Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

COVID-19 *in vitro* diagnostics

Guidance on ongoing requirements for sponsors and manufacturers

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Contents

Purpose

This guidance document provides sponsors and manufacturers of COVID-19 *in vitro* diagnostic devices, including nucleic acid tests (NATs), rapid antigen tests (RATs), and combination tests that detect SARS-CoV-2 in combination with other viruses, detailed information regarding their ongoing obligations to ensure that their products continue to perform as intended and are safe to use.

Sponsors and manufacturers must notify the Therapeutic Goods Administration (us) of any significant changes or updates to their devices, meet all conditions of inclusions (COI), and continue to monitor device performance and safety, to ensure compliance with conformity assessment procedures and the essential principles. As part of ongoing monitoring, sponsors and manufacturers should continue to take steps to screen for and mitigate risks brought on by sub-variants of SARS-CoV-2 as they emerge. In response to signals and potential risks, we can request sponsors to provide evidence of the manufacturers' ongoing monitoring, to demonstrate continued safety and performance.

Post market review of IVDs

In vitro diagnostics (IVDs)

In vitro diagnostics (IVDs) refer to any devices or reagents used to detect, identify, or quantify a particular marker or substance in a sample. IVDs are typically tests that are used to examine human samples to assist with diagnosing and managing a patient's health and are regulated as medical devices. They include reagents, kits, calibrators, controls, laboratory analysers and software, as well as tests used at the point of care, or in the home, such as COVID-19 rapid antigen self-tests and glucose monitoring tests for diabetics.

Post market reviews

We conduct post-market reviews to ensure that IVD medical devices remain compliant with safety, performance, and quality standards, and that sponsors meet their regulatory obligations and the conditions of their inclusion or exemption in the Australian Register of Therapeutic Goods (ARTG). Post-market reviews of IVD medical devices can be initiated due to, but not limited to, the detection of a trend or signal, or identification of a safety or performance issue, related to the type of IVD medical device.

It is expected that sponsors and manufacturers will continue monitoring the safety and performance of their IVD medical devices, as part of their ongoing quality management and risk assessment procedures, throughout the lifecycle of the device during ARTG inclusion.

Ongoing responsibilities

Sponsors and manufacturers of IVDs have a responsibility to ensure that their product complies with the *Therapeutic Goods Act 1989*, and continues to be safe and reliable to use.

Responsibilities of the manufacturer

Manufacturers have ongoing legal obligations for IVD medical devices they manufacture that are being supplied in Australia, including:

- Maintaining compliance with conformity assessment procedures (CAPs) including ongoing compliance with the manufacturer's nominated standard.

  - The TGA is transitioning to new manufacturer evidence requirements, including the use of market authorisation evidence from comparable overseas regulators or assessment bodies.

- Holding evidence to demonstrate compliance with Essential Principles (EPs).
- Notifying us or the sponsor of revisions and changes to the device.

Responsibilities of the sponsor

The main requirements for ongoing responsibilities for sponsors are:

- Compliance with any automatic conditions of inclusion
- Compliance with any additional conditions of inclusion
- Reporting of adverse events
- Undertaking recall and non-recall actions of therapeutic goods
- Applying for consent for circumstance preventing compliance to Essential Principles for a limited period of time
- Notifying the TGA for lapsing or lapsed manufacturer's conformity assessment certificate
- Compliance with the Therapeutic Goods Advertising Code
- Report of any suspected counterfeit or tampering of devices
- Payment of annual charges
- Ensuring TGA contacts are up to date on eBusiness Portal.

Ongoing monitoring of device performance

It is the manufacturer's obligation to undertake ongoing monitoring as part of their Quality Management System (QMS) processes. The manufacturer is expected to monitor new variants of concern of SARS-CoV-2, as defined and tracked by the World Health Organisation (WHO), and identify if any variants cause impacts to the performance of their device. Should any impacts be identified, the manufacturer and sponsor have an obligation to inform the TGA if there is any effect on device safety, quality, or performance.

Manufacturers should ensure they have a proactive monitoring plan in place, to be able to assess the performance of their device in an ongoing manner. This is relevant for all COVID-19 devices, including RATs and NATs. The United States Food and Drug Administration (U.S. FDA) has published guidance that may assist manufacturers in the development and maintenance of their proactive monitoring plan.

If the sponsor of an IVD medical device is undertaking their own monitoring, the process must be endorsed by the manufacturer. Endorsement requires the manufacturer to acknowledge that the monitoring being undertaken is part of the manufacturer's QMS processes and meets the required standards.

We have published guidance documents that outline the clinical and analytical requirements for COVID-19 IVDs:

- The COVID-19 self-test guidance
- The seasonal influenza rapid antigen and combination tests guidance

The guidance documents listed above detail the expected requirements for analytical and clinical studies, however we also accept that manufacturers may be undertaking other types of studies as part of their ongoing monitoring. Types of testing that we consider to be acceptable for the purposes of ongoing monitoring includes clinical and analytical studies. Epidemiological evidence can also be used

to monitor SARS-CoV-2 variant prevalence. Sponsors should be aware that some types of tests will have additional monitoring requirements, including self-tests, to ensure ongoing usability, combination tests, where monitoring for all viruses detected by the device is required, and NATs, where sequence alignment can be used as a monitoring tool.

Clinical studies

Clinical studies should be completed using a cohort relevant to the testing landscape in Australia, to establish the clinical performance of the device for SARS-CoV-2 variants relevant in Australia. If required, clinical studies can be organised by the sponsor and undertaken in Australia, if the study has been endorsed by the manufacturer.

Clinical studies are required to meet the same thresholds as required of submissions made during application for inclusion, specifically, for each claimed specimen type:

- Clinical sensitivity of at least 80% (for specimens collected within 7 days of symptom onset)
- Clinical specificity of at least 98%

Manufacturers should determine what is an adequate number of samples to be able to confidently demonstrate the required thresholds of 80% sensitivity and 95% specificity and are expected to be able to justify their reasoning for the number of samples tested.

We have published guidance documents that outline the clinical evidence requirements for IVDs:

- The clinical evidence guidelines for medical devices
- The clinical evidence guidelines supplement for IVD medical devices

These guidance documents include examples of the IVD medical device standards that we consider relevant to clinical evidence. If the manufacturer chooses to complete their obligations to a different standard than referenced in the guidance or chooses not to follow the specifications of a recognised standard, a strong justification for the approach must be provided.

Analytical studies

Analytical studies can be undertaken to determine if there has been any change in the analytical sensitivity cited in the instructions for use (IFU) of the device against emerging variants of concern.

An analytical sensitivity study is expected to demonstrate the limit of detection (LoD), the lowest concentration at which the virus is consistently detected 95% of the time. Measurement of the LoD requires 20 replicates at each relevant dilution, to be able to demonstrate that sensitivity meets the 19/20 (95%) threshold.

Recommended details to include in clinical and analytical studies

When the manufacturer is undertaking studies as part of their ongoing monitoring requirements, they are encouraged to record the following details:

- Test kit details including batch number and expiry date
- Protocol used
- For analytical studies:
  - Characteristics of virus used, such as source, isolate name, variant identity, and stock concentration
  - Number of replicates and dilutions used
  - Result measured in $TCID_{50}$/mL, Ct-value, and/or RNA copies/mL

- For clinical studies:
  - Study location and dates completed
  - Number of participants
  - Infection characteristics for each participant, including days-post-onset, identification of SARS-CoV-2 variant, and viral load (Ct-value); ensure clinically sensitive or identifying information is not included.
  - Samples should be collected from participants across 0-7 days-post-onset and a range of Ct-values, including at least 20% of samples having Ct-value >30.

If, later, evidence is required to be submitted to the TGA as evidence of continued performance, or as evidence of a change in safety or performance identified by the manufacturer, we expect the evidence to be submitted as a complete report.

This would require the evidence to be presented as a comprehensive report with a summary of methods and results, and a conclusion. Raw data, with no explanation or conclusion of results, would not be acceptable. If manufacturers have completed and submitted evidence for specific variants of concern and not for others, they are expected to provide a justification for their monitoring processes.

Epidemiological evidence

Manufacturers can monitor the relative prevalence of different SARS-CoV-2 variants and sub-variants in regions and populations of interest and identify from the WHO identification and tracking if particular variants require additional monitoring.

If this evidence is required to be submitted, it is expected that an explanation is provided from the manufacturer as to how the evidence is relevant to circumstances in Australia.

Additional monitoring requirements for self-tests

Ongoing surveillance of performance of COVID-19 IVDs for self-test use should include monitoring of the usability of the device.

COVID-19 IVDs for self-test use are required to submit usability studies at the time of application for inclusion, to demonstrate the performance of the device by the intended end-user. The requirements for usability studies are detailed in the COVID-19 test kit guidance.

If during surveillance of device performance, the manufacturer identifies signals related to the performance of self-tests that could be a usability issue, such as increased complaints about invalid results or other user issues such as difficulty using the device or interpreting results, the manufacturer would be expected to evaluate those issues, and complete additional usability studies if the issue is deemed to be significant.

If additional studies are required, usability studies for the purpose of ongoing monitoring should meet the requirements for testing sensitivity and specificity, as defined in the guidance:

- Diagnostic sensitivity, non-supervised – at least 30 lay users that are known antigen positive
- Diagnostic specificity, non-supervised – at least 60 lay users that do not know their status

Additional monitoring requirements for combination tests

Sponsors and manufacturers of combination tests have an obligation to undertake ongoing monitoring of device performance against all claimed specimen types, such as COVID-19, influenza A, influenza B, and respiratory syncytial virus (RSV).

Combination tests are expected to demonstrate ongoing performance in the same manner as other COVID-19 IVDs, such as demonstrations of clinical performance or analytical sensitivity.

Combination tests are required to submit cross-reactivity studies at the time of application for inclusion, to demonstrate the performance of the device for each specimen type. The requirements for cross-reactivity studies are detailed in the seasonal influenza rapid antigen and combination tests guidance.

If during the course of surveillance of device performance, the manufacturer identifies signals related to the performance of combination tests that could be related to the emergence of new variants or subtypes of the viruses detected by the device, or potential cross-reactivity between the viruses detected, the manufacturer would be expected to evaluate those issues, and complete additional studies – for analytical or clinical sensitivity, or cross-reactivity – if the issue is deemed to be significant.

Sequence alignment for molecular tests

Molecular tests, including polymerase chain reaction (PCR) assays and other NATs, require ongoing monitoring to evaluate the impact of SARS-CoV-2 mutations on device performance. As molecular test performance depends on the fidelity of primers and probes used, they are highly susceptible to virus mutations if those mutations occur in the sequences recognised by the test.

Manufacturers are expected to monitor device performance as new variants of SARS-CoV-2 emerge, such as use of sequence alignment to identify if mutations present in new variants overlap with the primers and probes used in the test.

The U.S. FDA has published guidance that provides further information for manufacturers on proactive monitoring of molecular test performance. This guidance includes details of the steps that manufacturers are encouraged to take if a mutation is found, including *in silico* calculation of hybridisation temperature, wet laboratory testing of isolated genetic material, and wet laboratory testing of virus isolates or clinical samples.

Ensuring compliance with Essential Principles

Medical devices including IVDs must comply with the Essential Principles (EPs), which set out fundamental safety and performance requirements. The EPs are detailed in Schedule 1 of the Therapeutic Goods (Medical Devices) Regulations 2002.

The Essential Principles checklist may help you identify the Principles that apply to your device, give a rationale for each of the Principles that aren't relevant, and summarise the evidence you hold in support of each of the relevant Principles.

Consent to Supply

There may be extenuating circumstances preventing compliance to one or more EPs for a limited period of time. In such circumstances, sponsors may request consent to import, supply or export IVD medical devices that are not compliant with an EP.

When consent to supply (CTS) is granted for a medical device or IVD that is non-compliant with the EPs, the ongoing regulatory responsibilities of the sponsor remain.

There are criminal offences under section 41MA and civil penalties under section 41MAA of the *Therapeutic Goods Act 1989* (the Act), for importing, supplying, or exporting medical devices that do not meet the EPs for safety and performance, unless consent has been granted by the Secretary of the Department of Health and Aged Care.

Conformity Assessment Certification

The sponsor and manufacturer are responsible for ensuring that the manufacturer's conformity assessment certification for the Device is current and valid. Certification may no longer be valid due to the certification expiring, or if it has been suspended or revoked.

There are criminal and civil penalty sanctions if a sponsor fails to notify us within 60 days of becoming aware that their conformity assessment certificate used to support the application for inclusion in the ARTG (other than a conformity assessment certificate issued by the TGA) has been restricted, suspended, revoked, or is no longer in effect.

Forms of acceptable certification include TGA Conformity Assessment Certificates, overseas market authorisation evidence, or conformity assessment documents relating to the manufacturer's quality management system from a comparable overseas national regulatory authority, such as the Medical Device Single Audit Program (MDSAP).

Many sponsors and manufacturers of IVD medical devices will need to transition to new manufacturer evidence due to:

- The new European Union IVD Regulation 2017/746 (EU IVDR) that replaces the EU IVD Directive 98/79/EC (EU IVDD)
- The end of the transition period for us to accept many ISO 13485 certificates as manufacturer evidence.

Sponsors who are supplying IVD medical devices from a manufacturer that is transitioning to new evidence may find that they hold stock that was manufactured under a valid IVDD certificate, but the certificate has since expired. Sponsors may be able to continue supply of this stock if their ARTG entry remains active.

There may be cases where the manufacturer becomes aware, through recertification, that the IVD medical devices being supplied under the previous conformity assessment certification are now non-compliant with the EPs. In those cases, you should apply for consent to supply non-compliant IVD medical devices if you wish to continue to supply those devices.

Record keeping

Under section 41FO of the Act, sponsors of IVD medical devices supplied in, and exported from, Australia are required to keep distribution records to:

- Expedite any recalls of batches of the medical devices; and
- Identify the manufacturer of each batch of devices.

Sponsors are not required to maintain records of the individual users of IVD medical devices, but should maintain records of distribution centres, hospitals and export countries the device has been supplied to.

Sponsors must retain their records for five or ten years after the last product has been distributed, depending on the classification of the device. These records, or copies of the records, must be provided when requested by us.

Reporting adverse events and complaints

Reports about complaints, adverse events, and near adverse events can be submitted to us by manufacturers, sponsors, health care professionals, and consumers. This allows us to monitor the safety and performance of IVD medical devices in the real world and identify trends that may indicate emerging safety or performance issues. The primary function is to improve the health and safety of patients, health care professionals, users, and others by reducing the likelihood of adverse events being repeated.

It is an automatic condition of inclusion under 5.7 of the Therapeutic Goods (Medical Devices) Regulations 2002 that sponsors of an IVD medical device report adverse events and near adverse events to the TGA.

Consumers, health professionals and individuals in the medical device industry can also submit reports voluntarily and are encouraged to do so.

Sponsors and manufacturers can report an event via the Medical Device Incident Reporting & Investigation Scheme (IRIS) database.

It is expected that the report specifies identifying features of the device, such as ARTG entry, device name and model, manufacturer, supplier, catalogue information such as batch or serial number, and expiry date. Images of the device are also encouraged.

The report should also include a comprehensive description of the event and the outcome, or in the case of a "near event" the possible outcome, had intervention not taken place. It is often useful to include a clinical history of the patient involved.

Contact details for both the person writing the report and the person for whom the event happened should always be included. These details can remain confidential but are needed by the TGA to be able to progress with the investigation and to provide feedback.

Sponsors are expected to notify the TGA of complaints or adverse events in line with the legislative time frame, being within forty-eight (48) hours for serious threats to public health, ten (10) days for events that have led to death or serious deterioration in the state of health of the user, and thirty (30) days for events, occurrence or reoccurrence that might lead to death or serious deterioration. Additional information, such as the completed report from the manufacturer's investigation, can be provided later.

Advertising COVID-19 IVDs

Advertisers of rapid antigen tests, including suppliers of COVID-19 rapid antigen tests and testing service providers, must ensure that any advertising is compliant with the Therapeutic Goods Advertising Code and the conditions imposed on the supply and use of rapid antigen tests.

Advertisement of COVID-19 IVDs is subject to Restricted Representations, that limit the permitted advertising due to the severity of the disease. It is an offence to advertise therapeutic goods to consumers using restricted representations unless we have issued a relevant approval or permission.

We have published guidance for advertising COVID-19 IVDs, including details of the legally permitted representations.

Regulatory action due to non-compliance

The TGA can undertake regulatory action to ensure that devices that are not compliant with the Act are either brought back into compliance, or removed from the ARTG if compliance cannot be achieved.

Devices with deficiencies in performance, or non-compliance with conditions imposed either during device inclusion or after inclusion in the ARTG, may be subject to specific regulatory actions where applicable.

The TGA recognise that education and guidance are key to encouraging and assisting with compliance with Australian regulation. We regularly publish information, conduct training, and answer enquiries to assist industry in understanding and meeting the regulatory requirements provided for under the Act.

In the first instance, we will often work with the responsible entity to provide education and advice in order to achieve compliance. However, escalation of regulatory action will be considered if:

- There are repeated breaches and an unwillingness to comply; and/or
- There is a likely impact on the consumers' ability to use the therapeutic goods safely or appropriately.

The compliance and enforcement tools that we have available to ensure compliance includes:

- Warning letters
- Suspension or cancellation of the device from the ARTG
- Recall actions
- Advertising directions and prevention notices
- Infringement notices
- Enforceable undertakings
- Injunctions
- Civil penalties
- Criminal prosecutions.

Have more questions?

For any additional queries, please contact the post market review team at postmarketdevices@health.gov.au.

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Medical Devices Surveillance Branch	August 2023

Therapeutic Goods Administration

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