, then showing how they comply with each selected EP.

The EPs are divided into two main types:

- general principles – which apply to all medical devices, and
- specific principles – which are only applicable to some medical devices and include new principles specific to IVDs, for example: the IVD must be designed and manufactured in a fashion that ensures analytical and clinical characteristics will meet its intended use and addresses accuracy, precision, sensitivity, specificity, stability, control of known interference and

measurement of uncertainty. A full description of the EPs may be found at: <<http://www.tga.gov.au/ivd/presentation-principles.pdf>>

Conformity assessment

Having established how to comply with the relevant EPs, under the revised IVD framework, manufacturers will also need to demonstrate conformity with Australian regulatory requirements in order to place their product on the ARTG. The term “conformity assessment” defines those activities that a manufacturer must undertake to demonstrate conformity with applicable regulatory requirements. For Australian manufacturers, the degree of regulatory burden, time and cost, especially for inclusion of their higher risk products is substantial. As with EPs, the manufacturer is responsible for choosing the conformity assessment procedure that is appropriate to their IVD’s intended use and risk classification.

Procedures for demonstrating conformity include:

- manufacturer self-assessment (as for lowest risk IVDs).
- declaration of conformity (holding technical information but not submitting it for review).
- full regulatory review and certification of the quality management system (QMS) and product design by the TGA (as for Class 4 IVDs).
- in order to supply IVDs, a conformity assessment certificate will be required to be issued by the TGA for:
- Australian manufacturers of Class 2 or Class 3 IVDs.
- all Class 4 IVDs (for Australian AND overseas manufacturers).

In some circumstances a conformity assessment certificate issued by a notified body overseas may be accepted in lieu of the need for a TGA certificate.

What are manufacturer and sponsors requirements under the new regulatory framework?

The classification of the IVD will determine the minimum conformity assessment procedure(s) that the manufacturer must apply to demonstrate compliance with the EPs. The degree of regulatory compliance and scrutiny by the TGA increases with the degree of risk and therefore the higher the classification of the device. The degree of technical (quality and performance) evidence required to be held and submitted by the manufacturer and sponsor to the TGA for review, likewise increases,

progressively from Class 1 through to Class 4. Regulatory requirements may include:

- operation of a quality management system such as ISO 13485.
- documentation of clinical evidence to support the IVD’s intended use.
- product testing using in-house or independent vendors.
- the need for and frequency of independent external audit of the manufacturer’s QMS.
- independent external review of the manufacturer’s technical data.

The regulatory burden on the manufacturer and sponsor, will, therefore, under the new regulatory framework, be much greater than exists currently. The potential consequences of such an increase in regulatory burden are discussed below.

How could commercial IVDs be affected by the new framework?

For IVDs sold commercially in Australia, the conformity assessment procedures will generally incorporate those aspects already applied to medical devices, including certification of a QMS, surveillance audits and post-market vigilance. Based on the classification of the IVD the manufacturer will select an appropriate conformity assessment route from the In Vitro Diagnostic Medical Devices Directive (98/79/EC). The manufacturer will also need to make an Australian Declaration of Conformity (DOC) consistent with TGA requirements. The extent of technical documentation needed to be held by the sponsor and manufacturer for compliance to the Essential Principles (EPs) and Quality Management Systems (QMS) clearly increases in line with the risk and classification of the IVD. Documentation may range from self-declaration of conformity to the EPs and existence of a QMS (without TGA assessment) for certain Class I IVDs to the requirement for a fully compliant ISO 13485 (TGA certified) QMS, an assessment of the IVD’s design dossier and for certain Class 4 IVDs a full laboratory-based performance evaluation by the TGA.

How could “In-house” manufactured IVDs be affected by the new framework?

In-house IVDs are defined by NPAAC (2007; see also TGA 2009) as :

An IVD that is developed *de novo*, or developed or modified from a published source, or developed or modified from any other source, or its intended purpose, within the confines or scope of a laboratory or laboratory network. [...] Commercial IVDs being used clinically for purposes other

than that originally intended by the manufacturer are also classed as in-house IVDs.

Laboratories manufacturing in-house tests are currently subject to the NPAAC standard. With the introduction of the new IVD legislation, “in-house” tests that fall within the proposed TGA Classes 1, 2 and 3 for risk will be required to notify the TGA the types of IVDs manufactured in each laboratory for inclusion on a specially designed register. Each laboratory, as part of their NATA accreditation will be required to demonstrate compliance with standard on the validation of in-house IVDs as published by the National Pathology Accreditation Advisory Committee (NPAAC 2007) for each test. Importantly, this standard applies only to in-house IVDs that fall into the proposed TGA Classes 1, 2 and 3.

In-house IVDs that fall into Class 4 are subject to the full current TGA regulatory requirements for HIV and HCV as well as for the future Class 4 IVDs (TGA 2009). The laboratory will need to produce a report on method validation that shows the successful completion of appropriate validation studies for the IVD in question. Laboratories should understand well, that like the TGA’s proposed risk-based classification and assessment framework, the extent of validation of in-house tests should likewise be commensurate with the risks associated with the use and results derived by the IVD. Laboratories are already fully conversant with the NPAAC suite of standards for validation of in-house tests, and for Classes 1, 2 and 3 in-house tests, one would expect that any additional requirements will be satisfied by only minor modifications to the existing QMS within the laboratory.

Importantly, most of the documentation required to satisfy the requirements of the standard will need to cover validation of the in-house IVD.

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, as defined above. For detailed information on the relevant NPAAC standards refer to:

<<http://www.health.gov.au/internet/main/publishing.nsf/Content/health-npaac-dhaivd.htm>>

IVDs for self-testing (home use)

As defined by the TGA (2008), these are tests that are used at home or in a similar environment and are not supervised by a health care provider (e.g. glucose monitoring). Under the provisions of the proposed regulatory framework, the following self-testing IVDs will not be allowed to be marketed in Australia:

- IVDs used to test for pathogens or diagnose notifiable infectious diseases;
- tests to determine genetic traits;
- IVDs used to test for serious disorders, for example cancer or myocardial infarction.

Major issues of the proposed regulatory framework

From the TGA’s perspective, the proposed changes to the IVD regulations are intended to embrace a harmonised framework for risk-based classification and regulation of all IVDs. This “all encompassing” framework is intended to ensure that all tests undergo the extent of regulatory scrutiny that the TGA believes is commensurate with the risk of the IVD thereby enhancing public and personal health.

Whilst the TGA is pushing ahead with its unique regulatory framework, the proposed framework poses a number of significant issues for the pathology industry that will need to be resolved, if implemented in its entirety.

More than 95% of all IVDs are imported into Australia; however, the Australian sponsors or manufacturers may not hold or have readily available sufficient technical or conformity assessment documentation to cover TGA’s requirements. This will be particularly difficult for products that have been supplied to Australian laboratories for more than 20 years now.

The proposed regulatory framework ignores the quality of the results produced by the Australian laboratories and still requires manufacturer evidence that a particular test is safe instead of taking into account existing data (e.g., Royal College of Pathologists of Australasia Quality Assurance Program data and performance of the various tests)

International agreements (such as the Mutual Recognition Agreement) with Europe, Canada or the US are not yet in place for IVDs, so this would require duplication of conformity assessment by the local and international manufacturers.

From industry’s perspective, due to TGA’s 100% cost recovery policy, if not implemented carefully, with due consideration for its original intent to harmonise, streamline and reduce regulatory duplication, the TGA’s proposed framework for IVDs could, unfortunately, increase regulatory burden unnecessarily, increase costs significantly and potentially delay or prevent access to existing or new products to users.

Since the Australian IVD market overall is small, IVD sponsors will need to assess whether the added

regulatory burden and cost to sell their products in Australia is worth the effort. Furthermore, under the transition to the new framework, and as a result of the increased regulatory burden required to enter IVDs onto the ARTG, manufacturers or sponsors may opt to restrict the use of certain products in Australia or change the intended use of their IVDs, in order to fulfill a lower risk classification.

Suppliers of low volume tests and small companies may decide that it is not commercially viable.

For the laboratory, major changes stemming from the new regulations would include the need to “register” in-house manufactured tests and reagents in a specific TGA database and provide the full suite of accompanying validation documentation to NATA prior to gaining ARTG entry.

Conclusions

The reforms for IVD regulation as proposed by the TGA are yet to be finalised or implemented. Overall, the proposed new IVD framework presents the industry with a combination of potential advantages and disadvantages. The move to a risk-based classification and regulatory assessment scheme is a move in the right direction if handled correctly and sensibly. The major disadvantages stem from the increase in regulatory burden and costs to the IVD sponsor or manufacturer resulting in the potential for removal of long-standing pathology tests from the laboratory or a reduction in the introduction of new tests into the market.

Industry has seen how the TGA coped previously with the introduction of the new medical device regulations. Furthermore, the proposed IVD framework is far more complex than that proposed in other countries and more complicated than for devices.

IVDs do pose some significant challenges to the regulator in that they are very different from other medical devices and there is a question of whether the TGA has the expertise or will have enough resources to handle the influx of applications resulting from the implementation of their own far-reaching changes.

It will be interesting to see how the unresolved issues are tackled and how industry and laboratories will adapt to the new system. All of those affected should remain vigilant and carefully assess the potential implications of these changes now.

Ultimately, one hopes that new technology will continue to be made available to Australian laboratories in a timely, sensible and cost-efficient fashion.

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