Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Seasonal Influenza Rapid Antigen and Combination tests

Clinical performance requirements and risk mitigation strategies

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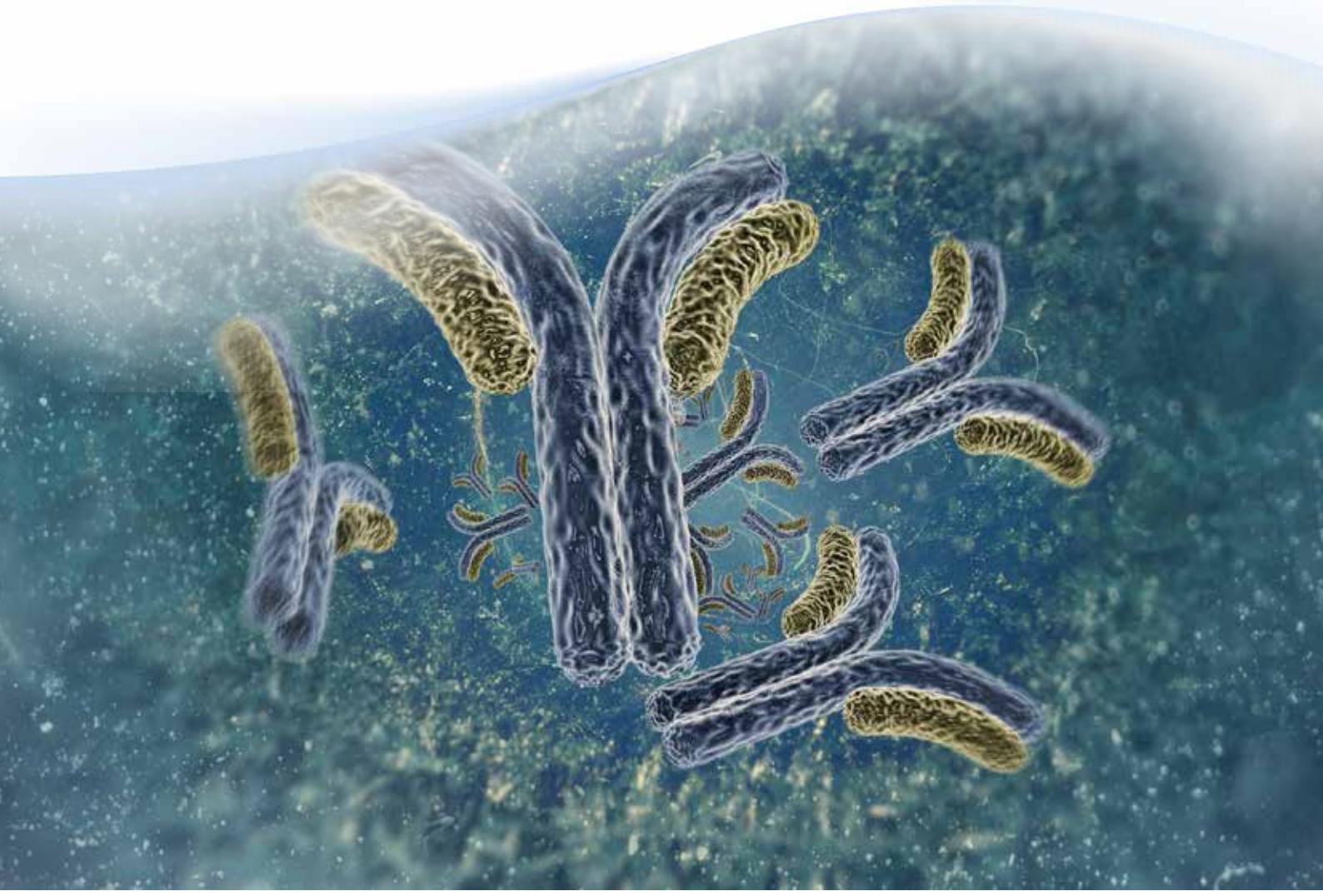

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Purpose

The purpose of this document is to provide manufacturers and sponsors with guidance on the Therapeutic Goods Administration's (TGA) expectations concerning performance requirements (i.e. analytical and clinical sensitivity and specificity) and risk mitigation for in vitro diagnostic medical devices (IVDs) intended to be used as seasonal influenza rapid antigen tests.

For manufacturers and sponsors of combination rapid antigen tests that are intended to detect multiple respiratory targets such as influenza A, influenza B, SARS-CoV-2 and/or respiratory syncytial virus (RSV) in a rapid antigen test format (combination RATs) both at the point-of-care (POC) and for self-testing, the influenza-specific requirements outlined in this document are applicable to the device and should be considered in conjunction with the SARS-CoV-2-specific performance requirements and risk mitigation strategies relevant to COVID-19 rapid antigen tests.

This document details key risks that must be mitigated and identifies conditions that may be imposed on these self-test kits if they are included in the Australian Register of Therapeutic Goods (ARTG). Additional risks and mitigation strategies, including conditions of inclusion may apply to individual devices on a case-by-case basis.

For further information on overall technical documentation and clinical evidence requirements for in vitro diagnostics, please refer to the *clinical evidence guidelines supplement: In vitro diagnostic (IVD) medical devices, application audit (technical file review) of IVD medical device applications* and guidance on the *classification of IVD medical devices*.

The analytical and clinical performance requirements in this guidance apply both to self-test and point-of-care rapid antigen tests for the detection of seasonal influenza, either as a single target or in combination with other respiratory viruses.

The requirements for usability studies are specific to rapid antigen self-tests, only.

This information is provided for guidance only and has been developed based on current knowledge of the subject matter.

It should not be relied on to address every aspect of the relevant legislation. You should seek your own independent legal advice to ensure that all legislative requirements are met.

If you require clarification of a particular requirements, email your enquiry to IVDs@tga.gov.au

Regulatory background on self-tests to detect seasonal influenza

The *Therapeutic Goods Act 1989* (the Act) provides a system of controls for the regulation of therapeutic goods in Australia. Home-use tests (also known as self-tests) are therapeutic goods.

Self-tests for serious diseases (for example. notifiable infectious diseases, sexually transmitted infections, cancer, genetic markers of disease) have been prohibited from supply in Australia since 1 July 2010 under the *Therapeutic Goods (Excluded Purposes)*

Specification 2010 (the Excluded Purposes Specification 2010). The exception was self-tests for Human Immunodeficiency Virus (HIV) which have been permitted since 2014.

In accordance with the *Legislative Instruments Act 2003*, legislative instruments are automatically repealed after a fixed period of time (subject to some exceptions). *The Excluded Purposes Specification 2010* sunset on 1 October 2020. Before the remaking of the instrument, it was a legal requirement to perform a review.

On 4 September 2020, after formally consulting stakeholders and following a review of self-testing regulations, the *Excluded Purposes Specification 2020* was made and came into effect on 1 October 2020. This allowed sponsors and manufacturers to apply to the TGA for the inclusion in the ARTG of specified IVD self-tests, including self-tests for seasonal influenza. Any tests allowed under the *Excluded Purposes Specification 2020* can only be supplied following evaluation of individual products by the TGA to ensure appropriate analytical and clinical performance requirements are met and risk mitigations are in place.

Definition of an IVD self-test

For an IVD medical device for self-testing, a lay person is defined as an individual who does not have formal training in a medical field or discipline to which the self-testing relates.

For the full definition, refer to Regulation 1.3 of the *Therapeutic Good (Medical Devices) Regulations 2002*.

Public health context

Influenza is a serious global health threat that affects all countries: every year, there are an estimated 1 billion cases, 3-5 million severe cases, and 290,000 – 650,000 influenza-related respiratory deaths worldwide[1].

The Global Influenza Strategy for 2019-2030 provides a framework for WHO, countries and partners to approach influenza holistically through robust national programmes – from surveillance to disease prevention and control – with the goal of strengthening seasonal prevention and control and preparedness for future pandemics[4].

Australian seasonal influenza infection rates fluctuate annually, depending on the circulating strains and do pose a serious health risk to priority/vulnerable populations. The appropriate use of anti-viral medication along with growing public awareness of adequate infection control procedures is aimed at reducing the incidence of circulating seasonal influenza within the Australian community.

The *Therapeutic Goods (Medical Devices – Excluded Purposes) Specification 2020* (the *Excluded Purposes Specification 2020*) allows manufacturers and sponsors to apply for inclusion of seasonal influenza self-tests in the ARTG, allowing for the legal supply of these self-tests in Australia (subject to TGA evaluation and approval). Legal supply of influenza self-tests may improve access for testing among priority populations and allow self-test kits to be safely and legally distributed in Australia. Reduced delays in testing may support earlier access to intervention and treatment, including antiviral medications that could assist in the reduction of transmission rates and the severity of complications associated with seasonal influenza.

[1] WHO - Global Influenza Strategy 2019-2030

However, it is recognised that rapid antigen self-tests for influenza are significantly less sensitive compared to viral culture and nucleic acid amplification tests (NAAT). Unlike viral culture or NAAT, antigen-based detection methods cannot achieve the lower limits of detection attained by amplified methods, thereby making it more heavily dependent on optimal sample collection and transportation than other methods. For this reason, NAAT is the preferred test for rapid diagnosis of acute influenza for clinical purposes[2]. Further, influenza rapid antigen self-tests are intended to be used in the home or similar environment by a lay person. Therefore, appropriate risk mitigation strategies must be implemented to ensure the quality and safety of these tests.

Serologic (antibody detection) testing is not suitable for diagnosis of influenza (as recent infection can only be reliably diagnosed by demonstrating a significant rise in influenza-specific antibody titres) and provides retrospective information only.

This guidance refers to seasonal influenza only and does not include self-tests to detect specific influenza strains that are novel or emerging (e.g. pandemic strains) which will remain prohibited for supply in a self-testing format.

Seasonal Influenza

Influenza, or 'the flu', is a viral infection of the nose, throat and lungs (the respiratory system). In Australia, it usually affects people during the winter months from June to September. The flu viruses that circulate every winter are often similar to those from the preceding winter, so there is already a level of immunity (body defences) in the community. Seasonal influenza most commonly affects the very young or the elderly[3].

Seasonal influenza strains (usually A (e.g. H1N1 and H3N2) and B) generally follow predictable seasonal patterns and occur annually. Only influenza type A viruses are known to have caused pandemics[4,5].

Influenza Pandemic

An influenza pandemic is when a new influenza A virus emerges that is very different from current and recently circulating human seasonal influenza A viruses[3]. New (novel) influenza A viruses infect people easily and spread from person to person in an efficient and sustained way[3].

Regulatory requirements for rapid antigen self-tests to detect seasonal influenza

An application for a point-or-care and/or self-test IVD to detect seasonal influenza is subject to a mandatory application audit prior to entry in the ARTG. Application audits are conducted to verify that devices submitted for inclusion in the ARTG meet the relevant legislative requirements. Information on the requirements for mandatory auditing can be found at auditing of medical devices, including IVD medical devices.

[2] Department of Health – Influenza Laboratory Case Definition
[3] Department of Health - types of influenza
[4] Adapted from World Health Organisation (WHO) - influenza (seasonal) fact sheet
[5] Adapted from Centers for Disease Control and Prevention (CDC) - pandemic influenza

This will involve a review of the technical file. The technical file provided will be used as supporting evidence to demonstrate that the IVD is safe to use and can perform to its intended purpose.

The following documents will need to be submitted for review:

- A cover letter outlining the scope of the application
- A table of contents (referencing all the performance validation study reports submitted in the application)
- Conformity assessment documentation
- Declaration of Conformity
- Device description
- Detailed risk documentation that addresses all identified risks related to point-of-care and/or self-test IVDs that use rapid antigen tests to detect seasonal influenza. This should include:
  - The impact of antigenic variation in circulating strains, or novel strains, on the performance of the test, leading to a potential increased risk of false-negative results. To mitigate this risk, it is expected that the manufacturer establishes analytical and clinical performance of the rapid antigen test against a range of influenza strains.
  - A plan for ongoing performance monitoring to address the potential variation in influenza rapid antigen test sensitivity because of seasonal changes in circulating influenza strains.
- Labelling and instructions for use – in a format appropriate for a lay-user
  - Instructions provided by the manufacturer for the collection of samples and how to perform the test should be well-designed, easy to read, locally adapted and user friendly.
  - Instructions should clearly describe the environmental conditions, incubation times, time between sampling and reading, and correct interpretation of positive and negative results, in an illustrated and accessible way so they can be easily followed by a lay person.
  - The instructions need to be usable by individuals of different literacy levels and availability in multiple languages should be considered.
  - Clear, detailed instructions with a stepwise process to follow can significantly reduce errors in the performance of a rapid self-test. Influenza self-tests (usually type A and B) that are intended to be used in the home or similar environment by a lay person.
  - Limitations should be clearly indicated in the Instructions for Use (IFU) for the test (see section ‘Requirements for the IFU’).
  - The IFU should provide sufficient instructions to inform the user on what to do when a result is produced. This should include:
    - Individuals with a positive result or who are unwell are advised to consult a medical practitioner for follow-up clinical care
    - A negative result does not mean a person does not have influenza, and if symptoms persist, the person should seek medical attention and further testing if required.
    - If an invalid result is produced, the user should retest with a new test.

- Full validation reports that support:
  - stability claims
  - analytical performance characteristics
  - clinical performance characteristics

Performance characteristics and risk mitigation strategies for IVD self-testing

All self-tests for serious diseases should demonstrate the highest possible standard of clinical performance relative to the intended purpose and classification of the test (essential principles 14 and 15 of the *Therapeutic Good (Medical Devices) Regulations 2002* (the *Medical Device Regulations*)).

Different clinical and analytical performance requirements and risk mitigation strategies, including imposing conditions of inclusion on the ARTG, may be applicable. This depends on the nature of the test and takes into consideration:

- the intended purpose of the test (e.g. an aid for diagnosis)
- the format of the test (e.g. single or multiple antigen targets)
- the environmental conditions under which the test would be conducted by a lay person (i.e. in the hands of an untrained/inexperienced user); and
- the specimen type (e.g. nasal swab).

The purpose of this approach is to balance the need for high quality tests with clinical characteristics that are fit for purpose.

Manufacturers must also meet the specific requirements for self-tests in accordance with essential principle 15:

- An IVD medical device for self-testing must be designed and manufactured so that it performs appropriately for its intended purpose, taking into account the skills and the means available to users and the influence resulting from variation that can reasonably be anticipated in the user's technique and environment.
- The information and instructions provided by the manufacturer of an IVD medical device for self-testing must be easy for the user to understand and apply; and
- An IVD medical device for self-testing must be designed and manufactured in a way that reduces, to the extent practicable, the risk of error in the use of the device, the handling of the sample and the interpretation of results.

Overall acceptability of any test for the purposes of inclusion in the ARTG depends on compliance of the test device with the essential principles and in particular, a demonstration that the test does not compromise health and safety, is suitable for the intended purpose and the benefits of the test outweigh any residual risks associated with its use (essential principles 1, 2 and 6).

Risks

False negative results are more likely to occur (for antigen tests) if a test is performed outside the window of highest viral shedding of the influenza virus (which is usually within the

first 4 days of onset of symptoms). The influenza antigen self-test has a lower level of sensitivity if testing is performed outside of this period. Self-tests may have different specifications for different specimen types and the quality of the specimen collected may also affect results. It is expected that the majority of seasonal influenza self-tests will be antigen based. False negative results are more likely to occur when influenza prevalence is high in the community, which is typically at the peak of the influenza season[6].

False positive results are more likely to occur when influenza prevalence in the community is low, which is generally at the beginning and end of the influenza season or periods in which influenza viruses are not circulating (e.g. summertime).

The above risks are exacerbated in a self-testing environment due to individual user variability in the correct performance and interpretation of the test and adequate specimen collection (i.e. the **risks are predominantly user focussed**). Additionally, in the self-test environment, follow-up testing is not easily encouraged or implemented. Therefore, appropriate measures must be in place to address the risk of follow-up testing where required.

Analytical requirements

The evidence required to demonstrate the analytical performance characteristics of the test must be provided. When submitting an application for inclusion in the ARTG, the technical file is expected to include analytical studies such as:

- **Sample stability** – studies relevant to self-collection of samples and conducting the test. Studies should cover all sample types intended for use with the test for the claimed sample storage time and temperature range.
- **Analytical sensitivity** - The limit of detection (LoD) is defined as the minimum concentration of the target analyte that the test can consistently detect. It is expected that this is confirmed using at least 20 replicates at the LoD concentration (determined through serial dilutions) and demonstrates that the virus is detected 95% of the time (19/20). The LoD must be evaluated for all claimed specimen types to be used with the test and each analyte that will be tested with the device utilising the entire test system from sample preparation to detection. The analytical sensitivity study should also determine the LoD for at least two strains representative of types or subtypes for each claimed influenza virus. The strains selected should be relevant to the Australian setting[7].
- **Analytical reactivity** - To demonstrate that the rapid antigen test can detect a range of influenza strains, it is expected that the manufacturer conducts analytical reactivity (inclusivity) studies using inactivated virus with a minimum of 10 strains for influenza A including as a minimum H1N1 AND H3N2, and 5 influenza B strains. Influenza A detection should be tested across all subtypes that have infected humans, at viral levels at or near the LoD. Influenza B strains representing both lineages (Victoria and Yamagata) must also be included. The influenza strains selected for the study should be relevant to Australian settings, reflect geographical and temporal diversity, with a focus on contemporary strains (i.e. those that have been in circulation within the last 5 years).

[6] Centers for Disease Control and Prevention (CDC) - information for clinicians on rapid diagnostic testing for influenza

[7] Australian Influenza Surveillance Report and Activity Updates - https://www1.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-ozflu-flucurr.htm#current

Refer to the TGA website for information on the Australian Influenza Vaccine Committee (AIVC) recommendations for the composition of influenza vaccine for Australia.

- **Analytical specificity** – studies to demonstrate cross-reactivity with other common respiratory viruses and/or interference by an unrelated pathogen or substance. Studies should include non-infected individuals, potentially interfering and cross-reactive samples, and other respiratory pathogens, including bacteria.
- **Precision** – studies that address potential variability within-lot, between-lot, within-day, between-day, within-site, between-site and between-user.
- **High dose hook effect** – study to address the potential for false negative results at high level concentration of target antigen present in the sample.
- **Stability studies** – including:
  - open and closed shelf-life studies for the kit (test strip, buffer) that consider the extremes of temperature and humidity the tests may be exposed to in Australia; and
  - transport simulation studies relevant to the claimed shelf-life and environmental conditions for storage, transport and use (e.g. temperature and humidity).
- **Validation of internal control** - all self-tests must include an internal control for the user to verify correct performance of the test.
- **External controls** – external controls are expected to be provided with a POCT so that the user can conduct appropriate quality control procedures. Evidence of traceability and validation of the external controls is required.

Evidence to support the analytical performance of a seasonal influenza rapid antigen test is required for both self-tests and point-of-care tests.

Guidance establishing the performance characteristics of IVDs for the detection, or detection and differentiation of influenza viruses, published by the US Food & Drug Administration (FDA) may support manufacturers seeking to compile technical documentation that addresses the minimum analytical and clinical performance requirements for their test

Clinical requirements

Evidence to support the clinical performance of a seasonal influenza rapid antigen test is required for both self-tests and point-of-care tests. A clinical study must be performed that best simulates a clinical setting. Published journal articles cannot be used as evidence to support the clinical performance characteristics of the device. Contrived samples are not acceptable in determining clinical sensitivity and specificity. Manufacturers need to clearly identify if their device is intended to detect influenza in symptomatic individuals only or also in asymptomatic individuals.

Symptomatic testing

Influenza rapid antigen tests are expected to provide clinical sensitivity and specificity studies that demonstrate the performance of the test when used to test symptomatic individuals. A clinical performance study which evaluates the device's performance using clearly characterised study participants and considers the range of variable factors associated with use of the device must be provided.

It is anticipated that self-tests will be predominantly antigen tests performed on nasal swabs. All claimed sample types, as stated in the intended purpose of the test, must undergo clinical evaluation. In addition, it is expected that sample stability will be demonstrated for all claimed specimen types intended for use with the test.

The clinical sensitivity and specificity must reflect the expected performance of the test with clinical specimens in comparison to the currently accepted reference method, for example. a reverse transcriptase polymerase chain reaction (RT-PCR) test. It is expected that the comparator PCR test has regulatory approval, either in Australia or from a comparable overseas regulator.

The TGA expects statistically relevant specimen numbers and sample selection appropriate to each strain of influenza detected, for the evaluation of an influenza rapid antigen test. Clinical sensitivity and specificity claims must include confidence intervals that reliably meet the minimum required level of performance. Positive samples are expected to be characterised (e.g., description of patient symptoms; day of collection post symptom onset; RT-PCR crossing threshold (Ct) values) and discordant results investigated using testing algorithms in accordance with a well-established laboratory case definition for influenza[8, 9]. Positive samples need to be collected across the full range of days post on-set of symptoms and the peak period for detection must be consistent with the claims made for the device. A representative number of positive samples (as determined by the reference method) from each age group must also be included (e.g. paediatric populations aged birth to 5 years, 6 to 21 years, adults aged 22-59, and greater than 60 years old). Data must be presented stratified by age, days post onset of symptoms and comparator RT-PCR Ct values in addition to the overall data summary table.

Influenza self-tests must meet minimum clinical performance requirements for clinical sensitivity and specificity for a self-test across the claimed specimen types such as nasopharyngeal, nasal or throat swab:

- an overall clinical sensitivity of at least 85%; and
- an overall clinical specificity of at least 95% for the detection of influenza infection[10].

Clinical performance studies should include information on when samples were taken and tested (i.e. days post symptom onset) and clearly demonstrate the optimal days for testing.

Asymptomatic Testing

The use of seasonal influenza rapid antigen tests to test asymptomatic individuals is generally associated with markedly reduced clinical performance, when compared with testing individuals who display typical signs or symptoms associated with influenza. In community settings that have low prevalence of seasonal influenza, there is also an

[8] Public Health Laboratory Network - influenza laboratory case definition
[9] European Union - case definition of influenza
[10] Based on current clinical sensitivity/specificity of influenza point-of-care tests included in the ARTG.

increased likelihood of false negative and false positive results, which further reduces the reliability of results.

Where manufacturers opt to include claims relating to testing of asymptomatic individuals, performance of the test when used in this sub-population must be demonstrated. It is recommended to include a substantial number of both symptomatic and asymptomatic individuals in your study population, and to provide detailed information on the prevalence of seasonal influenza in the setting in which the testing is conducted. The clinical data must be separately presented in the IFU. This will allow users performing a test to understand that the reliability of their results is expected to be reduced if they do not have symptoms.

Evidence to support the clinical performance of a seasonal influenza rapid antigen test is required for both self-tests and point-of-care tests.

Usability studies

As self-tests are predominantly performed by lay persons, clinical evidence in the form of usability studies is required to establish performance of the test in the hands of these users. It is expected that the clinical performance studies include clinical patient samples in their usability studies. Specific usability studies are not required for rapid antigen tests only intended to be used by a health professional at the point-of-care.

The manufacturer is not required to provide Australian-specific usability studies, but it is expected that studies will reflect the performance of the test in a comparable setting and relevant to the Australian population.

For a usability study, the study population should represent all ages of individuals intended to be able to use the test. Participants should represent varying education levels and ages and include individuals who may not use English as their preferred language. Participants with prior medical or laboratory training should be excluded. Participants who have prior experience with self-collection or self-testing should also be excluded.

Testing should include a minimum of 100 participants to examine each of the following usability characteristics and take place in an actual use environment or simulated environment with supervision, but without intervention by the supervisor/observer. The entire workflow should be performed by each individual participant doing the test, including sample collection, testing and results interpretation without assistance, influence, or guidance from the study observers.

Usability studies are expected to address the following usability aspects.

User comprehension

A usability study should take into account the ability of the user to interpret the IFU, and to ensure that the labelling is clear and easy to follow (e.g. a questionnaire to assess the ability of users to correctly comprehend instructions for use, limitations, diagrams, result interpretation and access to follow-up services).

The participants should be observed (either in person or by remote visual monitoring, such as a video conference) during sample collection and performance of the test and all difficulties noted.

Inter-reader variability

An inter-reader variability study should consider the ability at least 100 individuals to interpret pre-determined results and/or contrived results. The samples need to consist of strongly positive results, a high proportion of weakly positive results, negative and invalid results to fully assess the ability of the lay person to obtain the correct result.

If the test uses an app to analyse or assist in the interpretation of results this needs to be used in the study to demonstrate there is no negative impact on interpretation, particularly for weak positive results.

A significant inter-reader variability (e.g. ≥ 5%[11,12]) for clearly positive or negative results implies that the device is not easy to use, the IFU is not clear enough, or the test may be difficult to interpret resulting in an increased rate of false negative or positive results.

Invalid test rate

The incidence of operational errors and test system failures (e.g. failure to collect a sample correctly or complete each of the sequential steps required to perform the test, resulting in an invalid or unreadable result), or where the user is unable to interpret the result leading to an invalid result should be determined. This will provide an indication of the reliability and robustness of the test. Ideally the invalid test rate is expected to be ≤ 2%[13,14] of the total tested (this includes defective tests or components).

User sensitivity/specificity studies

Studies should be performed to confirm the clinical sensitivity and specificity of the test in hands of a lay person in the self-testing environment. The user sensitivity and specificity should be estimated in comparison to the true influenza status of the individual as determined by laboratory testing (e.g. RT-PCR). Where possible studies should include participants from high and low prevalence setting.

- 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.

Preferably, the user sensitivity should be ≥85%. A user sensitivity of <85% may be considered acceptable where evidence of significant public health benefits can be demonstrated and where thorough risk mitigation strategies have been put in place to minimise the risk of false negative and false positive results.

The suitability of these studies will be assessed on a case-by-case basis and will depend on how well the manufacturer has mitigated any risks and demonstrated that the overall benefits of the product outweigh any residual risks associated with its use. Demonstration of the benefit of a test and effectiveness of risk mitigation measures in the self-testing environment may be supported by a documented review of relevant published literature[15].

[11] WHO - HIV assays: operational characteristics
[12] TGA - clinical performance requirements and risk mitigation strategies for HIV tests
[13] WHO - HIV assays: operational characteristics
[14] TGA - clinical performance requirements and risk mitigation strategies for HIV tests
[15] the literature review may include data for devices used for similar intended purposes as the device under assessment

Additional risk mitigation strategies for self-tests

The proposed mitigating strategies recognise that self-tests differ from laboratory-based tests and point-of-care tests in that the user is responsible for all aspects of the testing process from sample collection to test interpretation.

The mitigating strategies for seasonal influenza self-tests are:

- The specimen collection process must be straightforward, the instructions for specimen collection must be clear and easy to understand, and the specimen able to be collected safely in the home testing environment
- The test must be easy to perform with minimal operator intervention or procedural steps. Extensive usability studies would be expected (e.g. device interpretation study, label comprehension study and observed self-testing studies)
- Access to additional resources or information to assist in the completion of the test e.g. online video for sample collection and test interpretation, and simple graphical instructions in the correct use and performance of the device.
- The stability of the product should be demonstrated across a range of operational and environmental conditions expected to be encountered geographically within Australia
- The strains of virus that can be detected by the influenza self-test should be appropriate for the detection of seasonal strains of virus that are circulating within the last five years, or prevalent within Australia.
- The public health implications of a false negative need to be considered and instructions for use must include the requirement that even with a negative test if symptoms are developed the individual must contact a health professional and seek medical assistance.
- A sponsor telephone helpline or on-line operators to be available to provide support. The operators must have been trained in the performance and interpretation of the self-test and be able to provide advice on what to do after obtaining a test result.

Requirements for the instructions for use (IFU)

In addition, the manufacturer/sponsor of an influenza self-test is also required to clearly outline the limitations of the test and provide clear advice, in the IFU and/or other information provided with the test, including the following:

- clear and simple instructions on how to perform and interpret the test (this may involve images or visual representation of the instructions, flow diagrams or QR codes linking to online demonstrations)
- available either in print or online in multiple languages (e.g. including local languages)
- specific influenza strains that the test detects, and any strains or subtypes that cannot be detected
- the clinical sensitivity and specificity of the test (i.e. in a self-testing environment) must be clearly identified (including information on the clinical sensitivity/specificity of the test at various time points post symptom onset)
- clear information on when testing should be performed (e.g. within the first 4 days of symptom onset when viral shedding is highest)
- clear warnings on the risk of false negative results, particularly if testing is not performed within the first 4 days of symptom onset.

- clear warnings that the tests are less reliable in the later phase of infection and in asymptomatic individuals.
- clear indication that influenza self-testing is for use as an aid for diagnosis only and individuals with a positive result or who are unwell are advised to consult a medical practitioner for follow-up clinical care
- If an invalid result is produced, the user should retest with a new test.
- A negative result does not mean a person is not infectious or does not have influenza. If symptoms persist the person should seek medical attention and further testing if required
- a negative result does not rule out infection with another type of respiratory virus
- information on other limitations of the test such as a positive result cannot necessarily determine whether a person is infectious
- a statement to the user that the test can only be used once
- warnings about the need for supervision in children
- warnings on safe and appropriate use of kit components and prevention of possible misuse
- information on how to safely dispose of the kit and its contents
- information on what to do if a positive result is received
- how to contact locally available support services including phone lines and websites; and
- how to contact the TGA to report poor performance or usability issues in the self-test environment (report an issue via the Users Medical Device Incident Report, email iris@tga.gov.au or call 1800 809 361).

It is also recommended that the IFU contain information to promote good infection control procedures of individuals to reduce the spread of viruses to the general population.

Other requirements for the IFU and information provided with a device, including product labelling, are detailed in essential principle 13 of *the Medical Device Regulations*.

Associated software and mobile applications

Any associated software or mobile applications (such as a tool to read or interpret the results of a test on a mobile phone) need to be simple and easy to use, with any risk of misuse reduced as far as possible. If your app is a simple tool for recording and transmitting patient results or generating a digital record, then it would not be considered a medical device. If it analyses the results or enables interpretation of the test result it will be a medical device. Australian privacy and data protection laws (the Privacy Act 1988) would still apply.

If the app is designed to analyse the test result it will be considered as separate analysis IVD medical device software and require separate inclusion in the ARTG. This applies regardless of the technology platform used, including cloud components – this document uses the term “app” solely for ease of reading. You will be required to provide:

- minimum specifications for the device (e.g. smartphone) you intend your app to operate on (e.g. memory, processor capability, minimum operating system requirements, browsers, smartphone models, etc.).
- evidence to validate the performance of the app with the self-test, including usability, functional and non-functional performance. This evidence must show how the specificity,

sensitivity and other performance criteria of the self-test is maintained when using the app, i.e. there should be no gap in accuracy when comparing the test alone to the test plus the app. The validation evidence should clearly set out all use cases/scenarios tested.

- data used for validation, including testing, training and generalisability where applicable.
- details of architecture and design of the app and associated hardware platforms, including cloud if applicable.
- evidence cybersecurity risks have been addressed and how data privacy has been managed as it relates to patient safety and Australian privacy and data protection law.
- clear instructions for lay people on how to use the app, as part of the IFU.

Post-market monitoring and standard conditions of inclusion

All sponsors of self-tests included in the ARTG have ongoing responsibilities under the *Act*, *the Medical Device Regulations* and the *Therapeutic Goods Advertising Code* (the *Advertising Code*), including conditions that apply automatically to all ARTG entries as described in the *Australian Regulatory Guidance for Medical Devices*. These conditions facilitate post-market monitoring and include, but are not limited to, the following:

- allowing entry and inspections of premises
- delivery of device samples upon request
- availability of information, such as facilitating access to technical documentation that demonstrates compliance with the essential principles
- ensuring any advertising material relating to the medical device complies with regulatory requirements; and
- reporting details of certain incidents and performance issues to the TGA, and any overseas regulatory actions to the TGA if the product involved is from the same batch or production run that was supplied in Australia.

All sponsors are required to report adverse events to the TGA through the Medical Device Incident Reporting Scheme https://www.tga.gov.au/medical-device-incident-reporting-investigation-scheme-iris (IRIS).

Additional conditions that may be applied

Depending on the performance of the test, the information provided in the IFU and robustness of the test, the TGA may impose additional non-standard conditions to mitigate any residual risk identified relating to the effective and safe use of the product or to facilitate the monitoring of potential trends.

These are likely to include a requirement that the sponsor:

- provide results of annual analytical evaluation of the test against new seasonal influenza virus circulating based on global surveillance data (IFU and labelling must be updated to reflect the results of any evaluation, such as any non-reactivity identified)
- provide results of testing for emerging novel influenza virus (IFU and labelling must be updated to reflect the results of any evaluation)

- provide additional support for users of the test through provision of information that will direct users to on-line support services and/or customer support phone line
- provide on their web-site instructional videos or on-line simple graphical instructions in the correct use and performance of the device
- provide to the TGA an electronic copy of the IFU to be displayed on the TGA website. Upon release of a new version of the IFU by the manufacturer, the sponsor must provide this to the TGA, within 3 busines days for display on the TGA website
- submit to the TGA through the medical device Incident Reporting and Investigation Scheme (IRIS) all complaints (including adverse events) related to the use of performance of the device, as soon as they are received by the sponsor, for the next five (5) financial years. This includes but is not limited to adverse events and reports of false positive and false negative results
- provide the TGA with regular (annual) reports on the distribution of the product, numbers of tests sold and numbers of any reported false positive or false negative results or problems with poor performance of the test in Australia and worldwide (this may be a combination of monthly and annual reporting requirements)
- may potentially only supply the device through specified distribution channels that allow relevant information/education to be provided to users at the time of purchase. This will be considered on a case-by-case basis and will depend on what risks need to be mitigated.
- provide the post-market reports to the TGA at the following email address, postmarketdevices@health.gov.au.

Post-market review

The TGA can conduct a post-market review of certain kinds of devices included in the ARTG. ARTG entries for influenza self-tests may also be subject to a post-market review. Sponsors will be required to provide evidence of the performance of their device with respect to the new circulating strains, as well as their risk management plans to ensure continued performance with the emergence of new strains. In addition, sponsors may be asked to provide a number of test kits for independent laboratory evaluation of the clinical sensitivity and specificity to verify their performance.

Please note:

Advertisements for IVDs, including self-tests, are subject to the requirements of *the Act*. For advertising to consumers, this includes the requirement to comply with *the Advertising Code*.

The Advertising Code requires advertising to consumers to be accurate and not misleading (including misleading through the omission of important information, like the limitations of an IVD).

The Advertising Code specifies the requirements for advertising therapeutic goods to consumers. Notably, the Advertising Code requires that advertising for therapeutic goods must:

- be accurate, balanced, and not misleading or likely to be misleading and that all information presented has been substantiated;

- be consistent with the intended purpose on the ARTG; and
- present the good in accordance with the directions/instructions for use.

Additionally, advertisements for therapeutic goods must not:

- contain any claim, statement, implication or representation that the goods are safe, their use cannot cause harm, that they have no side effects or that the goods are effective in all cases;
- exaggerate the efficacy or performance of the product or encourage inappropriate use;
- state or imply that the goods are approved or endorsed by a government authority (e.g. stating “TGA approved”);
- must not be likely to lead people to delay necessary medical attention; and
- must not be inconsistent with public health campaigns.

Consumer advertising for IVDs for detecting or diagnosing a serious disease, condition, ailment or defect is likely to contain a restricted (e.g. influenza) or prohibited (e.g. HIV) representation. Under *the Act*, the TGA must authorise these types of representations prior to their use in consumer advertising. More information is available at *https://www.tga.gov.au/restricted-representations.*

How to submit an application to the TGA for IVD self-test to detect seasonal influenza

Please refer to Including IVD medical devices in the ARTG for further guidance on how to submit an application for approval to the Pre-market IVD section to include a self-test IVD that detects Influenza onto the ARTG.

Once an application is submitted and has passed the pre-assessment stage (where an application fee is paid and all appropriate conformity assessment documentation is provided) this application will be selected for a mandatory audit under the *Therapeutic Good (Medical Devices) Regulations 2002* 5.3 (j) (ii) as it is an IVD medica device that is intended for self-testing.

The sponsor will be notified and sent an invoice for an application audit fee and a request to submit a technical dossier. The technical dossier should contain evidence to support the performance and safety claims of the device.

Version history

V1.0	Original publication	IVD Reforms, Medical Device Surveillance Branch	March 2021
V2.0	Revised to include more detailed analytical and clinical performance requirements,	IVD team, Medical Device Authorisation Branch	May 2022
V3.0	Amended the title of the document to reflect the guidance is applicable to Point of Care tests, updated department logo and TGA styles	IVD team, Medical Device Authorisation Branch	October 2022

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Reference/Publication #