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Department of Health

Therapeutic Goods Administration

Proposal for the regulation of IVD companion diagnostics

Consultation paper

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TGA Health Safety
Regulation



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Introduction

The coupling of the “genomics revolution” and its ability to target specific disease-causing mutations along with massive improvements in data analytics capacity has greatly assisted the development of biomarkers. Once a reliable biomarker for a disease or condition is identified, more specific diagnostic tests can then be developed. The precision medicine “revolution” has been driven largely by the increasing availability and affordability of a broad array of tests capable of generating large amounts of information about the characteristics of the patient and their disease or condition. The array of tests is matched by the growing number of rationally - designed treatments, which in the case of cancer may include cell-based therapies, immunotherapies, and targeted therapies.

At its full potential, precision medicine will enable a fuller transformation from current paradigms of providing health care for individual patients based on diagnostic procedures and medicines that had been developed through studies that were designed to measure population outcomes to one in which care is selected based on unique patient health and disease information. Four areas where precision medicine is already making a difference in health care include:

- **Diagnosing and preventing genetic disease** – diagnosis of biochemical and genetic abnormalities in monogenic and syndromic conditions. Whole genome sequencing can identify approximately half of the genes that are thought to contribute to severe developmental disabilities, so use in pre-conception screening is increasing.
- **Cancer diagnosis and treatment** – characterisation of mutations and their impact can lead drug development (e.g. tyrosine kinase inhibitors such as imatinib) and genetic screening of patients for cancer risk, or ordering of appropriate treatments according to mutation status.
- **Determining the suitability of medicines (pharmacogenomics)** – e.g. different forms of liver enzymes that metabolise drugs, some rare mutations that make particular medicines contraindicated.
- **Impact on population health and chronic conditions.** There is also an opportunity to improve single and multi-genic conditions – diabetes, heart disease – and for these increasingly prevalent diseases to move from diagnosis and treatment optimisation to disease prevention and early intervention.

Arising from these advances has been the development of targeted therapies. Targeted therapies are medicines or cellular therapies that are designed rationally after the establishment of a test, for example, to identify an individual tumour characteristic. In precision cancer medicine this has allowed diseases to be classified more specifically, prognoses to be determined more accurately and treatment choices to be selected based on an individual patient’s characteristics, molecular tumour profile and the likelihood of response to a particular therapy. It has led to improved response rates, and improvements in overall survival.

The success of precision medicine is reliant upon having accurate tests to detect specific biomarkers that are associated with an improved outcome with a particular medicine. In the in vitro diagnostic medical device (IVD) sector such a test is commonly referred to as a companion diagnostic (CDx). A CDx can be developed from a range of technology and includes immunohistology tests to tests based on whole genome next generation sequencing (NGS). With NGS, in some cases CDx status may be conferred only to a subset of biomarkers within a much broader panel that detects a wide range of biomarkers.

The definition of what constitutes a CDx for one of these targeted therapies has been defined by the United States (US) Food and Drug Administration (FDA) and in the recently released European (EU) IVD Regulations. In broad terms, the definitions define a CDx as a test or device

that provides information that is **essential for the safe and effective use** of a given therapeutic product. As yet, this term is not currently defined in our Australian IVD regulations.

This paper outlines a proposal to introduce a legal definition for an IVD CDx and a regulatory approach that ensures these devices are subject to an appropriate level of premarket scrutiny prior to supply in Australia, given their role in determining appropriate therapy. This has been identified as a priority area for reform in order to provide greater clarity to industry and greater assurance to healthcare professionals and patients in relation to the identification, classification and assessment of these kinds of devices.

Development and implementation of specific requirements for CDx's within the current IVD regulatory framework is also consistent with the implementation of the government-accepted recommendations from the Expert Panel Review of Medicines and Medical Devices Regulation (MMDR). Among these is the agreement that the Australian medical device regulatory scheme will be further aligned where appropriate with European regulatory requirements, and greater use of international regulators' assessments. Equally important to these proposals is maintaining capacity to undertake assessments of therapeutic goods for safety and quality, and retaining responsibility for approving the inclusion of therapeutic goods in the ARTG.

The focus of this consultation paper is specifically on options for the establishment of a regulatory framework for IVD CDx tests, including genetic and immune-based assays, since IVDs are currently the format in greatest use. At a later date we may consider how other tests (i.e. non-IVD), such as those based on imaging, can best be regulated where they may be used as a CDx in Australia.

With several medicines already in clinical use that target particular biomarkers, it is particularly important for there to be confidence in the specificity and sensitivity of the tests that are described as suitable for detection of those biomarkers.

It is also recognised that many of the medicines that target specific biomarkers are used in very ill patients e.g. those with various cancers or rare diseases. Equally, use of a targeted medicine in an inappropriate patient may expose that patient to serious side effects and provide little or no benefit.

We are looking for feedback on a proposed approach for implementing this change and for information on potential impacts on clinicians, patients and industry. This feedback will assist us to develop a proposed framework for Ministerial approval and address any unintended consequences.

The US FDA has introduced the term “complementary diagnostics” as referring to those IVDs that are considered to aid in the benefit-risk decision-making about the use of a medicine in a clinically meaningful way, but the test is not essential for safe and effective use of a medicine. Although it is not currently being proposed that this terminology would be adopted, a closer look at this will be undertaken at a later stage in the context of further harmonization with other international regulators.

Issues with the current Australian regulatory approach

Under the current Australian legislation the term IVD companion diagnostic is not defined in the *Therapeutic Goods (Medical Devices) Regulations 2002* (the Medical Devices Regulations). Unlike the US FDA and EU requirements for premarket assessment of an IVD CDx in conjunction with the corresponding therapeutic product, the TGA to date has not had a collaborative approach to the premarket assessment of an IVD CDx. Consequently, until now, the TGA has been undertaking assessments of the medicine/biological and the associated IVD CDx separately, which does not always allow comprehensive evaluation of the benefits and risks of using the medicine/biological and device together.

The issues associated with the current approach to the regulation of IVD CDx are summarised below:

- **“IVD Companion diagnostic” not defined in regulation**

The pre-market assessment of IVD CDx has not been consistent due to the absence of a clear definition of the term in the Medical Devices Regulations. The absence of a definition has resulted in difficulties identifying these devices in an application for the purpose of co-ordinating assessments, a lack of clarity in relation to classification and an inability to identify these devices once included in the ARTG. Along with addressing these concerns, the introduction of a definition will align the TGA with both the new EU IVD Regulations and the US FDA, ensuring a harmonised regulatory approach.

- **Lack of clarity in relation to classification under the current IVD framework**

While it is intended under the current Australian legislation that IVD CDx would be regulated as Class 3 IVDs, the current classification rules in Schedule 2A of the Medical Devices Regulations are not clear in relation to IVD CDx. Most IVD CDx have been appropriately classified as Class 3 IVDs and applications have been selected for audit assessment prior to inclusion on the ARTG. However, the current provisions in the Medical Devices Regulations do not ensure that this always occurs. Consequently some IVD CDx have been included in the ARTG as Class 2 IVDs. This means that they have not undergone an appropriate level of assessment prior to use in Australia. It is proposed that to provide greater clarity in relation to the classification of these devices that the IVD classification rules will be amended to clearly state that IVD CDx are Class 3 IVDs.

- **Difficulties identifying an IVD CDx in an application for inclusion**

It is not always apparent in an application for inclusion of an IVD in the ARTG whether the device is an IVD CDx (i.e. essential for defining safety and effectiveness of a particular treatment for a particular patient). Therefore these devices are not always appropriately assessed prior to inclusion in the ARTG by TGA in the context of their intended purpose and level of risk (including assessment of clinical evidence). Further, as IVD CDx are not readily identifiable in an application it is not always possible to align the assessments of the device and its associated medicine/biological. Consequently the TGA has been undertaking the assessment of the medicine/biological and the associated IVD separately, which does not always allow for the TGA to undertake a comprehensive evaluation of the benefits and risks of using the medicine/biological and IVD together.

It is important that all IVD CDx be identifiable in applications for inclusion (premarket) and identifiable after inclusion on the ARTG (post market) to facilitate a comprehensive review of safety and performance of the CDx and ensure safe and effective use of the corresponding medicine or biological.

- **Lack of consistency in level of premarket assessment**

Due to the interdependence between a particular medicine or therapeutic product and its corresponding IVD CDx a coordinated regulatory assessment approach is required. The inadequate performance of an IVD CDx leading to misdiagnosis could have severe therapeutic consequences for patients.

Currently applications for inclusion of Class 3 IVDs in the ARTG are subject to a compulsory audit by the TGA if there is no evidence of prior product review by a comparable international regulator. The audit involves desktop assessment of the application for compliance with the legislation and key elements (e.g. stability, analytical and clinical performance) of the manufacturer's technical file to ensure that the therapeutic goods will perform as intended.

Under the Medical Device Regulations, multiple Class 3 IVDs that represent a 'kind of medical device' can be included under a single ARTG entry and where this applies compulsory application audits are generally done on a sampling of one or more devices of the kind included in the application. Therefore, while the majority of Class 3 IVD applications are subject to compulsory audits, not all Class 3 IVDs, and therefore not all IVD companion diagnostics, have been assessed by the TGA prior to inclusion in the ARTG.

- **IVD CDx not identifiable in the ARTG**

Currently IVD CDx are not flagged in any way (i.e. are not readily identifiable) in the Australian Register of Therapeutic Goods (ARTG) and consequently it is not always possible to align assessments of the device and its related medicine/biological.

- **Fees charged do not reflect the review effort**

Under the current Medical Device Regulations, regardless of the number IVD CDx of the kind included in an application, an audit assessment fee can only be charged once per application.

Effective from 1 July 2018, the prescribed audit assessment fee in Schedule 5, Item 1.14A of the Medical Device Regulations is \$6,850. Therefore, should the TGA choose to audit all devices of the kind in an application the fee TGA could charge will still be only \$6,850 for the audit of all IVD CDx in the application. Given the detailed and highly technical nature of the information submitted for review to the TGA, a much more substantial review effort is required including a need for clinical review and co-ordination with the assessment of the medicine/biological. Under the current fee structures, full cost recovery cannot be achieved.

Similarly where a sponsor submits a change application to vary the intended purpose for an approved IVD or to include additional IVD CDx of the same kind under an ARTG entry, sponsors only pay an application fee, but no assessment fee can be charged by the TGA.

To address these problems, and to assist more broadly in international regulatory alignment, we propose that the definition, classification and assessment of IVD CDx adopted by the TGA should be harmonised with the definitions and requirements in other comparable regulatory jurisdictions. Both the new EU Regulation 2017/746 and the US FDA have definitions of CDx together with specific regulations to ensure an appropriate level of premarket assessment.

It is noted that the US FDA also applies the term *companion diagnostic* to non-IVD medical devices. For example, the FerriScan R2-MRI Analysis System used for in patients with non-transfusion-dependent thalassemia to determine the safe and effective use of Deferasirox, has

been considered to be a companion diagnostic by the US FDA¹. As of July 2018 this is the only non-IVD medical device known to be approved by the US FDA as a companion diagnostic and their guidance focuses primarily on the regulation of IVD CDx.

At this stage the TGA is proposing reforms only in relation to the regulation of IVD CDx. Based on the experience gained in the regulation and assessment of IVD CDx, non-IVD medical devices could be similarly regulated in future if there are significant developments in this market which require comparable regulatory oversight.



In order to ensure appropriate premarket assessment and post-market monitoring of a medicine/biological therapeutic good and its corresponding IVD companion diagnostic device, amendments to the Medical Devices Regulations are required to:

- define and consistently classify IVD CDx;
- ensure all IVD CDx are subject to an appropriate level of premarket review;
- ensure that all IVD CDx are identifiable on the ARTG following approval; and
- ensure our regulatory approach is harmonised with other jurisdictions, including the new EU Regulation 2017/746 on in vitro diagnostic medical devices (EU IVD regulations), and the US FDA.

Regulation of IVD companion diagnostics in other jurisdictions

“Companion Diagnostics” are defined and regulated as a specific subset of medical devices by the US FDA and in the new European regulations. The US FDA’s regulatory pathways for the pre-market assessment of companion diagnostics as used with the corresponding therapeutic goods are now well established. On the other hand, the EU has recently put in place the overarching regulations pertaining to companion diagnostics but is yet to publish the specific pathways for premarket assessment of those IVDs and their corresponding medicinal products.

The Australian Government has a policy of alignment of the regulatory requirements with those of other regulators unless there are good reasons not to do so.



MMDR Recommendation 20, which was accepted by Government, provides that the regulation of medical devices in Australia is, wherever possible, aligned with the European Union framework including in respect of the classification and essential principles/requirements of medical devices. Should Australia seek to apply specific requirements, there must be a clear rationale to do so.

¹ FerriScan is an MRI-based solution for measuring liver iron concentration (LIC) in patients with iron overload. Following a ten-minute MRI scan, patient image data are transmitted electronically to Resonance Health’s central image analysis facility over a secure network. A patented analysis method is applied to the liver images, providing a mean LIC value. (refer <http://www.resonancehealth.com/images/files/FerriScan/FerriScan%20Fact%20Sheet%20Mar%202015.pdf>)

The Government has also asked TGA to make greater utilisation of marketing approvals for particular devices from an overseas market in circumstances where the device has been approved by a comparable overseas regulator.

This also provides for use of conformity assessments by a body that has been designated to undertake conformity assessments by a comparable overseas designating authority, as is already the case in using conformity assessment certification from European notified bodies.

The US FDA regulatory approach

The US FDA considers that companion diagnostics (both IVD and non-IVD medical devices) carry the same risk profile as the corresponding therapeutic goods. For this reason, they are generally classified as class III devices and as such require premarket approval (PMA). FDA reviews each CDx device submission within the context of, and in conjunction with, its corresponding therapeutic product. US FDA reviews of the CDx device and the therapeutic product are carried out collaboratively between relevant FDA offices.

US FDA Definitions of CDx and IVD CDx

According to the US FDA website, a CDx is defined as:

*“a medical device, often an in vitro device, which provides information that is **essential** for the safe and effective use of a corresponding drug or biological product”².*

The US FDA further defines an IVD CDx (through guidance) as:

“an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product”.

The US FDA expands on this definition by commenting that an IVD CDx device could be “essential” for the safe and effective use of a corresponding therapeutic product to:

- Identify patients who are most likely to benefit from the therapeutic product
- Identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with the therapeutic product
- Monitor response to treatment with the therapeutic product for the purpose of adjusting treatment (e.g. schedule, dose, discontinuation) to achieve improved safety or effectiveness
- Identify patients in the population for whom the therapeutic product has been adequately studied, and found safe and effective, i.e. there is insufficient information about the safety and effectiveness of the therapeutic product in any other population.

The US FDA also qualifies this definition by stating that it does not include IVDs that are not essential to the safe and effective use of a therapeutic product. Uses of diagnostic devices that are **suggested but not required in therapeutic product labelling** (i.e. the PI and CMI) are not considered “essential”.

² Companion Diagnostics

<https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm407297.htm>

What is meant by “essential for the safe and effective use”?

The key term in the definitions of CDx, or IVD CDx, is the word “essential for the safe and effective use”. In their guidance material the US FDA advises that when **the use of a diagnostic device is required in the labelling of a therapeutic product** then use of the diagnostic device is considered to be ‘essential’. The US FDA requires that the use of an IVD CDx device with a therapeutic product is stipulated in the labelling of both the diagnostic device and the corresponding therapeutic product, including the labelling of any generic equivalents of the therapeutic product.

The EU regulatory approach

Companion diagnostic is defined in the new EU IVD regulations however, as there is no such term used in the EU Regulations 2017/745 on medical devices, CDx’s are limited only to IVD medical devices in Europe. These IVDs are Class C (or D³) IVD medical devices under the EU classification.

The notified body performing the assessment of a CDx is required to consult with the European Medicines Authority (EMA), or an equivalent competent authority, regarding the suitability of the device in relation to the corresponding medicinal product. The new EU IVD regulations were introduced in May 2017 (with a 5 year transition period) and the detail on how this consultation process between notified bodies and the EMA will operate in practice is yet to be clarified.

Definition of CDx in new EU IVD regulations

The definition adopted by Europe is limited to IVD medical devices as “Companion Diagnostics” whereas the US FDA definitions are applicable to both medical devices and IVD medical devices.

The EU IVD regulations define a CDx as:

*“a device which is **essential** for the safe and effective use of a corresponding medicinal product to:*

- a. identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or*
- b. identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product.”⁴*

It is further qualified in the EU IVD regulations that:

“Companion diagnostics are essential for defining patients' eligibility for specific treatment with a medicinal product through the quantitative or qualitative determination of specific markers identifying subjects at a higher risk of developing an adverse reaction to the medicinal product in question or identifying patients in the population for whom the therapeutic product has been adequately studied, and found safe and effective. Such biomarker or biomarkers can be present in healthy subjects and/or in patients.”⁵

The term “essential” is not defined in the EU IVD regulations but it is a requirement that the instructions for use (IFU) for the device must contain the International Non-proprietary Name (INN) of the associated medicinal product.

³ Equivalent to Class 3 IVD and Class 4 IVD in Schedule 2A of the MD Regulations

⁴ Chapter I (Introductory Provisions), Section 1 (Scope and definitions), Article 2 (Definitions), paragraph (7), of EU IVD regulations

⁵ Paragraph (11) of EU IVD regulations

Proposal for the regulation of IVD companion diagnostics

As previously discussed there are concerns with the current regulatory model, particularly in relation to the classification and pre-market assessment of IVD CDx (including difficulties aligning assessments of the device and corresponding medical/biological therapeutic good); and difficulties readily identifying these kinds of devices in the ARTG. Maintaining the status quo would not be consistent with other international regulators and contradictory to the government-accepted MMDR recommendation 20 that “the regulation of medical devices in Australia is, wherever possible, aligned with the EU Framework and harmonised with other regulatory jurisdictions”.

The following regulatory reforms are proposed below for feedback from stakeholders. Once feedback is received, it is anticipated that a proposal will be made for government consideration:

Proposed reforms

A definition of an ‘IVD Companion Diagnostic’

It is proposed that the Medical Devices Regulations should be amended to include a definition for an IVD CDx. This definition should be harmonised as closely as possible with the definition of an IVD CDx provided in the new EU IVD regulations and the US FDA guidance, as applied to IVDs only (as previously noted, it is not proposed to regulate non-IVD medical devices as CDx at this time).

Both the EU Regulation and the US FDA use the term *therapeutic product* whereas the *Therapeutic Goods Act 1989* uses the term *therapeutic good*. The definition of IVD CDx should refer to *therapeutic good* to remain consistent with the overarching term in the Australian Act.

The US FDA definition includes both ‘drug and biological product’ in its definition of CDx whereas the EU IVD regulations refer to ‘medicinal product’ only. However, ‘medicinal product’ is defined in EU Directive 2001/83/EC3 as:

- a. *Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or*
- b. *Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.*

It is proposed that the Australian definition refer to both ‘medicine’ and ‘biological’ therapeutic goods as they are separately defined in the Act. The US FDA definition of a CDx states that the device ‘is essential for the safe and effective use of a corresponding drug or biological product’ and clarifies that this includes to ‘monitor response to treatment with the therapeutic product’. The EU definition applies to IVDs that are essential for the safe and effective use of a corresponding medicinal product ‘before and during treatment’. The EU definition effectively captures monitoring response to treatment.

The EU and US FDA definitions of CDx are effectively the same in practice. To align with other regulatory changes being considered under the MMDR it is proposed that the EU definition form the basis of Australia’s definition of IVD CDx, with the changes discussed above.

The proposed definition is thus:

*“An ‘IVD Companion Diagnostic’ is an IVD medical device which provides information that is **essential** for the safe and effective use of a corresponding **medicine or biological therapeutic** good to:*

- a. identify, before and/or during treatment, patients who are most likely to benefit from the corresponding therapeutic good; or*
- b. identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding therapeutic good.*

IVD companion diagnostics are essential for defining patients' eligibility for specific treatment with a medicine or biological therapeutic good through the quantitative or qualitative determination of specific biomarkers identifying subjects at a higher risk of developing an adverse reaction to the medicine or biological therapeutic good in question or identifying patients in the population for whom the therapeutic good has been adequately studied, and found safe and effective.

The IFU of the device shall stipulate the corresponding medicine or biological therapeutic good for which it is an IVD companion diagnostic.

There are IVDs that are used in association with long established therapies such as blood transfusion, antibiotic and other drug treatments which could be confused with companion diagnostics. Other regulators have taken steps to avoid ambiguity or the unintended capture of these IVDs under the definition of CDx. It is therefore recommended that the following caveats be appended to the definition of an IVD CDx:

- a. IVDs intended to establish the matching of a donor’s blood, blood components, cells, tissue or organs with that of a potential recipient are not considered to be IVD CDx (*as per US FDA model*).
- b. IVDs that are intended to be used to monitor treatment with a medicine or biological therapeutic good in order to ensure that the concentration of relevant substances in the human body is within the therapeutic window, where the test is not specified as ‘essential’ for the safe and effective use of the therapeutic good, are not considered to be IVD CDx (*as per EU model*).

Questions for consideration – Proposal 1

Is the proposed definition of IVD CDx clear enough?

Is the proposed definition appropriately aligned with the EU and US FDA definitions?

Do you have any other comments or suggestions about the proposed definition?

Do you have any other comments or suggestions for alternative or additional strategies?



The meaning of ‘essential for the safe and effective use’

It is proposed that the meaning of the term “*essential for the safe and effective use*” as used in the definition of an IVD CDx is clarified in guidance (rather than in regulation), following the model

of the US FDA. This will facilitate amendments and updates to the definition as necessary to address unintended interpretations of the regulations or future developments in this area.

It is proposed that “**essential for the safe and effective use**” be limited to diagnostic tests that are required in the labelling of the medicine/biological to ensure its safe and effective use.



The meaning of “*essential for the safe and effective use*” is important for the purposes of defining an IVD CDx. It is suggested Australia should adopt the US FDA approach and interpretation of the term “essential” as being limited to diagnostic tests that are required in the labelling the medicine/biological to ensure its safe and effective use.

Should this approach be adopted, the labelling for the medicine/biological (i.e. the Product Information (PI) and consumer medicines information (CMI) and the IVD CDx (i.e. IFU)) will be expected to stipulate the corresponding device and vice versa. Such references may not be for a specific manufacturer’s IVD CDx but could include generic references to IVD CDx approved for that purpose. It is proposed that expectations in relation to wording in the PI and CMI for the medicine/biological would be negotiated on a case-by-case basis. Note, ‘approved’ IVD CDx could refer to either a commercially supplied IVD CDx or an in-house IVD CDx.

To illustrate this proposed approach, the following example is drawn from an US FDA approved precision medicine and its corresponding IVD CDx:

- The PI for Zelboraf (vemurafenib) is approved with Indications and Usage “for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an US FDA-approved test”.
- The IFU for the Roche Cobas 4800 BRAF V600E test is approved with the Intended Purpose “to be used as an aid in selecting melanoma patients whose tumors carry the BRAF V600E mutation for treatment with vemurafenib”.



Questions for consideration – Proposal 2

Is the meaning of “*essential for the safe and effective use*” as used in the definition of IVD CDx clear enough?

Do you have any other comments or suggestions about the proposal to include references to approved IVD CDx in the PI and CMI of corresponding medicines and biologicals?

Do you have any other comments or suggestions about the proposal for the IFU of approved IVD CDx to include references to the corresponding medicine or biological?

Amendment to clarify the classification of IVD CDx

Classification rule 1.3, Schedule 2A in the MD Regulations specifies those IVDs that are Class 3 IVD CDx are currently captured as Class 3 IVDs, specifically under subparagraph (f)(i). However some IVD CDx have still been included in the ARTG as Class 2 IVDs. To avoid ambiguity it is proposed that rule 1.3 be amended to include a new paragraph specifying that IVD CDx are Class 3 IVDs.

The changes to Rule 1.3 of Schedule 2A are thus proposed as:

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

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



Questions for consideration – Proposal 3

Do you have any comments or suggestions about the proposal to classify all companion diagnostics as Class 3 IVDs to ensure appropriate and consistent regulation of IVD CDx in future?

Is the proposed amendment to Rule 1.3 clear enough?

Amendments to allow for compulsory audits of ARTG inclusion applications for IVD CDx

It is proposed that Regulation 5.3 be amended to include IVD CDx in the list of devices for which an application must be selected for audit to ensure an appropriate level of scrutiny, including a clinical assessment, prior to inclusion in the ARTG.

The proposed amendment to Regulation 5.3 (1)(j) is as follows:

5.3 Selecting applications for auditing (Act s 41FH)

(1) For paragraph 41FH(1)(a) of the Act and subject to subregulation (2) or (2A), an application for any of the following kinds of medical devices to be included in the Register is prescribed:

(j) any of the following IVD medical devices:

(x) an IVD medical device that is intended to be used as a companion diagnostic.



Where suitable evidence of assessment by a comparable international regulator is provided it is proposed that the assessment could be abridged and the audit assessment fee reduced accordingly.



Questions for consideration – Proposal 4

Do you have any comments or suggestions about the proposal to require a compulsory audit of all IVD CDx prior to inclusion on the ARTG?

Is the proposed amendment to Regulation 5.3 clear enough?

Amendments to allow for the identification of individual IVD CDx in the ARTG or other database

An important objective of reform is establishment of a means for the identification of all IVD CDx in a way that facilitates coordinated evaluation, tracking and sharing of information about the IVD CDx and their associated medicine or biological therapeutic goods.

In relation to Class 3 IVDs, the legislation does not currently require or facilitate the identification of individual IVDs. The regulatory framework for IVDs allows for grouping of IVDs as ‘a kind of medical device’ on the ARTG (that is defined by the same GMDN term, manufacturer,

classification and sponsor), and does not mandate identification of individual Class 3 IVDs by a 'unique product identifier' (this requirement applies to Class 4 IVDs only).

To facilitate identification of IVD CDx at all stages from application through to inclusion on the ARTG, it is proposed that Regulation 1.6 of the MD Regulations is amended to require IVD CDx be included in the ARTG by a unique product identifier (UPI)⁶. This proposed amendment would mean that each IVD CDx would require a separate application for inclusion as well as a separate entry on the ARTG and would be readily identifiable as an IVD CDx for the purposes of premarket evaluation and post-market tracking.

While the use of UPI is proposed as the preferred option for identification of individual IVD CDx on the ARTG, comparable overseas regulators have adopted other options to ensure traceability of approved devices. For example, the new EU IVD Regulations require the manufacturer's Unique Device Identifier (UDI) to be placed on the device and included into the UDI database. The application of the UDI system in the Australian context is currently being considered in conjunction with industry and healthcare professionals and if implemented could provide a mechanism for tracking approved IVD CDx. It is not known at this stage how or when this implementation will occur and whether it will meet the specific requirements for consistent identification of IVD CDx particularly where more than one Class 3 IVD can be grouped under a single application for inclusion on the ARTG. Neither will it address the concerns discussed under Proposal 6 in relation to audit assessment fees for individual IVD CDx. In the Australian context, the adoption of UDI could enhance the post-market tracking of IVD CDx but not provide the broader benefits of adopting UPI under the existing IVD regulatory framework.

The US FDA publishes a list of cleared or approved companion diagnostic devices on its website to facilitate information sharing. While the TGA could consider a similar approach it would not necessarily address the identification of IVD CDx in premarket applications and therefore not facilitate coordinated assessments of devices and their related medicines or biologicals. A list could be considered in addition to the proposal to require the use of UPI.

Questions for consideration – Proposal 5



Do you have any comments or suggestions about the proposal to amend Regulation 1.6 to require a unique product identifier as a characteristic for identification of all IVD companion diagnostics in applications for inclusion on the ARTG?

Do you have any other suggestions for the effective identification of IVD companion diagnostics that are included on the ARTG?

Do you have any comments or suggestions regarding the publishing of a list of approved IVD companion diagnostics on the TGA website (similar to the US FDA approach)?

Assessment fees for initial applications and changes to existing entries on the ARTG

Under the current Medical Device Regulations, regardless of the number of IVD CDx of the kind included in an application, an audit assessment fee can only be charged once per application. Should more than one IVD CDx require audit assessment, the full cost recovery principles cannot be applied to that application.

⁶ Regulation 1.6 prescribes that the other characteristic used for the purposes of defining devices of the same kind is unique product identifier, this currently only applies to Class III, AIMD and Class 4 IVD devices

Should it be decided that IVD CDx will be identified in the ARTG by a UPI (see discussion above) then a separate application would be required for each device with a separate UDI, and an audit assessment fee under Schedule 5, Item 1.14A would therefore apply per application for each device with an individual UPI. It is proposed that where suitable evidence of assessment by a comparable international regulator is provided that the assessment could be abridged and the assessment fee reduced accordingly⁷.

If, as currently applies, IVD CDx are not identified in the ARTG by a UPI then other amendments would be required to allow for an audit assessment fee to be charged per individual IVD CDx required to be assessed rather than per application. Similarly amendments are required to enable the TGA to charge an assessment fee where a sponsor submits a variation to include additional IVD CDx of the same kind under an existing ARTG entry.



Questions for consideration – Proposal 6

As discussed under proposal 4, a compulsory audit to ensure the safety and performance of all IVD CDx could become a requirement. It is therefore proposed that an application audit fee should apply to all IVD CDx to ensure full cost recovery by the TGA for the assessments required. Do you have any comments or suggestions about the proposal that an application audit fee should apply to all IVD CDx applications for inclusion (subject to any fee reductions that may be applicable for abridged assessments)?

Do you have any other comments or suggestions about the proposal that an assessment fee should apply to applications to vary an ARTG inclusion of an IVD CDx where an assessment is required for a new intended purpose for the device?

Transition arrangements for IVD CDx already included on the ARTG

There are many IVDs that have been included on the ARTG with an intended purpose that meets the proposed definition of an IVD CDx. For those IVD CDx that are included on the ARTG prior to the commencement date of the new regulatory framework it is proposed that a transition period would apply during which the sponsor would need to apply for inclusion of the IVD as an IVD CDx which complies with the proposed new framework. As per the proposals outlined in this paper, compliance with the new framework would include application audit by the TGA, information in the IFU about the intended purpose as an IVD CDx and identification of the IVD as an IVD CDx on the ARTG.

For new applications as an IVD CDx for previously included IVDs, where there is no change in the intended purpose of the device, the following options are proposed:

- a. The IVD CDx could be fully audited as per the new framework, including a clinical evaluation of evidence for use as an IVD CDx; or
- b. if the IVD was previously subject to an application audit which included a technical file review prior to inclusion then the new application audit could be abridged and the audit fee reduced; or
- c. If the IVD CDx has been supplied in the Australian market and there have been no concerns regarding the safety and efficacy of the corresponding therapeutic good or the

⁷ Regulation 9.7 provides for the Secretary to reduce the amount of the assessment fee if the Secretary has information that allows the assessment to be abridged.

safety and performance of the CDx then, regardless of whether it was previously audited by the TGA the new application audit could be abridged and the audit fee reduced.

There are risks under options b) and c) that the IVD CDx may not be supported by appropriate clinical evidence and therefore not perform as intended. These risks would be mitigated where the IVD has a satisfactory history of use as an IVD CDx and there are no concerns regarding adverse outcomes for the corresponding medicine or biological.

Questions for consideration – Proposal 7



Do you have any comments on the proposal for transitioning of IVD CDx under existing ARTG entries to meet the proposed new requirements as outlined in this paper?

In particular, do you have any comments on options a, b and c for the auditing of existing IVD CDx transitioning to the new framework?

Timeframe for transition

The majority of IVD CDx have been and will continue to be developed in markets outside of Australia and manufacturers will seek to comply with regulatory requirements in jurisdictions such as the EU and the US. Therefore, in seeking to align with those jurisdictions it is proposed that any transition arrangements that are applicable in those jurisdictions should be taken into consideration.

The new European IVD Regulation 2017/746 came into force on 26 May 2017 with a transitional period of 5 years. Manufacturers of existing IVD CDx have until 26 May 2022 to comply with the new EU regulatory requirements. For new IVD CDx the manufacturers need to comply with the Regulation 2017/746 immediately. The US FDA's regulatory requirements have been in place for some time and many IVD CDx will already be compliant.

Therefore, for IVD CDx not already covered by an ARTG entry, it is proposed that any new requirements should apply from the date on which respective amendments in the Medical Device Regulations become effective. For IVDs that meet the definition of an IVD CDx and are already included on the ARTG at the commencement date of the new regulations, a transition period will apply. It is proposed that a transition period of 2 years should provide sufficient time for industry to meet the new requirements for IVD CDx that are already included in the ARTG at the commencement date of the new regulations.



Questions for consideration – Proposal 8

Do you have any comments on the transition timeframe proposed for existing IVD CDx to meet the requirements of the new framework?

IVD CDx that are in-house IVDs

As noted in the Introduction, it is envisaged that the main focus of regulation of IVD CDx would be on those products that are marketed commercially and making claims around being essential for the safe and effective use of a new medicine or biological. However, laboratory developed or

“in house” diagnostic tests rather than commercial IVD CDx are often used with targeted therapies.

The TGA regulates laboratory developed tests as in-house IVDs, but in a different manner to commercial IVDs (for a detailed discussion of [how in-house IVDs are regulated](#) please refer to the TGA website). It will thus be challenging, but important to consider how the proposed regulatory changes will impact in-house IVD CDx. Companion diagnostics that are Class 3 In-house IVDs (in-house IVD CDx) would normally not be subject to review by the TGA and are exempt from inclusion in the ARTG. However, it is important for the safety of targeted therapies relying on in-house CDx that the tests are supported by appropriate clinical evidence and analytical performance data.

It is proposed that the TGA will develop guidelines for clinical evidence and analytical performance requirements that would be applicable to IVD CDx, including in-house IVD. The TGA will work closely with the National Association of Testing Authorities (NATA), the Royal College of Pathologists of Australasia (RCPA) and the National Pathology Accreditation Advisory Council (NPAAC) to ensure that in-house IVD CDx are being adequately assessed. Under the Memorandum of Understanding between the TGA and NATA in relation to in-house IVDs, NATA may request the TGA to assist in the review of validation data for in-house IVDs such as IVD CDx.

Questions for consideration – Proposal 9



Do you have any comments or suggestions on the proposal that in-house IVD CDx should comply with the clinical evidence and analytical performance requirements applicable to all IVD CDx?

Do you have any other comments or suggestions regarding the compliance of in-house IVD CDx with the proposals outlined in this paper?

Coordinated Premarket Assessment of an IVD CDx and its Corresponding Medicine/Biological

IVD CDx's range from immunohistochemical assays intended to detect a single protein product; molecular or cytogenetic-based assays intended to detect single gene or chromosomal alterations; through to massively parallel sequencing platforms that allow simultaneous screening for multiple mutations/gene alterations. These tests may be intended for use with multiple specimen types such as DNA or RNA from fresh or paraffin embedded biopsy specimens or from circulating tumour cells in the blood (“liquid biopsy”).

All these variables influence the pre-analytical and clinical performance of the IVD CDx and can directly affect the efficacy and safety of the relevant therapeutic good in particular populations. Inadequate performance of an IVD CDx could have severe clinical consequences (e.g. withholding appropriate therapy or administration of inappropriate therapy). An IVD CDx provides information that is essential for the safe and effective use of a corresponding medicine/biological. Therefore, there is a need to assess the safety and performance of an IVD CDx as used with the medicine/biological.

One of the primary drivers for the regulatory framework for IVD CDx as proposed in this paper is the coordinated assessment of an IVD CDx and its corresponding medicine or biological to provide assurance of safety and performance of the targeted therapies. It is proposed that the TGA will review an application for an IVD CDx within the context of, and in conjunction with, its corresponding therapeutic good to ensure a comprehensive evaluation of the benefits and associated risks of the therapeutic goods when used for their intended purpose and indications.

The assessment of both the safety and performance of the device and suitability and clinical validity of the biomarker would be carried out collaboratively between the relevant assessors within the TGA.

Ideally, a therapeutic good and its corresponding IVD CDx should be developed contemporaneously, with the clinical performance of the IVD CDx and suitability of the biomarker established using data from the clinical trial of a therapeutic good. However, there will be many circumstances where concurrent applications for approval of an IVD CDx and its corresponding medicine/biological does not occur; e.g.

- A new medicine is submitted for approval and the IVD CDx has already been included on the ARTG for a different intended purpose; or
- An application is submitted for a new IVD CDx for a medicine that has already been approved for supply in Australia (and there are other IVD CDx for the same biomarker on the ARTG).

The co-development process may also be complicated by the devices and the medicine/biological being developed by different manufacturers and not necessarily within the same timeframe; or a manufacturer of a therapeutic good may partner with a diagnostic device manufacturer to modify an existing IVD diagnostic device to accommodate the intended use as a companion diagnostic. Further there may not be a commercially available IVD CDx and testing may rely on the use of in-house IVD CDx.

Consideration will also need to be given to the paradigm shift from single biomarker/therapeutic good combinations for a specific cancer type to approval of a therapeutic good for an indication based on multiplex biomarker analysis irrespective of the primary cancer/tumour type, and how this may impact the way clinical trials are undertaken. One of the main drivers of this change is the advent of NGS and the ability to identify multiple biomarkers simultaneously.

With detection of multiple biomarkers possible within a single test, only some will have a corresponding therapeutic good at the time of evaluation, and thus be eligible for consideration as a particular IVD CDx. Subsequent applications and evaluations will be required for the same IVD to establish and expand the list of approved uses as an IVD CDx as more targeted therapies are developed and submitted for registration. Thus, it is anticipated that a single device may require multiple variations over time, akin to the extensions of indications granted for therapeutic goods as the approved uses/indications expands.

For the two examples provided above of circumstances when concurrent application for approval of an IVD CDx and its corresponding medicine/biological would not be possible the following proposed assessment approach is presented for comment:

a. IVD CDx already included on the ARTG – new intended purpose

There may be occasions when the TGA receives an application for a new targeted therapy and the corresponding IVD CDx is already included on the ARTG with a different intended purpose. Satisfactory evaluation of the medicine/biological would require concurrent evaluation of the performance data for the IVD CDx, particularly the clinical evidence. Therefore, it is proposed that it should be a condition of inclusion in the ARTG that where there is a change in the intended purpose of an IVD CDx, a variation would need to be submitted notifying the TGA of the change. Depending on previous evidence submitted for the IVD, the sponsor may be requested to submit the performance data, including clinical evidence, for the new intended purpose.

b. New IVD CDx for a currently approved medicine or biological

It is anticipated that applications will be submitted from time to time for an IVD CDx where the medicine or biological has been approved for use with an alternative IVD CDx which detects the same biomarker. If the IVD CDx was not used in the clinical trials of the approved medicine/biological the performance data should include the results of concordance studies which demonstrate equivalent performance of the new IVD CDx with the reference test.

As noted above the PI and CMI of an approved targeted therapy will be expected to refer to the corresponding IVD CDx but such references could be generic for any IVD CDx, including an in-house IVD CDx, approved for detection of a particular biomarker rather than a specific manufacturer's IVD CDx. In this way, the PI should not need to be reviewed or amended to include each new IVD CDx which is included on the ARTG.



It is proposed TGA will develop guidance for sponsors and manufacturers of IVDs, medicines and biologicals on the requirements for clinical evaluations and labelling of IVD CDx and their related medicines and biologicals to assist in meeting regulatory requirements for a therapeutic good and its accompanying IVD CDx.

Guidance material will include information in relation to clinical trial requirements as the evaluation of the clinical performance of an IVD CDx is based on data from clinical trials for the corresponding therapeutic good conducted in patients identified by using the IVD CDx. If the IVD CDx in an application is not the same as that used in the clinical trial the manufacturer of the device would need to provide further evidence, such as concordance studies, to support its use as an IVD CDx.



Questions for consideration – Proposal 10

To provide assurance of the safety and efficacy of targeted therapies, an IVD CDx and its corresponding medicine or biological should ideally be evaluated and approved concurrently. Do you have any comments or suggestions regarding the ways in which concurrent evaluation may be facilitated?

Where concurrent evaluation is not possible, provision needs to be made for coordination and review of evaluations of an IVD CDx and its corresponding medicine or biological.

Do you have any comments on the proposal under a) above that a change in intended purpose of an IVD CDx would require an application to vary the ARTG entry and submission of evidence which supports the new intended purpose?

Do you have any comments on the proposal under b) above that any IVD CDx that was not used in the clinical trials of a targeted therapy must demonstrate equivalent performance to the reference test in concordance studies?

Version history

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