IVD AUSTRALIA

IVD Australia Response to the Review of Medicines and Medical Devices Regulation

Contents

ABOUT IVD Australia

IVD Australia is the peak body representing sponsors and manufacturers of in vitro diagnostics based in Australia.

In vitro, literally 'in glass', diagnostics (*in-vitro* diagnostics, IVDs) comprise the instruments, reagents and consumables that are used to perform pathology tests requested by General Practitioners, specialist Physicians, or other healthcare professionals, tests undertaken in the home such as blood glucose or home pregnancy tests, or those tests undertaken as part of a government screening program, such as the Bowel Cancer Program.

It is estimated that the results obtained from pathology tests are responsible for 70% of all medical diagnoses and almost 100% of all cancer diagnosis and make a significant contribution to the management of disease.[1]

These pathology tests are generally performed in accredited Public and Private pathology laboratories across Australia, but IVDs also include over-the-counter tests such as blood glucose meters for diabetes testing and point of care (PoCT) devices used in general practice and healthcare clinics to measure parameters such as INR or HbA1c. Supply of these IVDs in Australia is regulated for the Government by the Therapeutic Goods Administration (TGA).

IVD Australia was formed in July 2009 and currently represents Australian manufacturers, multi-national and local distributors of IVDs, as well as regulatory consultants working in the IVD sector. Our members currently supply products valued at over $800,000,000 per annum and they employ over 2500 staff in multinationals, local distributors, local manufacturers and exporters and regulatory consultant companies; the majority of which are SME's.

Three Key Projects Supported by IVD Australia

1. IVD Australia is a founding member of the newly formed **Global Diagnostic Alliance**, an international forum of Peak Bodies for IVDs across International borders, with the intent to share information, and work together on matters of international significance.
2. IVD Australia is concerned at the lack of Australia IVD Market statistical data and has entered into agreement with the European Diagnostic Manufacturers Association (EDMA) to capture data through the **Global Diagnostic Market Statistics program** (GDMS).
3. IVD Australia is a founding member of Pathology Awareness Australia, a group that represents interests across the entire field of pathology in Australia. This body is conducting the **Know Pathology, Know Healthcare Campaign** on behalf of public pathology laboratories, private pathology companies, pathology professionals and manufacturers and suppliers to industry.[2]

IVD Australia Position on Reduction of Red-Tape

IVD Australia promotes the value of innovative, safe, and effective diagnostic tests and advocates for risk-based regulation of all IVDs. In Australia, the Therapeutic Goods Administration (TGA) has regulatory oversight of all diagnostic tests, including those manufactured and sold as kits to laboratories, GP offices, and patients. Most tests that are developed and offered within a particular laboratory, called in-house tests are regulated through the National Association of Testing Authorities (NATA). The TGA intends to require high risk (Class 4) in-house tests to be included on the Australian Register of Therapeutic Goods (ARTG).

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1 Australian Association of Pathology Practices Inc, 2008 http://pathologyaustralia.com.au/wp-content/uploads/2013/03/Pathology-in-Australia.pdf

2 http://knowpathology.com.au/

IVD Australia advocates for the appropriate regulation of IVDs:

- Focus TGA's limited resources on tests that pose the highest risk to patients - regardless of where such tests are developed (ie: commercial or in-house, in Australia or internationally);
- Expedite patient access to lower risk tests by more efficient use of pre-market review process; and
- Ensure review of higher risk IVDs for safety and effectiveness by extending TGA oversight to higher risk tests developed by laboratories.
- Focus TGA resources on post-market monitoring of tests which is where the true value and performance of these products is established.

IVD Australia is committed to working with the Government, the Therapeutic Goods Administration, the Office of Device Authorisation, and the Office of Product Review to develop a regulatory framework for *in-vitro* diagnostics that, while providing the level of safety and reassurance required by the Australian community, imposes 'light touch' regulation on manufacturers and sponsors of *in-vitro* diagnostic medical devices

IVD AUSTRALIA EXECUTIVE SUMMARY and RECOMMENDATIONS

Executive Summary

IVD Australia appreciates the opportunity to provide comment on the *Review of Medicines and Medical Devices Regulation: Discussion Paper* (the *Discussion Paper*).

The structure of the IVD Australia response is to provide a concise answer to each question with additional discussion. The discussion includes general comments on the Discussion Paper with specific comments on the regulation of IVDs. IVD Australia will not comment on the issues dealing with regulation of Medicines (Chapters 4, 5 & 6). IVD Australia will also not comment on the issues dealing with regulation of Medical Devices that are not IVDs (Chapter 7).

It should be noted that the Discussion Paper contains inaccuracies with regard to the regulation of *in-vitro* diagnostic devices (IVDs). IVD Australia considers that the Discussion Paper was developed principally with non-IVD medical devices front of mind and that a number of questions are specifically not applicable to IVDs. Where we believe that IVDs are unaffected by an issue IVD Australia has made little or no comment.

The recent introduction of the IVD Regulations means that IVDs are in fact more 'up-to-date' with their regulatory framework than other medical devices.

IVD Australia has consistently said that IVDs possess characteristics that mean they demand separate consideration.

IVDs are not medicines or medical devices - while IVDs can be generally regulated in a similar manner as medical devices, they are inherently different to both medical devices and medicines.

IVD Australia Recommendation 1:

Adoption of processes relevant to medicines and medical devices should only be considered where there is a true benefit to IVD users.

These differences have been recognised by the Regulations generally permitting IVDs be grouped as a 'kind of medical device'. IVDs are supplied in a substantial number of formats and are generally packaged in a different way to other medical devices or medicines. IVDs require separate consideration, and this has been taken into account in previous negotiations with TGA on the regulation of IVDs. For example, the number of configurations of IVDs and the unique packaging and shipping/storage conditions required have a significant impact on how labelling must be managed.

IVD Australia Recommendations

IVD Australia supports the introduction of harmonised regulations for IVDs across all geographies. IVD Australia believes that the TGA should aim to ensure that therapeutic goods, and specifically IVDs, supplied in Australia are of acceptable quality and performance. However that has to be achieved within a framework of acceptable timeframes and costs.

IVD Australia Recommendation 1:

Adoption of processes relevant to medicines and medical devices should only be considered where there is a true benefit to IVD users.

IVD Australia Recommendation 2:

The TGA should be required to adhere to the *COAG Principles of Best Practice Regulation.*

IVD Australia Recommendation 3:

In line with comparable International Regulators, the TGA should be a Designating Authority, not a Notified Body.

IVD Australia Recommendation 4:

As a leading International Regulator, TGA should continue building an international network of 'trusted' or 'approved' regulators – judged against the requirements of the GHTF outcomes.

IVD Australia Recommendation 5:

'Australian-specific' changes should be minimised; and any changes should be negotiated with IMDRF and Industry.

IVD Australia Recommendation 6:

Australian approvals of IVDs already approved by trusted overseas regulators, this should include conditional/provisional approvals, and apply to all classes of IVDs.

IVD Australia Recommendation 7:

That the first step to an appropriate balance between managing risk and minimising unnecessary regulatory burden for the IVD sector of the Therapeutic Goods Industry is the introduction of specific *Therapeutic Goods (In-vitro Diagnostic Devices) Regulations.*

IVD Australia Recommendation 8:

That IVDs are distinct from other medical devices and should be regulated in their own right.

IVD Australia Recommendation 9:

IVD Australia would support a 30-50 work days' time-frame for ARTG entry for all Classes of IVDs.

IVD Australia Recommendation 10:

IVDs should have their own guidance - Australian Regulatory Guidelines (ARGIVD).

IVD Australia Recommendation 11:

For all IVDs it is considered that the general information about IVD decision making processes and the information provided on the public ARTG summary would be sufficient and appropriate to provide transparency.

IVD Australia Recommendation 12:

The TGA include on its application forms (whether electronic or paper) a requirement for an applicant to nominate the relevant code of practice to which it will subscribe as a condition of registration/listing on the ARTG.

IVD Australia Recommendation 13:

Sponsors of IVDs included in the ARTG for the purpose of patient self-testing should be able to make use of appropriate restricted representations without pre-approval.

ADDITIONAL COMMENTS FOR CONSIDERATION

The Australian IVD Sector

IVD tests are a key contributor to the Australian health care system, powering medical discoveries and transforming patient care. These tests are performed on samples taken from the body and are used in a broad range of applications. Diagnostic tests provide critical insights at every stage of medical care – prevention, detection, diagnosis, treatment, and successful management of health conditions. Diagnostic tests are often the least expensive component of the health care pathway, yet they influence more than 70% of health care expenditures. They facilitate evidence-based medicine, improve quality of care, promote wellness, enable early detection of disease, and reduce overall health care costs.

Technological advances and automation have made tests easier to use and more accurate, and have led to more precise and more timely reports. These advances have led to point of care tests that facilitate more rapid decision-making by medical practitioners. Other advances, made possible by discoveries about the human genome, have opened the door to personalised medicine approaches that can tailor medical treatment to individual patient needs, transforming modern medicine.

There are more than 1,600 different diagnostic tests currently included on the ARTG today and, in 2013 alone, some 50 million tests were performed in Australia.

From the genetic tests that inform personalised cancer treatment to the blood analysis that identifies the right antibiotic to fight an infection, diagnostic tests provide critical insights at every stage of medical care – pre-disposition, prevention, detection, diagnosis, treatment and successful management of health conditions.

Diagnostic tests using IVDs, are performed in laboratories, hospitals, doctors' offices, clinics, on the field, and in the home. They facilitate evidence-based medicine, improve quality of care, promote wellness, enable early detection of disease, and reduce overall health care costs.

Companion diagnostics are an emerging area of IVD use receiving a lot of attention. Companion diagnostics are IVDs that provide information about genomic and proteomic characteristics to help inform use of a specific drug or therapy.

Worldwide the IVD Sector is one of the most concentrated in the whole of the Health Sector. The ten largest IVD manufacturers represent over 75% of the total market and this concentration is increasing.

Thus, most IVD companies across the world are represented in Australia in one way or another – directly, via a subsidiary, via a distributor or via OEM sales to a third party. This has meant that there is substantial competition within the Australian market, perhaps in excess of any other developed market. This has resulted

in effective price competition and in many cases the lowest cost IVDs in the world. For example, the product cost of a panel of specific IgE tests for allergy is around $18.50 in Australia but is typically around $38.50 in Europe.

It should also be noted that whilst the expenditure on IVDs in Australia, including over-the-counter tests, is presently around $850 million per year, the Australian IVD suppliers also support much of the New Zealand market directly from Australia. Thus the total sales value supported in Australia by IVD companies is more likely to be in the order of AUD$1.0 billion.

Whilst Australia can be justifiably proud of its achievements in the area of Health, at present the Australian health system with its focus on hospitals and acute disease is ill-equipped to deal with the emerging challenges in health; chronic disease, increasing costs and increasing demands from a better informed population. It remains focused on numbers of doctors, hospital beds, and acute hospital funding as the measures of success in the Health sector. But hospital beds are expensive to create and expensive to maintain. Keeping people out of the acute medical system has to be one of the key goals that Australia aspires to over the next 20 years, and the use of pathology services and IVDs are essential in achieving that goal.

Global Harmonisation Taskforce

The Global Harmonization Task Force (GHTF) was a voluntary group of representatives from national medical device regulatory authorities and the members of the medical device industry, whose goal was the standardisation of medical device regulation across the world. The five founding members were the European Union, the United States, Canada, Japan, and Australia, each of which actively regulated medical devices using their own unique regulatory framework. Founded in 1992, the GHTF was created in an effort to respond to the growing need for international harmonization in the regulation of medical devices. The GHTF was disbanded late in 2012 and its role has been taken over by the International Medical Device Regulators Forum (IMDRF). The IMDRF is composed of regulatory agencies — **not industry** — around the world.[3]

The Australian Regulatory Framework for IVDs is based upon the GHTF model and Australia is the first major jurisdiction to implement IVD regulations based on this model. It is anticipated that the EU will move to implementation of regulatory approval based on this model in 2016-17 and other jurisdictions such as China and Japan will also move to adopt it over the longer term.

The GHTF model is a risk-based framework where higher risk products such as IVDs that are used to screen the blood supply, those testing for transmissible agents, and those sold directly to consumers are subject to a greater degree of regulatory scrutiny. These products are generally required to have a review of their analytical performance and clinical evidence undertaken by the TGA before they are entered onto the Australian Register of Therapeutic Goods (ARTG). Products of lower risk, for example those testing for hormones or for electrolytes, are subjected to a lower level of oversight, with most requiring only a review of the Manufacturer's Quality System.

As discussed above, the IVD Regulatory Framework was finally introduced on July 1st 2010 after 8 years of delay. The introduction was the subject of detailed negotiation both with the pathology community, and with the sponsors of IVDs, initially through the Medical Technology Association of Australia (MTAA) and then IVD Australia.

Whilst the IVD sector was not in complete agreement with all of the changes, particularly those that imposed greatly increased regulatory costs on the sector, it continues to work with the TGA within this new regulatory environment.

[3] http://imdrf.org/ghtf/ghtf-archives.asp

The Role of the TGA

As indicated previously, the introduction of the IVD regulations in 2010 has meant that all IVDs now require pre-market assessment under Australian legislation and are required to be entered onto the ARTG prior to their supply in Australia.

As part of the introduction of these regulations, the TGA was required to conduct a Cost Recovery Impact Assessment. Initial TGA estimates were that the cost to industry over the 4 year transition period and the first year of annual charges would be in the order of $16 million.[4] IVD Australia believes that the TGA study seriously underestimated the number of inclusions that will be made and believes that the true impact of this additional regulation will be in the order of $25 million over 5 years, including the indirect costs to industry of staff etc.

The cost of regulation to IVD suppliers **will need to be recovered from customers**. In addition, the additional costs of extra staff and delays to product launch caused by these regulations will add substantially to the IVD sector's costs. It is expected that, over the 5 years of the transition, more than 2,500 individual inclusions will be made onto the ARTG and over 600 technical file reviews (including Conformity Assessments) would be conducted by the TGA.

IVD Australia has worked closely with the TGA to ensure that this regulatory framework takes into account the practical and commercial needs of manufacturers and sponsors. We believe that the TGA is the most appropriate authority to regulate therapeutic goods. This structure, requiring an essentially independent regulatory authority is common around the world. It provides a level of confidence in the regulator that is not present if these functions are subsumed within a Government department.

Indeed, IVD Australia believes that the TGA should in fact be a totally independent Government Body in the same way as the National Blood Authority. This would establish it formally as independent of the Department of Health and not seen as an arm of Government. TGA should provide oversight of Notified Bodies in the same manner as a Designating Authority like the EU regulators.

One of Industry's major issues with the current structure is that the TGA is fully cost recovered. This means that the funding for the organisation comes solely from its 'customers'. This has led to the perception that the TGA is too close to the industry it regulates and thus makes decisions that favour the position of the industry sectors over that of the consumer. IVD Australia can confirm that this in fact is not the case.

US consumers believe that the FDA is beholden to the therapeutic goods sector. But, the current level of close to 40% is far less than that of the Australian situation of 100% recovery.

However to overcome this perception of industry bias, IVD Australia recommends that the TGA be set up as an Independent Authority but with block grant funding to support its community service obligations such as those covering post-market surveillance, community education and communication.

In addition, despite industry paying 100% of TGA costs and the ensuing high cost of registration to the industry, the level of 'service' provided by the TGA to industry is often significantly inadequate. The length of time for approvals, decisions, and even billing is not 'world-class', delaying the introduction of advances in testing, and make planning and budgeting very difficult for industry. The impact of budget cuts on the Department of Health is being felt on the TGA.

In-House IVDs

IVD Australia is concerned with the treatment of in-house IVDs under the Regulatory Framework. In-house IVDs are those made by laboratories themselves, either modifying commercial assays such as adding new

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[4] Therapeutic Goods Administration, September 2009, *Regulation of in vitro diagnostic devices – Cost Recovery Impact Statement*, TGA, Canberra

calibrators, sample types, de-novo from scientific literature or, more commonly, by taking reagents purchased from IVD Australia members and others and creating an assay that is then used to produce patient results. This practice is common in both public and private pathology. Almost all cancer in Australia is diagnosed via in-house assays and these assays are designated as Class 3 assays.

IVD Australia has a number of concerns with the 'system' as set up under the new regulations:

- There is no pre-market scrutiny of Class 1 to 3 in-house IVDs – only 'peer-reviewed' assessment by NATA post development and use; a lab can develop and use a test without any external assessment;
- NATA assessors are generally not skilled in assessment of manufacture and validation of IVDs; they are usually public laboratory scientists and pathologists;
- NATA resources are already stretched; when they are required to assess in-house assays, further time pressure will be put on these Assessors;
- As Class 1 to 3 in-house IVDs will not be included on the ARTG, this will require the development of a public – access TGA database. there will be no public access to the list of in-house assays, as there will be for commercial assays;
- NATA Accreditation visits are only held every 3 years. Thus an assay might be producing results for 3-5 years before there is any independent assessment of its safety and efficacy; and
- Awareness of recall procedures for in-house assays need to be substantially strengthened to ensure that adverse events resulting or possibly resulting from in-house assays are appropriately reported, documented and acted upon.

IVD Australia is not opposed to the use of in-house IVDs in pathology practice. There will always be assays that are not commercially viable, assays that are urgently required for public health (for example, SARS), assays at the cutting edge of technology, and new markers that extend the boundaries of diagnosis and monitoring that require the development of in-house assays.

TGA has recently undertaken to introduce reforms to the regulations in relation to in-house IVDs. IVD Australia recognises these reforms are required to create workable regulations for laboratories in relation to Class 4 in-house IVDs However, IVD Australia still believes these create an uneven playing field for commercial IVD sponsors.

While TGA has recognised the need for equivalent reforms for commercial Class 4 IVDs these will only be implemented after 'confidence-building exercises with European authorities and notified bodies'. There is no timeframe on when this is likely to occur and given the current reforms occurring in Europe and the fact that TGA today has no authority to oversight the European notified bodies this is unlikely to change prior to the end of the transition period.

In addition, laboratories will pay a 'one-off' fee to submit a declaration of the 'kinds of device' they manufacture in-house and will only ever pay a fee if they are required to update this declaration. There will be no public visibility on what assays (or even 'kinds of devices') they manufacture, as there is for commercial IVDs.

Third Party Conformity Assessments for Australian Manufacturers

Members of IVD Australia welcome the October 14, 2014 announcement, and November 5, 2014 implementation of the change in the conformity assessment process for Australian manufacturers in line with the Government's Industry, Innovation and Competition Agenda. This has been supported for a considerable time by industry and by IVD Australia as a means of levelling the playing field for Australian IVD manufacturers.

IVD Australia is of the opinion that this has the potential to save considerable time and money for Australian IVD manufacturers. It provides Australian manufacturers with a choice of conformity assessment pathways that is commensurate with those available to overseas manufacturers.

Cost to the Community of Regulation of IVDs

There are considerable costs to the community in the regulation of medicines and medical devices. IVD Australia is concerned that again the opportunity to reduce the burden on sponsors and manufacturers imposed through 100% cost recovery has not been fully addressed.

This has been a continuing issue for IVD sponsors in Australia as it has led to the highest cost for registration of IVDs in the developed world. While the overall cost to sponsors of the new IVD regulations have not yet been fully realised as the IVD Transition Period still has 17 months to run, it is likely that the cost will be in the order of 2% of turnover per annum which is far above the 0.5% originally promised when the IVD Framework was first proposed in 2002.

IVD Australia strongly believes that there should be some community contribution to the cost of regulation of therapeutic goods. This is the case in many equivalent economies.

Cost is not just about the dollars, but also about access to improved technologies and innovative solutions as discussed earlier in this section.

CHAPTER THREE: PRINCIPLES UNDERPINNING THE REVIEW

Q: Are there any additional principles that should be considered?

A: Yes, additional principles that should be considered – COAG. See discussion below.

Whilst IVD Australia has no issue with the idea of the principles listed in the Discussion Paper, it notes that Principle 2, *The level of regulation should be commensurate with the risk posed by the regulated products,* is very divisive in its current format. The parameters and in fact, the very definition, of risk has not been appropriately identified, particularly with regard to IVDs as separate entities to Medical Devices.

A critical factor, seemingly ignored, is that so-called 'high risk' IVDs in Class 4, do not pose the same level or type of risk as Medical Devices. That is, the risk must be defined by sector. See Theme 3, Issue 1.

IVD Australia believes that COAG has agreed that all governments will ensure that regulatory processes in their jurisdiction are consistent with the following principles:

1. *Establishing a case for action before addressing a problem;*
2. *A range of feasible policy options must be considered, including self-regulatory, co-regulatory and non-regulatory approaches, and their benefits and costs assessed;*
3. *Adopting the option that generates the greatest net benefit for the community;*
4. *In accordance with the Competition Principles Agreement, legislation should not restrict competition unless it can be demonstrated that:-*
   a) *The benefits of the restrictions to the community as a whole outweigh the costs, and*
   b) *The objectives of the regulation can only be achieved by restricting competition;*
5. *Providing effective guidance to relevant regulators and regulated parties in order to ensure that the policy intent and expected compliance requirements of the regulation are clear;*
6. *Ensuring that regulation remains relevant and effective over time;*
7. *Consulting effectively with affected key stakeholders at all stages of the regulatory cycle; and*
8. *Government action should be effective and proportional to the issue being addressed.*

IVD Australia Recommendation 2:

The TGA should be required to adhere to the *COAG Principles of Best Practice Regulation.*

CHAPTER SEVEN: REGULATION OF MEDICAL DEVICES

Theme 1: Duplication of Regulatory Processes

Issue 1 – How Might a Trusted Overseas Regulator be Defined?

Q: Should the TGA undertake its own assessment of the competency of EU notified bodies? If yes, how might this occur? If not, why not?

A: No, the TGA should not make its own assessment of the competency of EU notified bodies. The TGA should take on the role of a Designating Authority and work with other Designating Authorities to ensure the competency of Notified Bodies.

IVD Australia notes that there are currently proposals relating to additional confidence building with European Notified Bodies to lessen the need for TGA assessments. Given that the IVD sector is currently not part of the Mutual Recognition Agreement (MRA) with Europe covering medical devices[5], such confidence building will need to be progressed prior to the end of the transition period. On this basis, IVD Australia queries whether the TGA is better placed to work with the EU Designating Authorities, such as the UK Department of Health Medicines and Healthcare products Regulatory Agency (MHRA), rather than conducting assessments of its own at this time.

Confidence-building is not a one-off event that can occur prior to allowing certification issued under the MRA to be accepted. However IVD Australia submits that confidence building is, in fact, an on-going process that needs to be continually refined and evaluated in terms of its effectiveness and its cost.

Accordingly, if there is a lack of confidence in a Notified Body, this should be raised with the appropriate Designating Authority.

Although there may be instances in which the TGA believe that they should have the powers of a Notified Body; the TGA should be required to undergo the same external assessment processes as other Notified Bodies – by an independent Designating Authority.

In the current situation, TGA could be seen as trying to hold the powers of both a Notified Body and a Designating Authority – a conflict of interest.

Where the TGA has concerns, it should be able to:

- refer to an independent Notified Body (preferably in Australia/NZ); and then
- act as a Designating Authority and assess the competence of the Notified Body.

This would provide both industry and consumers with confidence of transparency of process and outcome.

IVD Australia Recommendation 3:

In line with comparable International Regulators, the TGA should be a Designating Authority, not a Notified Body.

[5] http://ec.europa.eu/enterprise/newapproach/nando/index.cfm?fuseaction=na.main

Q: Alternatively, given concerns with the EU system, should Australia look to recognise other international regulators as 'trusted' for the purpose of device approvals?

If yes, what criteria should apply in determining whether or not an overseas regulator is trusted?

Should any criteria take into account different device classifications? For example, a regulator could be designated trusted for some classes of devices but not others.

A: Yes, Australia should look to recognise other international regulators as 'trusted' for the purpose of IVD approvals in addition to Notified Bodies; TGA works with IMDRF; No, a trusted regulator should be designated trusted for all classes of devices

IVD Australia believes that the TGA should continue to recognise Certifications from EU Notified Bodies and Health Canada as is currently the case for IVDs (refer also to comments above), but also look to recognise other international regulators as 'trusted' for the purpose of device approvals in addition to the EU and Health Canada systems.

Due to differences in Europe over classification of IVDs, TGA has already accepted Health Canada licencing for IVDs and ISO 13485 certification only for lower risk (Class 2) devices. IVD Australia believes that this is appropriate unless the replacement is of equal burden. Not that this is an example where IVDs are different from other non-IVD medical devices so different approaches have already had to be taken.

Criteria could include:

- Rigorous system;
- Years in operation;
- Membership of GHTF;
- and potentially in the future
  - Membership of AHWP (see discussion below).

IVD Australia has been strongly supportive of the Office of Device Authorisation and its predecessor, the Office of Devices, Blood and Tissues, in their efforts to build a harmonised framework for the regulation of Medical Devices and IVDs. This is an important step towards enabling the global IVD industry to begin to operate in a harmonised regulatory environment, a crucial step towards reducing global regulatory burden, and a means of enabling patients to gain faster access to the latest healthcare technology.

The European Union is currently undertaking revision of the European Regulations covering medical devices and IVDs. IVD Australia continues to insist that as far as possible the Australian regulations are aligned with those that are being developed in Europe. Certainly over the past several years with the introduction of the IVD Framework in Australia in July 2010, the Australian requirements have been moving ahead of those in other jurisdictions, adding significantly to the regulatory and cost burden imposed on those manufacturers and sponsors seeking to supply IVDs into the Australian market. IVD Australia is pleased however that the European draft regulations covering IVDs seem to be drafted in a similar manner as the current Australian regulations (in line with GHTF) and this should lead to significant harmonisation post 2016/17.

The AHWP is well established, however, regulations for their members are not always well-established. The AHWP consists of the following member countries:

- Abu Dhabi
- Brunei Darussalam
- Cambodia
- Chile
- Chinese Taipei
- Hong Kong SAR, China
- India
- Indonesia
- Jordan
- Kingdom of Saudi Arabia
- Republic of Korea
- Laos
- Malaysia
- Myanmar
- Pakistan
- People's Republic of China
- Philippines
- Singapore
- South Africa
- State of Kuwait
- Tanzania
- Thailand
- Vietnam
- Yemen

Given that Australia represents **less than 2% of global sales** (for Medical Devices and IVDs), IVD Australia strongly supports the need for alignment with overseas regulations. TGA has used the GHTF model to claim alignment with overseas regulations but having been early adopters of the GHTF model the expectation seems to be that Europe, Canada, USA etc will (or ought to) align with GHTF to reduce the regulatory burden for Australian sponsors. The use of overseas certification (eg: EU EC certificates) has been critical to reduce the regulatory burden for Australian sponsors of medical devices in general. However, until recently, the TGA still conducted a high number of pre-market technical reviews due to (among other reasons):

- lack of alignment between actual regulatory systems. For example TGA will not accept FDA 'approval' to support registration in Australia because the FDA system, whilst requiring them in spirit, does not specifically include compliance with Essential Principles or use the conformity assessment model to prove compliance.
- In addition, the TGA does not recognise the predicate device model upon which the 510(k) 'approval' path is based;
- lack of confidence in overseas certification bodies;
- lack of alignment with overseas regulations (e.g. classification – a significant issue for IVDs where the high number of self-certified products in Europe mean certificates of conformity do not generally exist); and
- the need for TGA to be seen to be directly reviewing and approving the supply of high(er) risk therapeutic products in Australia.

IVD Australia Recommendation 4:

As a leading International Regulator, TGA should continue building an international network of 'trusted' or 'approved' regulators – judged against the requirements of the GHTF outcomes.

Issue 2 – Is There a Good Reason for Australia to Impose Additional Requirements?

Two key features distinguish the Australian IVD market from all others and it is prudent therefore, when discussing important reforms such as these that we fully consider the context in which they will be applied:

1. The Australian market for IVDs represents less than 2% of the world market for these products; and
2. More than 95% of the IVDs supplied to the Australian market are imported; locally manufactured IVDs account for less than 5% of IVDs supplied to the Australian market; and the majority of Australian manufacturers rely on exports to recoup development costs (most local manufacturers are small business).[6]
3. Australia is such a multicultural melting pot that 'Australian' clinical populations could not truly be described as 'uniquely Australian' – and this should be taken into account at the trial stage. Given the multicultural nature of societies these days, manufacturers must also ensure their product is 'fit for purpose' for all possible subtypes.

IVD Australia would be concerned at any reforms that introduce indiscriminate or systemic 'Australian-specific' requirements that could devastate the Australian market.

[6] In 2003, the TGA commissioned a survey of the IVD market in Australia, for the purpose of preparing the initial RIS for the introduction of the new IVD regulatory framework.
Therapeutic Goods Administration, September 2009, Regulation of in vitro diagnostic devices – Cost Recovery Impact Statement, TGA, Canberra; https://www.tga.gov.au/book/background-2#ris

Q: Should the TGA approve the inclusion of a medical device on the ARTG on the basis that it has been approved for the same purpose by a 'trusted' overseas regulator?

- **If yes:**
  - **should this occur regardless of the class of the device?**
  - **How could concerns about the quality of some overseas conformity assessments be managed?**
- **If not, why not? What value do you believe an assessment by the TGA adds?**

Are there aspects of safety, quality or efficacy that need to be considered in the Australian context? If so, what aspects?

A: Yes, TGA should approve the inclusion of a medical device on the ARTG on the basis that it has been approved for the same purpose by a 'trusted' overseas regulator; Yes, it should be regardless of the Class of the IVD; concerns could be managed by the TGA continuing to build a network; the is no added value if the assessment is duplicative; there are no aspects of safety, quality or efficacy that need to be considered in the Australian context.

A key issue here is that it is hard to argue that TGA should accept overseas certification if the overseas regulator assigns a product to a lower class.

The TGA needs to further align with overseas regulators (particularly GHTF members) on classification. They should directly adopt the same classification as Europe when bringing in reforms and then both industry and TGA should have minimal issues. TGA should renegotiate the class if different and make the IVD the same class – then the burden of regulation should be the minimal.

This question implies that there needs to be a careful weighing of the benefits of streamlined international arrangements against the risk to patient safety. However, as has been pointed out by numerous stakeholders, there is **no** evidence that increased scrutiny during premarket assessment can be a substitute for appropriate post-market surveillance.

The Senate Committee that looked at the issues regarding the PIP breast implants did so in an environment where the manufacturer had falsified the records regarding the product. It is clear that fraudulent and illegal behaviour such as this will never be detected via a pre-market assessment process, and it cannot justify increased premarket assessment of all products in a misguided attempt to prevent criminality.

IVD Australia still however believes that for IVDs, including Class 4 IVDs, **100%** third party conformity assessment using notified bodies would offer a more streamlined process than the system currently in place. Manufacturers, including Australian Manufacturers, could then get all their required certificates from one on-site audit. As an additional benefit, the cost of TGA accrediting these Notified Bodies may be significantly less than the current cost recovery mechanism.

Finally, it should be noted that under the IVD regulations the use of CMDCAS Registrars (Canadian Medical Devices Conformity Assessment System) as well as European notified bodies is of significant benefit to IVD manufacturers and sponsors.

Q: Where there are differences in device classification between Australia and the EU, should sponsors be required to meet additional conformity assessment requirements? If not, why not?

Should Australia adopt the EU classification system? If not, why not? What are the strengths of the Australian device classification system that cannot be found in the EU system?

Should Australia maintain Australian specific requirements with respect to labelling and post-market monitoring? If not, why not? If yes, what value do these requirements add?

A: There should be no differences with GHTF, changes should be negotiated through GHTF; Yes, Australia adopt the EU classification system, there are no strengths of the Australian device classification system

that cannot be found in the EU system; Although Australia should maintain the ability to impose specific requirements, they should be negotiated through the IMDRF and comply with the COAG Principles.

Sponsors should be required to meet the requirements of the Class of IVD in which the IVD is assigned. It is expected that under EU requirements, which are standardised, IVDs world-wide should fall under the same Class. Unfortunately even Australian classifications are not identical to EU.

Industry negotiated different outcomes for some areas – partly due to the costs associated. IVD Australia believes that all countries should exactly align with European classification, and all regulators should accept EU (GHTF) classification; which with reforms that allow greater acceptance of overseas certification should reduce costs to compensate for any changes in classification. This is indicative of the need for reconsideration by the GHTF.

It should be noted here, that although the Sponsor may be ultimately the responsible party in Australia, it is the manufacturer that provides this evidence.

There would be no added value in the development of Australian-specific labelling requirements. The IVD Industry in Australia is a well-integrated component of the global market and such specifications would damage importation and potentially exportation of products in and out of Australia – a devastating outcome.

Post-market monitoring is substantially equivalent across the major jurisdictions, particularly GHTF member countries, but TGA must remove Australian-specific requirements, eg the specific naming of customer letters as is imposed under the URPTG.

IVD Australia Recommendation 5:

'Australian-specific' changes should be minimised; and any changes should be negotiated with IMDRF and Industry.

Issue 3 – What is meant by Product Approval?

Q: Should a difference in a medical device that has been approved by a trusted overseas regulator necessitate a further assessment by the TGA in circumstances where that difference may impact safety, quality or performance? If not, why not?

If yes, should the assessment by the TGA be limited only to those aspects of the application that are impacted by the difference?

Would this approach apply to all classes of medical devices?

A: This would depend on whether there is a true (as versus perceived) impact on safety, quality, or performance; Yes, assessment by the TGA be limited only to those aspects of the application that are impacted by the difference; This approach should only apply to all classes of IVDs where technical review is already required.

This is not applicable to all IVDs, particularly Classes 1 and 2 – where ARTG entries are grouped within one entry. In situations where a Sponsor is importing a different IVD than that covered by a specific EU Certification, determination of the necessity of further assessment by the TGA should be required. IVD Australia is currently working with the TGA on 'what changes constitute a significant shift in the risk profile of the IVD.

Where the product is the same 'kind of device' and therefore contains the same inherent risk level, and the TGA has already allowed the inclusion on the basis that overseas certification is adequate then the new product should not need further scrutiny as the manufacturer QMS has been deemed satisfactory for the manufacturer of this 'kind of device'.

Q: If Australia was to accept approvals of medical devices by trusted overseas regulators, should this include conditional/provisional approvals? If not, why not?

Would this approach apply to all classes of medical devices?

If yes, should the marketing conditions/provisions imposed by the trusted overseas regulator also apply in Australia? If not, why not?

Should there be capacity for Australia to impose its own conditions, either in addition to, or in place of, those imposed by the trusted overseas regulator and if so, why?

A: Yes, Australian approvals of IVDs already approved by trusted overseas regulators, should this include conditional/provisional approvals; Yes, this should apply to all classes of IVDs; Yes, marketing conditions/provisions imposed by the trusted overseas regulator should also apply in Australia; Australian impositions of its own conditions would depend on whether there is a true (as versus perceived) issue with safety, quality, or performance.

It would be expected that The same conditions as applied by the overseas regulator should apply in Australia unless these conditions do not make sense for the Australian market, eg additional stability studies would be applicable globally unless the overseas regulator required additional data to compensate for external conditions significantly lower than 0·C for extended periods as this is unlikely to be a factor in Australia.

Marketing conditions would be more difficult to implement, given the complexity of international regulations in this area. IVD Australia has addressed this area more fully in response to the questions raised in chapter 8.

Australia should have the capacity to impose its own conditions, however, these should be restricted to specific safety concerns and not be indiscriminately imposed. IVD Australia believes that except in significant public safety issues, these should be imposed only if an issue arises post-market that requires an Australia-specific response.

IVD Australia Recommendation 6:

Australian approvals of IVDs already approved by trusted overseas regulators, this should include conditional/provisional approvals, and apply to all classes of IVDs.

Theme 2: Lack of Flexibility

Issue 1 – Accelerated Access

Q: Should Australia introduce an accelerated approval program(s) for higher risk medical devices? If yes:

- **What eligibility criteria should apply to the accelerated approval pathway? That is, under what circumstances could a sponsor apply for accelerated approval of a device?**
- **What are the potential risks and benefits of such programs and how might the risks be managed and the benefits maximised?**

A: The focus here should be on acceptance of overseas certification AND acceptance of accelerated approvals from other 'trusted' regulators with the equivalent conditions in place from those regulators.

If TGA worked closely with other regulators/designated authorities to ensure sharing of experience in relation to accelerated products then issues post-market could come to light earlier and/or full approval gained sooner based on the shared knowledge. That is, by allowing a manufacturer to conditionally market the product in multiple jurisdictions, the manufacturer can collect better data, across multiple markets, to support full approval/safety and efficacy to satisfy all regulators.

Q: If higher risk medical devices were to be provisionally approved, based on more limited clinical data than is traditionally required for a full approval:

- **What additional requirements, if any, might be appropriate to alert clinicians and/or consumers to the provisional approval and its implications?**
- **What requirements would need to be in place to manage withdrawal of the device from the Australian market if safety or efficacy concerns emerged?**

What additional post-market surveillance would need to be in place for medical devices that were provisionally approved?

A: Yes; Additional requirements would have to be determined on a case-by-case basis depending on what the provisional approval was for. In some cases, no additional requirements/information may be needed; requirements for managed withdrawal are already in place; Manufacturer must supply data required for full pre-market approval.

There are examples for IVDs that an accelerated approval would be good for. Examples are when you might want to put an assay on a different platform. The assay reagents are effectively the same but aspects of the instrument, consumables, packaging may be different. Limited equivalency studies may be done pre-market with further testing being done post-market to give greater assurance all is OK.

Issue 2 – Ability to Accommodate Technological Developments

Q: Is the current regulatory framework and classification system flexible enough to accommodate new and emerging medical device technologies? If not, why not? How could it be improved?

A: IVD Australia maintains that the current regulatory framework and classification system should be flexible enough to accommodate new and emerging IVD technologies; given it is based on the GHTF model and GHTF tried to write guidance that took into account advances in technology, then it should be flexible enough.

There are limitation and the difficulties tend to lie in processes and interpretation and are still based on decisions by individual assessors within the TGA, for example the current Changes to the ARTG Entries issue.

Over the past 20 years there has been a rapid development in IVD technology. Analytical methodologies have greatly improved the throughput of analysers and dramatically reduced the level of detection for many analytes.[7]

New technologies have enabled the development of multi-analyte and multiplexed assays from a single tiny sample.

New point-of-care technologies have bought the benefit of improved diabetic and coagulation control to millions of patients.

Advances in computer control and mechano-optics have improved the reliability of analysers and lowered the cost per test whilst greatly increasing the throughput.

Tests that previously required the intervention of a skilled technician or pathologist over a number of hours can now be done in minutes on a point-of-care instrument.

[7] For example: enzyme immunoassay, homogeneous assay technology, chemiluminescence, and fluorescence detection.

Improvement in both throughput and cost has led to a dramatic rise in the availability of genomic and companion diagnostics.[8] Over the next several years the number of these tests is expected to rise exponentially. Pharmaceutical companies are more routinely now looking to introduce a companion diagnostic (IVD) alongside their latest gene therapy in order to improve its effectiveness or reduce unwanted side effects in specifically targeted patients In the past, IVD tests were generally developed over several years, and pathologists and the health system could adopt new tests at a measured rate.

Due to these advancements in IVD and genomic technology, new tests are being introduced every day, and old ones superseded. IVD Australia believes that pressure from patients and healthcare practitioners will lead to increased demands for these newer and better tests. Regulation of these within the Australian context will of course require applications to be made through the TGA followed by reimbursement through MSAC.

Both MSAC and TGA processes, although somewhat improved, are slow and the current system cannot keep up with the level of applications as new tests are requested by consumers and implemented by pathology providers. The TGA can, and often does, take up to two years to complete a pre-approval process and over the last decade, the evaluation, assessment, and final approval of some tests subject to MSAC application has taken up to 4-5 years to process. Given the increasing level of demand expected over the next few years this is unacceptable. The problem is apparent as a number of current applications for IVD assessments have been in the MSAC system for over 3 years. So, as previously stated, the issues aren't necessarily with TGA but with other government processes.

Theme 3: Regulatory Requirements are not Commensurate with Risk

Issue 1 – The Balance between Risk Management and Regulatory Burden

Q: Does the current regulatory framework for medical devices in Australia provide an appropriate balance between managing risk and minimising unnecessary regulatory burden? If not, why not? Please provide examples.

A: No, it is near impossible in the current system, see discussion below.

The regulatory system for therapeutic goods is currently based on one Act and several sets of regulations[9]:

Therapeutic Goods Act 1989	Therapeutic Goods Regulations 1990
	Therapeutic Goods (Medical Devices) Regulations 2002
Therapeutic Goods (Charges) Act 1989	Therapeutic Goods (Charges) Regulations 1990

Ostensibly, this means that the regulatory system is based on whether a product is a (1) medicine or (2) device. Although on the surface, the division of products into two types appears logical, in reality and in commercial application, it causes too many unnecessary hurdles, some of which even the TGA have admitted must be ignored until guidance documents can be finalised. One example of this is the Guidance on Changes to Entries on the ARTG.

IVDs were 'written in' to the Medical Devices regulations, which caused many issues to be overlooked and has caused significant unintended consequences. One example is included here, but others can be provided. For example, software and IVDs - originally TGA intended assay software (software which sets the parameters for running a particular test) to be registered in the same class and with the assay in question. However, an oversight in the 'writing in' of IVDs into the medical device regulations means that all assay software that influences an instrument is Class 1.

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[8] The cost of gene sequencing has also fallen dramatically over the 8 years since the completion of the Human Genome project. It is now possible to sequence the genome of an individual for less than $10,000 within a week, and this cost and the time required are expected to fall considerably over the next few years.

[9] http://tga.gov.au/legislation-legislative-instruments

Although the TGA website is quite an effective tool now with recent changes, examples of regulatory confusion can be found on the TGA website (see screen shots on the following page)[10]:

- This page describes six (6) 'types of products';
- This page describes seven (7) 'types of products'.

To find the appropriate balance between managing risk and minimising unnecessary regulatory burden, there needs to be significant change and simplification of change to the structure of the Regulations.

IVD Australia believes that the Therapeutic Goods Act should sit above seven sets of Regulations as shown below:

Therapeutic Goods Act 1989	Therapeutic Goods (Medical Devices) Regulations
	Therapeutic Goods (In-vitro Diagnostic Devices) Regulations
	Therapeutic Goods (Prescription Medicines) Regulations
	Therapeutic Goods (Over-the-Counter Medicines) Regulations
	Therapeutic Goods (Complementary Medicines) Regulations
	Therapeutic Goods (Blood, Tissues & Biologicals) Regulations
	Therapeutic Goods (Other Therapeutic Goods) Regulations
Therapeutic Goods (Charges) Act 1989	Therapeutic Goods (Charges) Regulations 1990

Key Advantages

- This would enable the TGA to find the appropriate balance between managing risk and minimising unnecessary regulatory burden for each sector of the Therapeutic Goods Industry.
- Improved industry, government and consumer understanding
- Ease of oversight

Key Disadvantages

- Potential siloing of expertise and activities within the TGA.

IVD Australia Recommendation 7:

That the first step to an appropriate balance between managing risk and minimising unnecessary regulatory burden for the IVD sector of the Therapeutic Goods Industry is the introduction of specific *Therapeutic Goods (In-vitro Diagnostic Devices) Regulations.*

[10] http://tga.gov.au/industry; http://tga.gov.au/overview-supplying-therapeutic-goods-australia#determine- type-therapeutic-good-relevant-regulatory-guidance

Determine the type of therapeutic good and the relevant regulatory guidance

Different application processes and regulatory requirements apply depending on the type of therapeutic good that is to be supplied. You are advised to review the relevant guideline document before making further enquiries to the TGA.

- A prescription medicine is generally a medicine that requires a prescription from a registered health care practitioner.
  Approval of a generic prescription medicine follows a similar process to new prescription medicines.

  For more information see Australian regulation of prescription medical products.
  - The Australian Regulatory Guidelines for Prescription Medicines (ARGPM) will assist sponsors to prepare applications to register new prescription or other high risk medicines for human use in Australia.

- An over-the-counter (OTC) medicine is generally a medicine that can be purchased without a prescription but from a pharmacy or in some cases from the supermarket.

  For more information see Australian regulation of over-the-counter medicines.
  - The Australian Regulatory Guidelines for OTC Medicines (ARGOM) will assist sponsors to prepare applications for a new OTC medicine for human use in Australia.

- A complementary medicine is generally a herbal or 'traditional' medicine, and includes vitamins and homeopathic products.

  For more information see Regulation of complementary medicines in Australia.
  - The Australian Regulatory Guidelines for Complementary Medicines (ARGCM) will assist sponsors to prepare applications for new complementary medicine for human use in Australia.

- A medical device includes a range of goods such as bandages, pacemakers, x-ray equipment, and in vitro diagnostic medical devices.

  For more information see Medical devices regulation basics, and Regulatory framework for in vitro diagnostic medical devices.
  - The Australian Regulatory Guidelines for Medical Devices (ARGMD) will assist manufacturers and sponsors of medical devices in meeting the regulatory requirements for legally supplying a medical device in Australia.

- A biological is generally a product of human origin, such as bone grafts or stem cells.

  For more information see Australian Regulatory framework for biologicals.
  - The Australian Regulatory Guidelines for Biologicals (ARGB) will assist sponsors to prepare applications to register a new biological for human use in Australia.

- An other therapeutic good (OTG) includes things such as disinfectants and tampons.

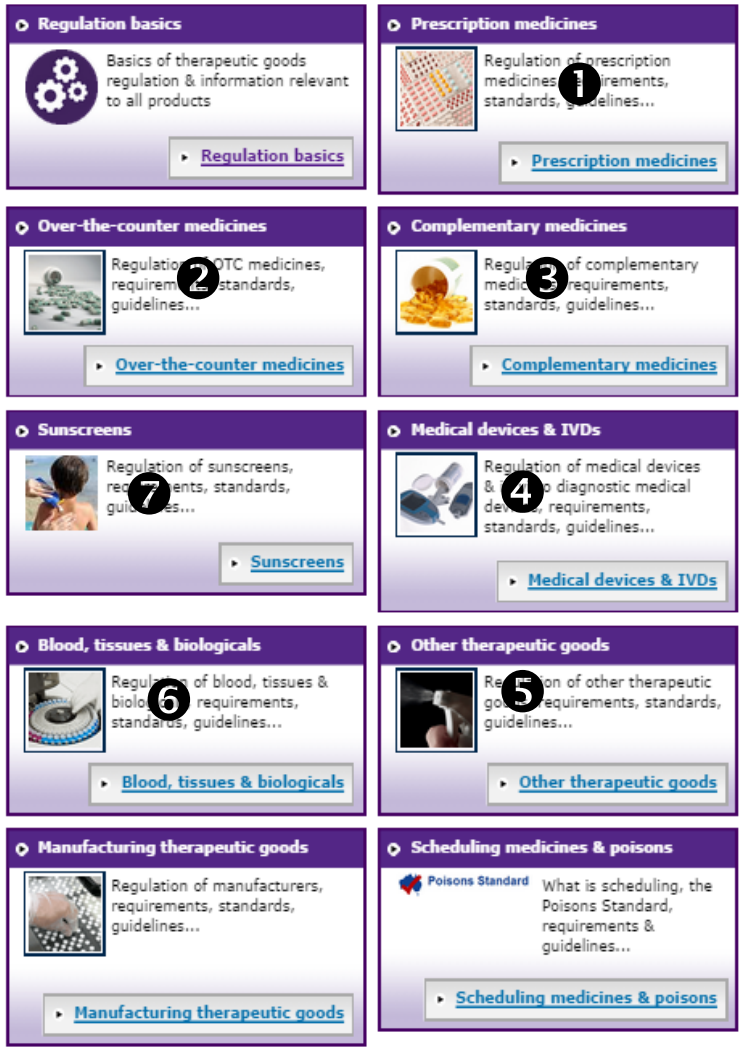
  For more information see Other therapeutic goods.
  - The device/medicine boundary products information on the TGA website, and the OTG information on the TGA website will assist sponsors to prepare applications to register a new OTG for human use in Australia.

- A combination product incorporates two or more of the above product types. It is strongly recommended to review device/ medicine boundary products information on the TGA website.

Industry

Do you supply and/or manufacture therapeutic goods or want to?

This section includes information about the regulation of therapeutic goods in Australia, including standards and guidelines for different product types.



Q: Should low risk medical devices that are not subject to an independent conformity assessment be included on the ARTG?

- **If not, why not? Are there any risks involved in not including such products on the ARTG?**
- **If yes, why? What are the benefits of these products being included on the ARTG?**

A: Yes, low risk medical devices that are not subject to an independent conformity assessment should be included on the ARTG; The benefit of these products being included on the ARTG is that is known that they are legally supplied to the Australian market.

Yes, they should because without a complete list (even if products are grouped into one ARTG entry), there is no way of finding out what products are actually legally on the market in Australia.

The TGA should be able to communicate succinctly that entry on the ARTG means a product is legally available in Australia.

Many low risk IVDs are currently entered onto the ARTG using only ISO 13485. This standard provides evidence that the manufacturer has a suitable QMS for the manufacture of medical devices (and IVDs). For low risk IVDs in particular this is adequate. IVDs do not 'touch the patient' and low risk IVDs do not lead to 'life-threatening' decisions in patient management. Post-market review and oversight is much more appropriate.

Benefits are availability of 'state of the art' testing which can assist in keeping people 'well' and thus reducing burden on the health system.

Issue 2 – Variations to Medical Devices

Q: Should Australia adopt a risk-based regime for variations, which allows notifications and/or annual reporting for changes to medical devices that are at low risk of impacting the quality, safety, or performance of the device?

If yes, what might such a regime look like? How might notification/reporting procedures be designed so as to minimise burden on sponsors?

If not, why not?

A: Yes, Australia should adopt a risk-based regime for variations, which allows notifications and/or annual reporting for changes to medical devices that are at low risk of impacting the quality, safety, or performance of the device; see discussion below.

The current regime is risk-based and only for high risk devices is it currently necessary to notify changes which could impact quality, safety or performance. However, with the move to greater acceptance of overseas certification, a requirement to notify annually of changes to high risk medical devices might be acceptable.

This question only refers to notification of 'low risk' changes. If the terminology of 'substantial change' is taken to mean 'high risk' then the IVD industry already does not need to notify 'low risk' changes and this is appropriate. The premise of the current regulations is that 'low risk' changes are managed under the **manufacturers QMS** and there is no requirement to report 'low risk' changes now.

IVD Australia is currently working with the TGA on *Guidance on Changes to ARTG Inclusion.* IVD Australia has two overall concerns:

1. The aim driving guidance documentation should be to provide clarity to current procedures, not to develop new procedures accompanied by regulatory change. Industry considers the processes and procedures to vary ARTG entries are generally adequate and appropriate but there are cases where the particular procedure or form required for a change is not clear. It can be a particular challenge for smaller

or less experienced sponsors to identify how to make a specific change to an ARTG entry. The focus needs to be on 'clarity of current process' not regulation change and IVD Australia would prefer to see no regulation change until the current process is clear and a definite need has been established.

2. With Class 4 IVDs as notable exceptions, IVD Australia queries whether the inherent risks of change to an in-vitro diagnostic device are comparable to those for medical devices. This is evidenced particularly in the table at Attachment A of the *TGA Working Group Update: Guidance on Changes to ARTG inclusion*, where many of the changes identified are not critical changes for IVD inclusions.

   IVD Australia has included at page 24 of this document, an example of the table it would prefer to be developed as it clarifies (1) the impact on the product's risk profile of the intended change, (2) the actions required and (3) the legal underpinning for the action required.

IVD Australia believes that:

1) Processes to change ARTG entries should, as much as practical, be easy to use and 'fit for purpose'. A large proportion of ARTG variations are relatively simple administrative changes and any potential change to the variation process should ensure that the processing of such changes is painless for both industry and the TGA.
2) Industry agrees that fees charged should be commensurate with the level of TGA review required. For example, if the review primarily relates to a review of a manufacturer's QMS then a single fee should be charged for the review and not a fee charged per ARTG entry.
3) It is not agreed that responsibility for the safety and performance of a device is, or should be, transferred to the TGA when an ARTG variation is reviewed. It is entirely appropriate that the risk remains with the Sponsor.
4) If such a transfer of risk is now considered to be a concern, in contrast with ARTG variation procedures that have been used to date, then a preferable option would be for the Sponsor to re-make the declaration under 41FD of the *Therapeutic Goods Act* 1989. Currently, Sponsors of IVDs are required to make this declaration for an eBS IVD variation and a similar system could be used for all medical device ARTG variations.
5) It has been stated that the legal basis for changing ARTG entries is unclear or not appropriate. Industry remains unclear of any legislative changes required in relation to changes to ARTG entries, and seeks clarification on this issue. Unless a legal reason related to current practice underpins the need for a change to the regulations, industry believes this is not required. No legal reasoning has been provided to industry.
6) *'Additionally, under Section 41BE of the Act, a medical device is of the same kind as another medical device if it has the same manufacturer, sponsor, GMDN code and same classification and so can be supplied under a single ARTG entry. A separate ARTG entry would be required where these details (ie: GMDN code etc) change.'* This is one of the few areas IVD Australia has identified that may, potentially, necessitate the need for amendment to the regulations. The provisions under Regulation 10F of the *Therapeutic Goods Regulations* 1990 allow for a change of sponsor for an ARTG entry. If the regulations allow for a change to one aspect of the 'kind of device', provided all products under the entry still are the SAME kind of device, certain other changes could be made to an ARTG entry.

Additionally:

7) In cases where the 'action required' is a new application for ARTG inclusion, the change is no longer a 'change to an ARTG entry'. The Assessment then becomes that appropriate for an initial Application for Inclusion.
8) IVD Australia is concerned that the allocation of the risk level is arbitrary for the examples given with the statement 'likelihood that a change to the ARTG entry will result in change to the risk profile of the device' IVD Australia would like to see the assessment of risk according to a conventional protocol as on page 25 of this document.
   For example:

a. Classification defines the level of inherent risk not the GMDN code. If there is no change to the device itself or its intended purpose, a change to the GMDN code does not alter the level of risk.
b. If it is the SAME manufacturing site, and the LEGAL manufacturer is just a different part of the same overall company then the risk is likely to be LOW.

9) Unless the UPI is part of the 'kind of device', eg: Class 4 IVDs, it is possible to expand the intended purpose of a 'kind of device' to cover new UPIs or variants so long as they are still covered by the same GMDN code, ie still the same 'kind of device'.
10) A Notified Body may not issue a report and this would cause unnecessary red-tape for Sponsors. A statement and documentary evidence, eg: updated certificate from the manufacturer should suffice.
11) Industry agrees that fees charged should be commensurate with level of review but notes, for example, if the review primarily relates to a QMS review, then the fee should be commensurate with such a review and should be charged once not per ARTG entry.

IVD Australia remains committed to participate in the process to clarify the requirements for **Guidance on changes to ARTG inclusion**, but would like to see changes to the process used, particularly with regard to risk assessment and instances where IVDs differ from medical devices.

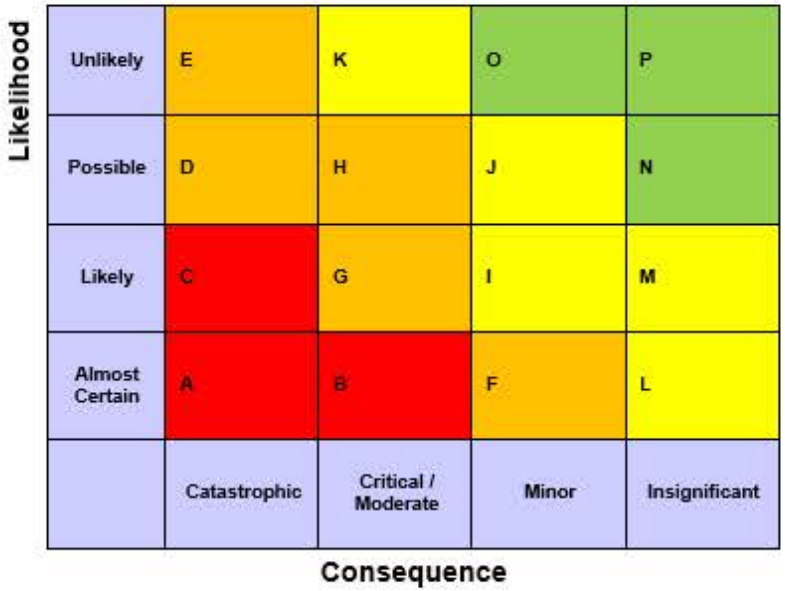
In-vitro Diagnostic Devices – Changes to ARTG Entries - Risk Outcomes Table

Specifics of the Change		Potential Risk	Risk Rating	Applicable Process & Forms	Legal Underpinning	Fee Applicable*
ARTG number	No change – would be a new ARTG entry					
Product Description	Is this the functional description? If so this is the same as the intended purpose for an IVD. Alternatively is it Product Details which is the UPI and only relevant for Class 4 IVDs which will have undergone TGA conformity assessment and therefore the change is assessed prior to change to the ARTG entry. See below.					
	Or is this where the actual product name needs to be added to the ARTG entry? If so, this is covered by IVD variation. This change comes under 'Standard Conditions' and therefore doesn't apply here – As agreed by TGA and Industry at last IVD WG meeting.					
Device Classification	No change permitted (currently) – to be debated					
Sponsor's Details						
Manufacturer's Details	Change of Name Change of Address Change of Legal Manufacturer within same corporation	Minimal				
	Change of Ownership	Change to QMS to be assessed				
ARTG Start Date	No change – It is what it is					
GMDN Code						
Intended Purpose						
UPI	Change to UPI of a Class 4 IVD UPI only applies to Class 4 IVDs therefore change has undergone TGA CAC. Should be automatic change.					
Range of Variants	Not applicable for IVDs					
Conditions of Inclusion	Change initiated by Sponsor Change initiated by TGA					

* This could be a flat administrative fee or just state 'commensurate with review needed' Also needs to state whether it is per ARTG entry or per change.

Risk Assessment Chart

Impact	Description	Probability
Catastrophic	Death	>80%
Critical/Moderate	Medical assistance	40% - 80%
Minor	Minor Injuries	5% - 40%
Insignificant	No injury	<5%



Likelihood	Description	Probability
Unlikely	May only occur only in exceptional circumstances. This event is known to have occurred elsewhere – once every 5+ years	<5%
Possible	Might occur at some time – once every 3 years	5% - 40%
Likely	Will probably occur - once during the year	40% - 80%
Almost Certain	Is expected to occur in most circumstances - frequently during the year	> 80%

Issue 3 – Post-Market Surveillance and Supportive Data Collection and Analysis

Q: Does Australian have the balance right between pre-market and post-market regulation of medical devices?

If not, why not? How could it be improved?

What are the features of an effective post-market surveillance system?

A: Although IVD Australia would like to see a greater emphasis on post-market monitoring, the Transition Period is due to finish in 2017 and this is required to balance emphasis. Industry may not be as aware of their post-market obligations due to this.

Pre-market assessments would benefit from less repetition of assessments done internationally and this would potentially allow for more resource allocation in preparation for increased post-market surveillance.

IVD Australia believes that in order for proper balance to be evident the Australian post-market system will need to be more closely aligned to the GHTF. It an appropriate system for IVDs and allows international actions and outcomes. Terminology remains the key contentious issue. For example, product corrections are not the same as recalls.

Issue 4 – Access to Unapproved Medical Devices

Q: Is the Special Access Scheme efficient and effective for Category A patients? Are there issues or concerns with the way in which the Scheme currently runs?

Should the Special Access Category B and the Authorised Prescriber schemes be revised to narrow the range of circumstances in which TGA approval is required for use of an unregistered medical device?

- **If yes, what criteria might be applied to determine when an approval is required?**
- **If no, why not? What do you perceive as the risks of such an approach?**

A: The Special Access Scheme is appropriate for IVDs.

The **Authorised Prescriber Scheme** is used for IVDs, particularly in cases where the customer applies for a specific clinical application, prior to the device being included on the ARTG.

The recent RIS stated (emphasis added):

> *Regulations may be required (as referred to in Proposal 2C) to address some of the outstanding stakeholder concerns regarding continued access to specialised IVDs, particularly Class 4 in-house IVDs, in certain circumstances. Exemption provisions are already provided in the Act for medical devices subject to conditions in the Regulations* ***however they do not adequately address exemptions for IVD medical devices****. Amendments to the Regulations may be required to allow the supply of IVDs for special or experimental purposes in certain circumstances. Suppliers of commercial IVDs and manufacturers of in-house IVDs would potentially be eligible for an exemption if appropriate.*[11]

[11] Therapeutic Goods Administration, *Regulation impact statement Amendments to the new regulatory framework for in vitro diagnostic medical devices (IVDs),* Version 1.0, October 2014

Issue 5 – Regulation of IVDs

The inclusion of the 'Regulation of IVDs' as an issue demonstrates the need for separation of IVDs from medical devices in the regulations (see Theme 3, Issue 1 above). All medical device questions in this Discussion Paper have been answered by IVD Australia from the specific perspective of **IVDs**.

IVD Australia Recommendation 8:

That IVDs are distinct from other medical devices and should be regulated in their own right.

Q: Has the regulatory framework for IVD's resulted in a reduced emphasis on clinical best practice? If so, how. Please provide examples.

A: Regulations, one way or the other, are not the driving force behind clinical best practice for IVDs. The market, (pathologists, scientists and the clinicians they serve), drive clinical best practice in the IVD market. Therefore the emphasis on clinical best practice is unchanged.

IVD Australia believes that it is very rare for an IVD to be subjected to a full randomised double blind controlled trial. At best most IVDs have a body of clinical evidence that can be used to validate the test. Often it is very difficult to obtain quality material for a test which will cover the range of expected clinical situations. However there are multiple references in the literature of real or potential prognostic benefits from the use of specific biomarkers. For example:

- **CYP2C19*2 polymorphism is associated with increased survival in breast cancer patients using tamoxifen.** phgs 11(10):1367-75 (2010), Rikje Ruiter et al
- **Breast Cancer Treatment Outcome with Adjuvant Tamoxifen Relative to Patient CYP2D6 and CYP2C19 Genotypes.** J Clin Oncol 2007 25 (33) 5147-9, W Schroth et al
- **Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis.** JAMA (2010) 304: 1821-30, JL Mega et al
- **Prognostic and predictive impact of EGFR and K-ras mutation, and GFR gene copy number in patients with advanced non-small cell lung cancer (NSCLC) who received first-line cytotoxic chemotherapy**. J Clin Oncol 27:15s, 2009 (suppl; abstr 8096), Y. Tambo et al.

These papers clearly demonstrate the prognostic benefits of specific biomarkers in the treatment of disease but none of these are based on controlled trials.

Q: Should there be statutory timeframes for assessment of applications for inclusion of an IVD on the ARTG?

A: Yes, but this question does not only apply to IVDs

The Discussion Paper states that there are no statutory timeframes for assessment of IVDs under the regulations introduced in 2010, however, this is not correct. Because IVDs are a subset of medical devices, and therefore the same statutory time frame that exists for other non-IVD medical device also applies to IVDs. For example, Class 4 IVDs subject to a TGA Design Examination (as part of a Conformity Assessment) have the same 255 work days' time-frame as any other non-IVD medical device.

IVD Australia recommends that the TGA set clear guidelines for the various steps in approving an application for inclusion on the ARTG. At present there are no specific timeframes and thus the process is not transparent to sponsors who have no clear idea on when they can expect applications to be approved or rejected. Timeframes for approval of applications - in particular, conformity assessment applications - are of immense commercial importance to sponsors as they heavily influence the launch and marketing of products and the associated costs. IVD Australia accepts that we are currently 4 years into the 6 year transition period for the

new Regulations but believes that it should now be possible to determine reasonable timeframes that can be communicated to the industry.

One of the areas of concern to IVD Australia has been the lack of regulated timeframes for assessment of **IVDs** under the regulations introduced in 2010. These have been a feature of the Medicines approval process for some time but have not been adopted as part of the IVD framework. Whilst it is appreciated that we are currently in a transition period, IVD Australia is concerned about the length of time being taken to assess applications for conformity assessment. This creates an issue under the Transition Period particularly for higher risk IVDs as they require conformity assessment before a valid application for inclusion can be lodged.

IVD Australia Recommendation 9:

IVD Australia would support a 30-50 work days' time-frame for ARTG entry for all Classes of IVDs.

Theme 4: Overly Burdensome Processes

Issue 1 – Multiple Systems and Manual Processes

Q: What TGA processes do you consider most burdensome and why? How might these be improved?

A: Conformity Assessments, IT System, and Variations.

Conformity Assessments are a primary concern with regard to regulatory burden. The root cause may in fact, be lack of transparency. Applicants have no feel for how an application is progressing and there is no certainty of progress.

The TGA's **IT System** is rapidly becoming not 'fit for purpose' and it is driving the way the TGA does business because of its limitations. For example, when issues are identified and requests made to modify the system to better align to TGA and industry needs, we are being advised that it is not possible. IVD Australia believes that the IT system should be driven by the regulatory environment.

Variations to ARTG entries and CA applications also suffer from lack of transparency. There is no clarity of process; and interpretation of the regulations is an issue.

Issue 2 – Process for Inclusion of Medical Devices on the ARTG

Q: How might the processes required to include a device family on the ARTG be streamlined without undermining public health and safety?

Are there other concerns with the inclusion of devices on the ARTG? How might these be addressed?

A: IVDs are included at the 'family' level for Class 1, 2 and 3 IVDs, this is appropriate; see discussion below.

It is not the inclusion process that needs streamlining, it is the post-market maintenance of that information. Notwithstanding that it may be controversial, IVD Australia believes that there may be some benefit to clarifying the exact contents of an ARTG entry.

Issue 3 – Instructions for Medical Devices

Q: Should the TGA allow a broader range of permissible formats for instructions for the use of medical devices? If not, why not?

A: Yes, the TGA should allow a broader range of permissible formats for instructions for the use of medical devices.

IVD Australia would support the introduction of e-labelling. For high-volume IVD tests, the inclusion of instructions for use leads to excessive wastage. For example, if a laboratory uses 10,000 tests of the same type within one day, supply of one set of written instructions per lot number (which could easily be obtained on-line as required) then one set per box is unnecessary. Therefore, the ability to provide e-instructions would be invaluable with hard copy instructions remaining available upon request.

Industry would appreciate consultation of improvements to instructions for use.

Issue 4 – Registration of Additional Intended Purposes for a Device

Q: Do current regulatory requirements, costs, and timeframes act as a disincentive to the registration of additional intended purposes for medical devices?

If yes, how might the regulatory framework or processes be changed to reduce the disincentives and/or provide incentives for the registration of additional intended purposes?

A: Lack of certainty and clarity with regard to regulatory requirements, costs, and timeframes act as a disincentive to the registration of IVDs, rather than additional intended purposes.

IVD Australia has noticed that there is wide industry variation in ability to write intended purposes that are fit for purpose. This is caused by gaps in understanding in the regulations and the newness of the regulations. GMDN Codes for IVDs are not overly specific and enable efficient intended purposes. IVD Australia participates in the Industry Sponsor Training Day with other medical device industry bodies and the TGA, a proven effective and popular program. IVD Australia also provides specific industry training sessions and has 'Writing Intended Purposes' on its list. **Training for industry will ensure a better understanding of how to write an intended purpose for the 'kind of device' for an IVD, which in turn, will minimise regulatory burden.**

See also the discussion under Theme 2, Issue 2, Variations to Medical Devices.

Theme 5: Complex Regulatory Framework

Issue 1 – Categorisation[12] of Medical Devices

Q: Is the classification system for medical devices too complex? If yes, how might it be simplified without impacting public health and safety?

Do manufacturers require assistance, such as online decision tools, to assist them to correctly classify medical devices? If not, why not?

If yes, what sorts of assistance would be most effective?

Is the pre-market assessment of medical devices considered overly complex in other ways? If yes, in what way? What are the major pressure points and how might these be addressed?

A: The classification system for IVDs is appropriate, but the inclusion of IVDs into as an afterthought has generated issues that are unnecessary; On-line decision tools such as guidance documents and flow-charts are always useful, the TGA website is much improved in this regard; Pre-market assessment is discussed in Theme 5, Issue 2.

Also, yes, pre-market decision tools needed for IVDs to ensure classification comes before selection of GMDN codes as many codes can be used for multiple classes of IVDs

Q: Is there a role for the TGA in providing a regulatory advice service to product developers / manufacturers / sponsors? If not, why not?

If yes, what should the nature and scope of this advice service be? How could risks of regulatory capture be avoided?

Is current guidance material easy to locate, navigate and understand?

If not, what are the main issues and concerns? How might this material be improved? Is the TGA website easy to navigate? If not, how might it be improved?

A: Industry consultants fulfil this role; current guidance material is under construction and would be improved by separate IVD regulations as discussed in Theme 3, Issue 3.

In addition, adoption of overseas guidance documents in a similar manner to the adoption of overseas standards would benefit industry without massive burden to TGA as long as the regulators continue to work towards harmonisation.

The main issue is that the ARGMD does not focus on IVDs AT ALL. While there are IVD specific guidances on some aspects of the regulations, in other instances the ARGMD is deemed to meet the requirements of both industries. The ARGMD is dated and in many instances provides incorrect advice to IVD sponsors and manufacturers.

The current work of the TGA to create a new web-based guidance portal is well-received but initially will have NO IVD-specific content.

IVD Australia Recommendation 10:

IVDs should have their own guidance - Australian Regulatory Guidelines (ARGIVD).

[12] This should read **Classification**

Issue 2 – Transparency of Regulatory Decisions

Q: Should information about regulatory decisions in respect of medical devices be publicly available? For example, an evaluation report or other relevant information.

- **If not, why not? What do you see as the risks?**
- **If yes, how would this benefit consumers, clinicians and industry? How could any risks be managed?**

Should other regulatory findings relating to medical devices be made public, for example, reports on audits or post-market reviews?

- **If not, why not? What do you see as the risks?**
- **If yes, how would this benefit consumers, clinicians and industry? How could any risks be managed?**

A: IVD Australia supports in general the TGA's move to greater transparency and accountability regarding its decision making. However we do have concerns with regard to implementation.

In part, these concerns stem from the differences between medicines and medical devices. It should be remembered that medical devices (including IVDs) are supplied in significantly greater numbers and formats than medicines, and hence there are a far greater number of inclusions of medical devices on the ARTG. Thus the administrative burden on both sponsors and TGA in publishing details of its decisions must be considered when contemplating a significant change such as the one proposed.

Medical devices and IVDs have a significantly shorter life-cycle than medicines and there are constant updates to products. This means that any system that seeks to keep abreast of the decisions made regarding the application, inclusion or rejection of medical devices must be designed to cope with the large numbers of medical device inclusions on the ARTG. Additionally, while medicines typically take 5 – 10 years to bring to market, medical devices and IVDs, even high risk devices, can be brought to market in the span of a year. This means that deficiencies identified during premarket review can be relatively quickly addressed but the impact of a negative decision in respect of a medical device would persist for a considerable time.

Finally, while the active ingredient for a medicine is generally the same globally, specific variations of medical devices may be created for the clinical needs of regional markets. In the case of the publication of a negative TGA decision regarding a region specific IVD, the manufacturer could be adversely affected by the decision in other jurisdictions.

The practical implementation of the proposed system does raise some specific concerns for IVD Australia and whatever process is implemented for publication of TGA decisions, it should be appropriately resourced and must not delay approval of inclusions. Any public material required to support the decision should be prepared after the product has been included on the ARTG, rather than holding up the inclusion until all material is approved.

IVD Australia does not support publication of any decisions regarding conformity assessment. Decisions regarding conformity assessments offer an opportunity for manufacturers to easily demonstrate assessment by the TGA which are valuable for regulatory approvals in other jurisdictions. However publication of such conformity assessment decisions would need to be carefully managed to prevent potentially commercially sensitive material being published. An example of such sensitive information would be the development of a new product which is not yet ready for market launch for another 6 months. The publication of the conformity assessment regulatory decision has the potential to provide competitors with advanced information of such a product.

IVD Australia Recommendation 11:

For all IVDs it is considered that the general information about IVD decision making processes and the information provided on the public ARTG summary would be sufficient and appropriate to provide transparency.

The proposal regarding publishing decision information for '*more interesting*' lower risk devices is not supported by IVD Australia. It would be difficult to develop criteria on what constitutes '*interesting*' that could be applied in a consistent and systematic manner. Such publication could also give the erroneous impression that 'interesting' devices are subject to premarket review while others are not.

IVD Australia strongly recommends that individual negative decisions should not be published. We believe such a policy would be prejudicial to sponsors and manufacturers, and could potentially discourage manufacturers of IVDs from bringing innovative medical devices to Australia. Justified or not, a negative decision would have an adverse impact on the product in other jurisdictions. Even if the deficiency that caused the negative decision is subsequently corrected and the product is approved in Australia, the association with the negative decision would persist with the product.

Overall, it is considered that the publication of regulatory decisions should consist of the basis of approval for higher risk medical devices. A mechanism for providing such information could be the public ARTG summary, provided that this does not delay the issuing of the actual ARTG certificate to the manufacturer. With any publication of regulatory decisions it should be clearly noted and clearly explained that the level of review does not equate with level of safety or performance of the product.

Aside from the publication of individual regulatory decisions, another measure to increase the transparency and accountability of the TGA's decision making processes in respect of IVDs could be the publication of aggregate reports on an annual or six-monthly basis. Such reports could include:

- Number of conformity assessment and ARTG inclusion application approvals
- Number of conformity assessment and ARTG inclusion application rejections
- Number of conformity assessment and ARTG inclusion application withdrawals
- Product de-identified reasons for rejection
- Average review time for the different classes of medical devices

Such information would provide stakeholders with information on the TGA's decision making processes and provide industry with information on common deficiencies which could be used to improve product submissions overall.

IVD Australia submits that:

- The proposal as structured runs the risk of unwarranted prejudice against certain types of products and against rejected products where for example additional data may lead to approval.
- That the TGA needs to spend much more time initially ensuring that the public comprehends the process for approval of ARTG inclusion so that there is an appropriate background understanding for assessment of any published decisions
- An alternative proposal could involve publication of 'decisions' only when the TGA has actually undertaken some review of the product. This would mean that 'decisions' regarding auto-included products such as Class 1 IVDs would not be published, nor would decisions regarding conformity assessment as these are not specific to the inclusion of a product on the ARTG.
- Finally there needs to be an all or nothing approach taken to the 'kinds of devices' to which this Proposal is applied. All devices of an equivalent kind need to be treated equally and an equivalent level of information required.

Q: Could the regulation of medical devices be made more transparent in other ways? If so how, and what would be the risks and benefits of the proposed approach?

A: Yes, see discussion below

IVD Australia would also suggest that, whilst the Review Terms of Reference are strongly focussed on 'public information' and transparency for consumers, it is equally important that transparency for sponsors is not forgotten.

IVD Australia has a number of concerns at present regarding the transparency of evaluations and document reviews of IVDs under the new regulations.

Whilst the TGA processes in respect of medical devices are generally well understood, for many manufacturers and sponsors of IVDs this is the first time that they have had to make application for an inclusion onto the Australian Register of Therapeutic Goods (ARTG). IVD Australia believes it is critical that the TGA process are made as clear and as transparent as possible in order to minimise the burden of regulation on Australian industry.

We have several areas of concern at present that impact on the transparency of the TGA processes:

i. **Progress of Applications** - sponsors are supposedly able to determine the current progress of applications at present via the eBS system. However, the information provided is limited and at times 'cryptic'. IVD Australia believes that it should be possible to allow the progress of applications to be easily and transparently monitored electronically thus allowing sponsors to check on progress and relieving the TGA of the burden of follow-up phone calls which are a waste of time for all concerned.

ii. **Clear Decision Trees** - IVD Australia believes that the TGA needs to produce clear decision trees setting out the pathways for ARTG applications for IVDs. In addition, there should be regular updating of guidance documents provided by the TGA on the website.

iii. **Clear Time-frames** - IVD Australia recommends that the TGA set clear guidelines for the various steps in approving an application for inclusion on the ARTG. At present there are no specific timeframes and thus the process is not transparent to sponsors who have no clear idea on when they can expect applications to be approved or rejected. Timeframes for approval of applications are of immense commercial importance to sponsors as they heavily influence the launch and marketing of products and the associated costs. IVD Australia accepts that we are currently only 4 months into the 5 year transition period for the new Regulations but believes that it should now be possible to determine reasonable timeframes that can be communicated to the industry.

iv. **All Questions Upfront** - IVD Australia recommends that the TGA amend its processes for ARTG inclusion to ensure that sponsors are not subject to a serial list of queries regarding an application. Members have indicated that they have experienced a process whereby they have received and answered one question regarding their application only to have it followed by another unrelated question that could have been asked at the same time as the initial query. This has the potential to prolong the approval process.

Issue 3 – Interaction with Other Regulatory Frameworks

Q: Is the system overly complex for manufacturers / sponsors of devices using hybrid / convergent / co-dependent technologies? If yes, how could the process be streamlined without undermining public health and safety?

A: No, the TGA component of approval for the IVD is appropriate. The issue is with PBAC/MSAC approval – a separate body.

> *Co-dependent technologies (PBAC, AU): health technologies are co-dependent if their use needs to be combined (either sequentially or simultaneously) to achieve or enhance the intended clinical effect of either technology*
>
> *– Mostly drug + test*
>
> *Co-dependent products are products that depend on the use of a diagnostic test to meet their labelled safety and effectiveness claims (FDA).*[13]

The development of companion diagnostics is exploding across the developed world. Many of these IVDs target gene mutations which are specific for the use of novel, mostly antibody based, pharmaceuticals. The regulation and reimbursement of both the pharmaceutical and diagnostic however raise issues:

- In many cases the number of patients are small and developing acceptable clinical evidence and scientific validity for these assays is difficult; and
- The medicine requires PBAC approval for reimbursement while the IVD requires MSAC approval. The MSAC process despite its recent overhaul is still lengthy and cumbersome.

IVD Australia will continue to work with TGA on developing the requirements for scientific validity and clinical evidence through the IVD Industry Working Group. It is to be hoped that the Genetics Subcommittee established under the Pathology Agreement Advisory Council (PAAC) can determine a mechanism to further improve and speed up the MSAC process, at least for genetic based assays.

IVD Australia participated in the Review of Health Technology Assessment (HTA) undertaken jointly by the Department of Health and Ageing and the Department of Finance in 2009. IVD Australia was broadly supportive of the 16 recommendations that came out of the review and the Government's undertaking to implement 13 of them. However IVD Australia believes that the referral to the Committee is premature. These Recommendations are currently in the process of being implemented, and we believe that it is too early to comment yet as to the effectiveness or otherwise of the implemented Recommendations.

IVD Australia continues to have concerns regarding the HTA / Medical Services Advisory Committee processes:

> *Firstly, we are concerned that the reforms undertaken in MSAC are not altering the speed of the process overall. In fact, we believe that the reforms have simply moved the delays in the system from the middle of the process where the assessment of the evidence was undertaken, to the front of the process where there will be lengthy delays in the Protocol Advisory Subcommittee (PASC). Hence the overall speed of assessment and recommendation of an IVD will not change dramatically.*
>
> *Secondly we are concerned about reports that applications to the Pharmaceutical Advisory Committee (PAC) that involve a co-dependent technology such as an IVD are*

[13] *How to assess co-dependent technologies*, Dr Mira Pavlovic-Ganascia, Deputy Director for HTA, Haute Autorité de Santé, France. Downloaded from http://www.ispor.org/congresses/Berlin1112/presentations/IP8_Pavlovic.pdf.

being delayed unless the IVD application is submitted at the same time as the PAC submission.[14]

Even with the new process, whereby an HTA submission is a joint one, there continues to be delays caused by either component.

Issue 4 – Consumer Understanding of Medical Devices Regulation

Q: Is the regulation of medical devices transparent enough in terms of informing health professionals and consumers about the level of scrutiny that a device has undergone? If not, how could it be improved?

A: At present both general information on pathology assays and details on specific products used by consumers is readily available. See discussion below.

IVD Australia is supportive of the right of consumers to access details of IVDs that they use themselves and information regarding pathology tests on samples that they provide.

For those tests that consumers use directly, information is always available with the product itself, usually in the form of instructions for use. These generally cover issues such as:

- How to use the product safely;
- What does the result mean;
- What to do when you get an abnormal result; and
- How to dispose of the test safely.

In addition, all tests sold over the counter have both the manufacturer's name and address, as well as the sponsor's name and contact details available with the product, enabling consumers to find out further information if required. Sponsors often offer toll-free phone numbers for consumer information regarding these products.

In general, most consumers are not concerned about obtaining specific information regarding the particular kit or test that was used to generate their pathology result. Their primary concern is to understand the result and its implications for their health. This is of course most commonly obtained from consultation with their GP or the requesting health professional.

If consumers are seeking details about the analyte or procedure in general rather than the information on a specific manufacturer's kit, this may be available from a variety of sites. The most informative of these is Lab Tests Online (www.labtestsonline.org.au), a comprehensive site supported by the Department of Health and maintained by the Australasian Association of Clinical Biochemists but there are many other sites available internationally. Specific details of the manufacturer of a particular pathology assay performed in a particular laboratory are however not going to be easily available to consumers.

Thus, at present both general information on pathology assays and details on specific products used by consumers is readily available. IVD Australia is not supportive however of extending this by developing a database of information on manufacturers' assays that is available to be accessed by consumers.

We would have a number of concerns with such a proposal:

- Consumers may not have specific details of the particular kit that has been used and may access incorrect information;

[14] IVD Australia, *Response to Consultation Paper on Assessment of Co-dependent Technologies*, December 2010.

- There are potential risks to consumers in accessing information regarding IVDs that may only comprise part of their clinical diagnosis.
- The information may require updating and this is an additional burden particularly for sponsors who often distribute for a number of manufacturers; and
- The role of IVD manufacturers and sponsors and the TGA is not to provide information on pathology, clinical practice or disease states. Health consumers should be seeking this information from their physician or healthcare professional or from peer reviewed sites such as Lab Tests Online.

Q: Should there be a system for medical devices similar to the AUST R and AUST L system for medicines? If not, why not?

A: No, this has been the past system for medical devices and has been replaced. Experience shows that the simple two-tiered system is also inadequate and very problematical for medicines (these being: prescription; OTC and complementary medicines) and does *not* allow for proper risk assessment.

For IVDs, four classes (based on risk) have been identified but there are only 2 classes in the AUST L/R system.

Cross sector uses of the same legislation and regulations has proven difficult for industry in terms of compliance and the TGA in terms of assessment as it means trying to force products into systems that are designed for a different type of product.

For example, IVDs are not medical devices – they have different:

- Philosophies
- Reasons for use
- Risk profiles –
  - IVD risk is based on the risk posed to the health of the public or an individual, which relates to the risk of an incorrect result arising from the use of the IVD.[15]
  - Medical device risk is based on how invasive within the human body the product is, the duration of use and the risk it poses to the patient, user or other person.[16]
- Classes – based on risk profiles (a class III medical device is not equivalent to a class 3 IVD).
- Background of regulatory development

[15] https://www.tga.gov.au/ivd-guidance-documents

[16] http://www.mtaa.org.au/docs/position-papers/mtaa-consolidated-position-paper-on-regulatory-reform-august-2012-final.pdf?sfvrsn=0

CHAPTER EIGHT: FRAMEWORK FOR ADVERTISING THERAPEUTIC GOODS

Issue 5 – Advertising of Medical Devices

Q: Is the current self-regulatory scheme for advertising of medical devices effective? If not, why not? Please provide examples of where the system has failed.

A: No, Recommendation 5 from the Working Group Report should have been implemented; Sponsors of IVDs included in the ARTG for the purpose of patient self-testing should be able to make use of appropriate restricted representations without pre-approval. See discussion below.

Advertising to Professional Laboratories and Healthcare Professionals

IVD Australia, along with the other industry Associations, was pleased that the Parliamentary Secretary under the previous government supported the development of the sector Codes of Conduct through allocation of $1.4 million over 4 years in the 2012 Budget. However, any benefit of this allocation has yet to be realised. This is not a TGA issue, it is a Department of Health issue.

IVD Australia was a member of both the Working Group on Promotion of Therapeutic Products and the Code of Conduct Implementation Advisory Group.

Like all the other members of the Working Group, IVD Australia also supported the recommendation to require all sponsors (regardless of association membership) to subscribe to a nominated industry code of practice as a condition of registration or listing.

Recommendation 5 from the Working Group Report stated that:

> *The working group recommends that TGA include on its application forms (whether electronic or paper) a requirement for an applicant to nominate the relevant code of practice to which it will subscribe as a condition of registration/listing on the ARTG.*

Unfortunately, the Government in response to the Working Group's Report did not support this recommendation. We now have what can only be described as an inequitable situation in which members of the industry associations are held accountable to their Code of Practice and non-members are free to promote their products to healthcare professionals without oversight or sanction.

Adoption of such a recommendation would allow control through the self-regulatory codes of practice backed by the force of the Therapeutic Goods Act and the Therapeutic Goods Regulations. In concert with this all IVDs should be required to adhere to the IVD Australia Code of Practice, regardless of other Codes that an individual company may be required to adhere to. For example: some IVD Australia members are also sponsors of other medical devices and medicines.

The majority of IVDs are supplied to professional laboratories or healthcare professionals, and hence, appropriately, are outside the scope of the Therapeutic Goods Advertising Code (TGAC). These IVDs are not the same as medicines, which are then supplied directly or indirectly to consumers, and thus should be addressed by a regulatory approach that takes these differences into account.

A major concern with the advertising of *in-vitro* diagnostics is in fact with those products that promote themselves as IVDs but are not included on the ARTG. IVD Australia also recommends that changes to the regulations address the issue of the advertising of products that purport to be IVDs but that are not included, or are excluded from, entry on to the Australian Register of Therapeutic Goods (ARTG). IVD Australia supports reforms that will enable TGA to take speedy action to force the withdrawal of such non-compliant advertisements.

There is currently no advertising pre-approval process for IVDs. IVD Australia, in general, does not believe there is any reason to create a process for IVDs that would result in additional delays and cost for sponsors. The few IVDs that are supplied directly to consumers are already covered by the regulations and hence are subject to the current complaints procedure, which provides adequate oversight in IVD Australia's opinion.

IVD Australia Recommendation 12:

The TGA include on its application forms (whether electronic or paper) a requirement for an applicant to nominate the relevant code of practice to which it will subscribe as a condition of registration/listing on the ARTG

Advertising to Consumers

Another major concern for IVD Australia is that sponsors of IVDs included in the ARTG for the purpose of patient self-testing should be able to make use of appropriate restricted representations without pre-approval. For example: advertisements for blood glucose test strips cannot use the word *diabetes*; HIV Self-Testing Kits will not be able to use the word *HIV*.

In this era of growing consumer awareness it makes little sense in restricting advertisements for blood glucose test strips mentioning the word 'diabetes' when, for example, the intended purpose of the IVD in the ARTG inclusion says '… test strips designed to measure blood glucose in blood when used in combination with a dedicated blood glucose meter by people with diabetes or their health care professionals'.

IVD Australia thus, also strongly recommends the removal of prohibited and restricted representations for IVDs. Sponsors should be able to make representations for IVDs advertised to the consumer in line with the intended purpose of the IVD as included on the ARTG. The Medical Device (what's the advertising review board called) would still be able to take action should inappropriate use of these representations be undertaken by the sponsor.

IVD Australia Recommendation 13:

Sponsors of IVDs included in the ARTG for the purpose of patient self-testing should be able to make use of appropriate restricted representations without pre-approval

IVD AUSTRALIA SUMMARY LIST OF ANSWERS

CHAPTER THREE: PRINCIPLES UNDERPINNING THE REVIEW

Q: Are there any additional principles that should be considered?

A: Yes, additional principles that should be considered – COAG.

CHAPTER SEVEN: REGULATION OF MEDICAL DEVICES

Theme 1: Duplication of Regulatory Processes

Issue 1 – How Might a Trusted Overseas Regulator be Defined?

Q: Should the TGA undertake its own assessment of the competency of EU notified bodies? If yes, how might this occur? If not, why not?

A: No, the TGA should not make its own assessment of the competency of EU notified bodies. The TGA should take on the role of a Designating Authority and work with other Designating Authorities to ensure the competency of Notified Bodies.

Q: Alternatively, given concerns with the EU system, should Australia look to recognise other international regulators as 'trusted' for the purpose of device approvals? If yes, what criteria should apply in determining whether or not an overseas regulator is trusted? Should any criteria take into account different device classifications? For example, a regulator could be designated trusted for some classes of devices but not others.

A: Yes, Australia should look to recognise other international regulators as 'trusted' for the purpose of IVD approvals in addition to Notified Bodies; TGA works with IMDRF; No, a trusted regulator should be designated trusted for all classes of devices.

Issue 2 – Is There a Good Reason for Australia to Impose Additional Requirements?

Q: Should the TGA approve the inclusion of a medical device on the ARTG on the basis that it has been approved for the same purpose by a 'trusted' overseas regulator? If yes: should this occur regardless of the class of the device? How could concerns about the quality of some overseas conformity assessments be managed? If not, why not? What value do you believe an assessment by the TGA adds? Are there aspects of safety, quality or efficacy that need to be considered in the Australian context? If so, what aspects?

A: Yes, TGA should approve the inclusion of a medical device on the ARTG on the basis that it has been approved for the same purpose by a 'trusted' overseas regulator; Yes, it should be regardless of the Class of the IVD; Concerns could be managed by the TGA continuing to build a network; the is no added value if the assessment is duplicative; there are no aspects of safety, quality or efficacy that need to be considered in the Australian context.

Q: Where there are differences in device classification between Australia and the EU, should sponsors be required to meet additional conformity assessment requirements? If not, why not? Should Australia adopt the EU classification system? If not, why not? What are the strengths of the Australian device classification system that cannot be found in the EU system? Should Australia maintain Australian specific requirements with respect to labelling and post-market monitoring? If not, why not? If yes, what value do these requirements add?

A: There should be no differences with the GHTF outcomes, changes should be negotiated through GHTF (or IMDRF and industry); Yes, Australia adopt the EU classification system, there are no strengths of the Australian device classification system that cannot be found in the EU system; Although Australia should

maintain the ability to impose specific requirements, they should be negotiated through the IMDRF and industry and comply with the COAG Principles.

Issue 3 – What is meant by Product Approval?

Q: Should a difference in a medical device that has been approved by a trusted overseas regulator necessitate a further assessment by the TGA in circumstances where that difference may impact safety, quality or performance? If not, why not? If yes, should the assessment by the TGA be limited only to those aspects of the application that are impacted by the difference? Would this approach apply to all classes of medical devices?

A: This would depend on whether there is a true (as versus perceived) impact on safety, quality, or performance; Yes, assessment by the TGA be limited only to those aspects of the application that are impacted by the difference; This approach should only apply to all classes of IVDs where technical review is already required.

Q: If Australia was to accept approvals of medical devices by trusted overseas regulators, should this include conditional/provisional approvals? If not, why not? Would this approach apply to all classes of medical devices? If yes, should the marketing conditions/provisions imposed by the trusted overseas regulator also apply in Australia? If not, why not? Should there be capacity for Australia to impose its own conditions, either in addition to, or in place of, those imposed by the trusted overseas regulator and if so, why?

A: Yes, Australian approvals of IVDs already approved by trusted overseas regulators, should this include conditional/provisional approvals; Yes, this should apply to all classes of IVDs; Yes, marketing conditions/provisions imposed by the trusted overseas regulator should also apply in Australia; Australian impositions of its own conditions would depend on whether there is a true (as versus perceived) issue with safety, quality, or performance.

Theme 2: Lack of Flexibility

Issue 1 – Accelerated Access

Q: Should Australia introduce an accelerated approval program(s) for higher risk medical devices? If yes: What eligibility criteria should apply to the accelerated approval pathway? That is, under what circumstances could a sponsor apply for accelerated approval of a device? What are the potential risks and benefits of such programs and how might the risks be managed and the benefits maximised?

A: The focus here should be on acceptance of overseas certification AND acceptance of accelerated approvals from other 'trusted' regulators with the equivalent conditions in place from those regulators.

Q: If higher risk medical devices were to be provisionally approved, based on more limited clinical data than is traditionally required for a full approval: What additional requirements, if any, might be appropriate to alert clinicians and/or consumers to the provisional approval and its implications? What requirements would need to be in place to manage withdrawal of the device from the Australian market if safety or efficacy concerns emerged? What additional post-market surveillance would need to be in place for medical devices that were provisionally approved?

A: Yes; Additional requirements would have to be determined on a case-by-case basis depending on what the provisional approval was for. In some cases, no additional requirements/information may be needed; requirements for managed withdrawal are already in place; Manufacturer must supply data required for full pre-market approval.

Issue 2 – Ability to Accommodate Technological Developments

Q: Is the current regulatory framework and classification system flexible enough to accommodate new and emerging medical device technologies? If not, why not? How could it be improved?

A: IVD Australia maintains that the current regulatory framework and classification system should be flexible enough to accommodate new and emerging IVD technologies; given it is based on the GHTF model and GHTF tried to write guidance that took into account advances in technology, then it should be flexible enough.

Theme 3: Regulatory Requirements are not Commensurate with Risk

Issue 1 – The Balance between Risk Management and Regulatory Burden

Q: Does the current regulatory framework for medical devices in Australia provide an appropriate balance between managing risk and minimising unnecessary regulatory burden? If not, why not? Please provide examples.

A: No, it is near impossible in the current system.

Q: Should low risk medical devices that are not subject to an independent conformity assessment be included on the ARTG? If not, why not? Are there any risks involved in not including such products on the ARTG? If yes, why? What are the benefits of these products being included on the ARTG?

A: Yes, low risk medical devices that are not subject to an independent conformity assessment should be included on the ARTG; The benefit of these products being included on the ARTG is that is known that they are legally supplied to the Australian market.

Issue 2 – Variations to Medical Devices

Q: Should Australia adopt a risk-based regime for variations, which allows notifications and/or annual reporting for changes to medical devices that are at low risk of impacting the quality, safety, or performance of the device? If yes, what might such a regime look like? How might notification/reporting procedures be designed so as to minimise burden on sponsors? If not, why not?

A: Yes, Australia should adopt a risk-based regime for variations, which allows notifications and/or annual reporting for changes to medical devices that are at low risk of impacting the quality, safety, or performance of the device.

Issue 3 – Post-Market Surveillance and Supportive Data Collection and Analysis

Q: Does Australian have the balance right between pre-market and post-market regulation of medical devices? If not, why not? How could it be improved? What are the features of an effective post-market surveillance system?

A: Although IVD Australia would like to see a greater emphasis on post-market monitoring, the Transition Period is due to finish in 2017 and this is required to balance emphasis. Industry may not be as aware of their post-market obligations due to this.

Issue 4 – Access to Unapproved Medical Devices

Q: Is the Special Access Scheme efficient and effective for Category A patients? Are there issues or concerns with the way in which the Scheme currently runs? Is the Special Access Scheme efficient and effective for Category A patients? Are there issues or concerns with the way in which the Scheme currently runs? Should

the Special Access Category B and the Authorised Prescriber schemes be revised to narrow the range of circumstances in which TGA approval is required for use of an unregistered medical device? If yes, what criteria might be applied to determine when an approval is required? If no, why not? What do you perceive as the risks of such an approach?

A: The Special Access Scheme is appropriate for IVDs.

Issue 5 – Regulation of IVDs

Q: Has the regulatory framework for IVD's resulted in a reduced emphasis on clinical best practice? If so, how. Please provide examples.

A: Regulations, one way or the other, are not the driving force behind clinical best practice for IVDs. The market, (pathologists, scientists and the clinicians they serve), drive clinical best practice in the IVD market. Therefore the emphasis on clinical best practice is unchanged.

Q: Should there be statutory timeframes for assessment of applications for inclusion of an IVD on the ARTG?

A: Yes, but this question does not only apply to IVDs

Theme 4: Overly Burdensome Processes

Issue 1 – Multiple Systems and Manual Processes

Q: What TGA processes do you consider most burdensome and why? How might these be improved?

A: Conformity Assessments, IT System, and Variations.

Issue 2 – Process for Inclusion of Medical Devices on the ARTG

Q: How might the processes required to include a device family on the ARTG be streamlined without undermining public health and safety? Are there other concerns with the inclusion of devices on the ARTG? How might these be addressed?

A: IVDs are included at the 'family' level for Class 1, 2 and 3 IVDs, this is appropriate.

Issue 3 – Instructions for Medical Devices

Q: Should the TGA allow a broader range of permissible formats for instructions for the use of medical devices? If not, why not?

A: Yes, the TGA should allow a broader range of permissible formats for instructions for the use of medical devices.

Issue 4 – Registration of Additional Intended Purposes for a Device

Q: Do current regulatory requirements, costs, and timeframes act as a disincentive to the registration of additional intended purposes for medical devices? If yes, how might the regulatory framework or processes be changed to reduce the disincentives and/or provide incentives for the registration of additional intended purposes?

A: Lack of certainty and clarity with regard to regulatory requirements, costs, and timeframes act as a disincentive to the registration of IVDs, rather than additional intended purposes.

Theme 5: Complex Regulatory Framework

Issue 1 – Categorisation of Medical Devices

Q: Is the classification system for medical devices too complex? If yes, how might it be simplified without impacting public health and safety? Do manufacturers require assistance, such as online decision tools, to assist them to correctly classify medical devices? If not, why not? If yes, what sorts of assistance would be most effective? Is the pre-market assessment of medical devices considered overly complex in other ways? If yes, in what way? What are the major pressure points and how might these be addressed?

A: The classification system for IVDs is appropriate, but the inclusion of IVDs into as an afterthought has generated issues that are unnecessary; On-line decision tools such as guidance documents and flow-charts are always useful, the TGA website is much improved in this regard; Pre-market assessment is discussed in Theme 5, Issue 2.

Q: Is there a role for the TGA in providing a regulatory advice service to product developers / manufacturers / sponsors? If not, why not? If yes, what should the nature and scope of this advice service be? How could risks of regulatory capture be avoided? Is current guidance material easy to locate, navigate and understand? If not, what are the main issues and concerns? How might this material be improved? Is the TGA website easy to navigate? If not, how might it be improved?

A: Industry consultants fulfil this role; current guidance material is under construction and would be improved by separate IVD regulations as discussed in Theme 3, Issue 3.

Issue 2 – Transparency of Regulatory Decisions

Q: Should information about regulatory decisions in respect of medical devices be publicly available? For example, an evaluation report or other relevant information. If not, why not? What do you see as the risks? If yes, how would this benefit consumers, clinicians, and industry? How could any risks be managed? Should other regulatory findings relating to medical devices be made public, for example, reports on audits or post-market reviews? If not, why not? What do you see as the risks? If yes, how would this benefit consumers, clinicians, and industry? How could any risks be managed?

A: IVD Australia supports in general the TGA's move to greater transparency and accountability regarding its decision making. However IVD Australia does have concerns regarding implementation.

Q: Could the regulation of medical devices be made more transparent in other ways? If so how, and what would be the risks and benefits of the proposed approach?

A: Yes

Issue 3 – Interaction with Other Regulatory Frameworks

Q: Is the system overly complex for manufacturers / sponsors of devices using hybrid / convergent / co-dependent technologies? If yes, how could the process be streamlined without undermining public health and safety?

A: No, the TGA component of approval for the IVD is appropriate. The issue is with PBAC/MSAC approval – a separate body.

Issue 4 – Consumer Understanding of Medical Devices Regulation

Q: Is the regulation of medical devices transparent enough in terms of informing health professionals and consumers about the level of scrutiny that a device has undergone? If not, how could it be improved?

A: At present both general information on pathology assays and details on specific products used by consumers is readily available.

Q: Should there be a system for medical devices similar to the AUST R and AUST L system for medicines? If not, why not?

A: No, this has been the past system for medical devices and has been replaced. Experience shows that the simple two-tiered system is also inadequate and very problematical for medicines (these being: prescription; OTC and complementary medicines) and does *not* allow for proper risk assessment.

CHAPTER EIGHT: FRAMEWORK FOR ADVERTISING THERAPEUTIC GOODS

Issue 5 – Advertising of medical devices

Q: Is the current self-regulatory scheme for advertising of medical devices effective? If not, why not? Please provide examples of where the system has failed.

A: No, Recommendation 5 from the Working Group Report should have been implemented; Sponsors of IVDs included in the ARTG for the purpose of patient self-testing should be able to make use of appropriate restricted representations without pre-approval.

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