Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Understanding rules for in-vitro diagnostic (IVD) self-tests for chlamydia, gonorrhoea and syphilis

Guidance on our expectations concerning clinical performance requirements and risk mitigations for in vitro diagnostic medical devices intended to be used as self-tests for chlamydia, gonorrhoea and syphilis.

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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 clinical performance requirements (i.e., clinical sensitivity and specificity) and risk mitigations for in vitro diagnostic medical devices (IVDs) intended to be used as self-tests for *Chlamydia trachomatis* (chlamydia), *Neisseria gonorrhoeae* (gonorrhoea) and *Treponema pallidum* (syphilis).

This document identifies key risks that must be mitigated and identifies conditions that may be imposed on these self-test kits if they are to be 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. Other aspects of demonstrating safety and performance, such as analytical performance studies or stability studies are not addressed in this document.

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.

Legislation

Therapeutic Goods (Medical Devices) Regulations 2002

Therapeutic Goods (Medical Devices—Excluded Purposes) Specification 2020

Therapeutic Goods (Therapeutic Goods Advertising Code) Instrument 2021

Background

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 (e.g., 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 Therapeutic Goods (Medical Devices – Excluded Purposes) Specification 2020 (the Excluded Purposes Specification 2020) was made, and came into effect on 1 October 2020. Sponsors and manufacturers will now be able to apply to the TGA for the inclusion in the ARTG of specified IVD self-tests,

including self-tests for chlamydia, gonorrhoea or syphilis. Any tests allowed under the Excluded Purposes Specification 2020 can only be supplied following evaluation of individual products by the TGA to ensure appropriate clinical performance requirements are met and risk mitigations are in place.

Public health context

Sexually transmissible infections (STIs), including chlamydia, gonorrhoea and syphilis, have remained a significant public health issue in Australia. The prevalence of these STIs have risen within the general Australian population, with significant increases in the notification rate of all three STIs within the last decade. In combination with emerging issues that require public health monitoring, STI's are a persistent and growing issue within the Australian population. These STI's are all treatable with antibiotics, however early detection is key to reducing the transmission and associated complications.

The Department of Health in 2018 published the fourth National Sexually Transmissible Infections Strategy 2018-2022. Outlined in these strategies are key areas of focus including; increasing the STI testing coverage in certain populations and to reduce the prevalence of chlamydia, gonorrhoea and syphilis. This strategy in combination with the fifth National Aboriginal and Torres Strait Islander Blood Borne Viruses and Sexually Transmissible Infections Strategy 2018-2022 and the Action Plan: Enhanced response to addressing sexually transmissible infections (and blood borne viruses) in indigenous populations aims to increase accessibility to testing and treatment for STIs.

The Excluded Purposes Specification 2020 allows manufacturers and sponsors to apply for inclusion of chlamydia, gonorrhoea and syphilis 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 chlamydia, gonorrhoea and syphilis self-tests may improve access for testing among certain populations and allow self-test kits to be safely and legally distributed in Australia. Reduced delays in testing may support earlier access to intervention, increase access to support services for individuals who test positive, and increase access to appropriate treatment that could reduce prevalence and acute health consequences associated with these STIs.

Clinical 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 performance requirements and risk mitigation strategies, including conditions of approval, are applicable depending on the nature of the test and take into consideration:

- the intended purpose of the test (e.g., presumptive screening test)
- the format of the test (e.g., antigen or antibody)
- 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., finger stick whole blood, first pass urine or swabbing).

> 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 the Therapeutic Goods (Medical Devices) Regulations 2002.

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, 3 and 6).

> 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 Therapeutic Goods Advertising Code (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).
>
> Consumer advertising for IVDs for detecting or diagnosing a serious disease, condition, ailment or defect is likely to contain a restricted (e.g., hepatitis B virus) or prohibited (e.g., chlamydia, gonorrhoea and syphilis) representation. Under the Act, the TGA must authorise these types of representations prior to their use in consumer advertising. More information is available at restricted representations.

Clinical requirements for chlamydia, gonorrhoea and syphilis self-tests

Chlamydia, gonorrhoea and syphilis self-tests are rapid presumptive screening tests intended to be used in the home or similar environment by a lay person. Follow up with a medical practitioner is required for confirmation of positive results using a laboratory test and for reporting of a notifiable disease.

Clinical characteristics and clinical performance requirements for chlamydia and gonorrhoea self-tests

Chlamydia and gonorrhoea self-tests are expected to demonstrate a high level of clinical sensitivity and specificity.

Chlamydia and gonorrhoea self-tests must meet minimum clinical performance for the claimed clinical sensitivity and specificity for a self-test across the relevant specimen types such as vaginal, anal or urine samples:

- an overall clinical sensitivity of at least 95%; and
- an overall clinical specificity of at least 99%.

This reflects the expected performance of the test with clinical specimens in comparison to a currently accepted reference standard (e.g., Polymerase Chain Reaction (PCR)). It is expected that the self-test shall have an overall performance equivalent to that of the established device.

The TGA will expect statistically appropriate specimen numbers and sample selection for the evaluation of a chlamydia or gonorrhoea test. Positive samples are expected to be characterised and discordant results investigated using testing algorithms in accordance with a well-established laboratory case definition for chlamydia or gonorrhoea. Manufacturers claiming that their kit detects chlamydia or gonorrhoea in different sample types must conduct parallel testing to demonstrate specimen equivalence. Contrived samples would not be acceptable in determining clinical sensitivity and specificity. Clinical performance studies should include information on when clinical samples were taken, the type of sample tested (i.e., days post symptom onset) and clearly identify the optimal period for testing. It is expected that sample stability will be demonstrated for all claimed specimen types intended for use with the test.

As self-tests would predominantly be performed by a lay person, clinical evidence in the form of usability studies would be required to establish performance of the test in the hands of these users. It is expected that the clinical performance studies would include clinical patient samples in their usability studies.

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.

Clinical characteristics and clinical performance requirements for syphilis self-tests

Syphilis self-tests are expected to demonstrate a high level of clinical sensitivity and specificity.

These tests may involve alternative specimen types to what is utilised in clinical settings, including finger stick whole blood, and may not necessarily perform to the same standard as laboratory tests that are intended for professional use.

Self-tests for syphilis will most likely be in the form of antibody tests (i.e., treponemal testing), and will only be clinically relevant in users who have previously not tested positive for syphilis.

Syphilis self-tests must meet minimum clinical performance for the claimed clinical sensitivity and specificity for a self-test across the relevant specimen types including whole blood (finger stick):

- a clinical sensitivity of at least 95%; and
- a clinical specificity of at least 98%.

This reflects the expected performance of the test with clinical specimens in comparison to a currently accepted reference standard (e.g., third or fourth generation enzyme immunoassay (EIA)). It is expected that the self-test shall have an overall performance that is equivalent to that of the established device.

The TGA will expect statistically appropriate specimen numbers and sample selection for the evaluation of a syphilis self-test. Positive samples are expected to be characterised and discordant results investigated using testing algorithms in accordance with a well-established laboratory case definition for syphilis. Contrived samples would not be acceptable in determining clinical sensitivity and specificity. Clinical performance studies should include information on when clinical samples were taken; the type of sample tested and clearly identify the optimal period for testing (i.e., outside or within the window period of seroconversion). It is expected that sample stability will be demonstrated for all claimed specimen types intended for use with the test.

As self-tests would predominantly be performed by a lay person, clinical evidence in the form of usability studies would be required to establish performance of the test in the hands of these users. It is expected that the clinical performance studies would include clinical patient samples in their usability studies.

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 prevalence to the Australian population.

Usability studies

Usability studies are required to address the following topics.

User comprehension

A usability study should take into account the ability of the user to interpret the instructions for use (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).

Inter-reader variability

An inter-reader variability study should take into account an individual's ability to interpret pre-determined results (e.g., positive results, weakly positive results, negative and invalid results).

A significant inter-reader variability (e.g., ≥ 5%[1, 2]) 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 sample correctly resulting in an unreadable result or user not being able to interpret the result) that lead 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 would be expected to be ≤ 2%[1, 2] of the total tested (this includes defective tests or components).

User sensitivity/specificity studies

Studies should be performed to confirm 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 chlamydia, gonorrhoea or syphilis status of the individual as determined by laboratory testing (e.g., EIA or PCR). Studies should include participants from high and low prevalence settings.

Preferably, the user sensitivity should be ≥95% for chlamydia, gonorrhoea and syphilis self-tests. A user sensitivity of <95% 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[3].

Risks

It is expected that the majority of self-tests for chlamydia and gonorrhoea will be antigen based. Whereas self-tests for syphilis will most likely be antibody based. The quality of the specimen collection may affect the results and false negative results are more likely to occur for antigen tests if the patient is asymptomatic.

False negative results are also more likely to occur for antibody tests if a test has a lower level of clinical sensitivity (less than 100%), if the person has waning immunity from a past infection and if testing is performed during the 'window' (e.g., seroconversion) period for the device[4]. There is a risk that if testing is performed early in the active phase of the infection, and prior to seroconversion, that a false negative result might occur. Syphilis serology can produce a false negative despite the presence of symptoms.

False positive results are also more likely to occur if these tests are used in lower prevalence populations. The risk of a false positive is exacerbated in a self-testing environment due to individual user variability in the correct performance and interpretation of the test (i.e., the risks are predominantly user focussed). Additionally, in the self-test environment, follow up testing may not easily be encouraged or implemented.

Antibody tests for syphilis are cross reactive with a number of pathogens and could result in a false positive, and some persons with autoimmune conditions can produce antibodies that may interfere with the test results[5]. Antibody tests for syphilis are also unable to distinguish between an active infection a past, treated infection, infectious activity or progression of associated complications.

Despite the limitations described above, the benefits gained from utilising chlamydia, gonorrhoea and syphilis self-tests may outweigh the risks (i.e., a false positive or false negative result), especially for kits with high levels of clinical sensitivity and specificity.

Mitigation strategies

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.

Self-tests for chlamydia, gonorrhoea and syphilis will be subject to mandatory application audits prior to entry in the ARTG.

The mitigating strategies for chlamydia, gonorrhoea and syphilis 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); and
- The stability of the product should be demonstrated across a range of operational and environmental conditions.

Requirements for the instructions for use (IFU)

In addition, the manufacturer/sponsor of a chlamydia, gonorrhoea or syphilis 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:

- clearly states what the kit is testing for (i.e., antigen or antibody testing)

- 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)
- 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)
- the user clinical sensitivity and specificity of the test (i.e., in a self-testing environment) must be clearly identified
- clear information on when testing should be performed (e.g., symptomatic/asymptomatic testing)
- clear warnings on the risk of false negative results and if testing is performed in the 'window period' for syphilis (and a clear explanation of what the window period is)
- clear warning of the risk of false positive syphilis results when using antibody self-tests due to previous syphilis infections that have been treated and resolved
- clear indication that chlamydia, gonorrhoea and syphilis self-testing is for presumptive screening only and the need to consult a medical practitioner for confirmatory testing of positive results by a laboratory test and for advice regarding treatment if required
- warning that negative results obtained for syphilis within three months of a high risk event should be repeated at three months to confirm the initial negative result[6]
- warning about testing in particular situations (e.g., testing for syphilis in a pregnant woman and the need to seek medical advice particularly if they suspect they have syphilis or have been exposed to syphilis)

- negative results may not mean that a person is not infectious and if symptoms persist to seek medical assistance
- a negative or positive result obtained when using a self-test to detect one sexually transmitted infection does not preclude infection from other sexually transmitted infections or the presence of other conditions
- 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
- information on how to safely dispose of the kit and its contents
- how to contact locally available support and counselling services including phone lines and websites
- 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); and
- IFU contains information to promote safe sex particularly during pregnancy and the need for individuals engaging in high-risk behaviours to undergo regular testing for other sexually transmitted infections and blood borne viruses. Additionally, it should contain information in regards to the risk of maternal syphilis and the risk of passing on congenital syphilis to the foetus.

It is also recommended that the IFU contain information to promote good infection control procedures of individuals to reduce the spread of sexually transmitted infections 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.

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, 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 also required to report adverse events to the TGA.

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 additional support for users of the test through provision of information that will direct users to on-line support services and/or 24/7 phone line
- 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.

Any further conditions would be applied on a case-by-case basis and would depend on the evaluation of an individual product, the overall benefits, and how well any risks have been mitigated.

Post-market review

The TGA can conduct a post market review of certain kinds of devices included in the ARTG. ARTG entries for chlamydia, gonorrhoea or syphilis self-tests may also be subject to a post-market review and 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.

Footnotes

1. World Health Organisation (WHO) - HIV assays: operational characteristics
2. TGA - clinical performance requirements and risk mitigation strategies for HIV tests

3. The literature review may include data for devices used for similar intended purposes as the device under assessment
4. Communicable Diseases Network Australia (CDNA) National Guidelines for Public Health Units - syphilis
5. WHO Syphilis Rapid Diagnostic Test - technical specifications
6. Australian STI management guidelines - syphilis

Topics: In Vitro Diagnostic medical devices (IVDs)

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