Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration

Understanding clinical performance requirements for in-vitro diagnostic (IVD) self-tests for hepatitis B and C

Guidance on clinical performance requirements and risk mitigation strategies.

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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 hepatitis B virus (HBV) and hepatitis C virus (HCV).

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 product stability studies are not addressed in this document.

Self-tests for HBV and HCV are classified as Class 4 IVDs (the highest classification within *Therapeutic Goods (Medical Devices) Regulations 2002* (*the Medical Device Regulations*)). TGA conformity assessment certification must be obtained for manufacturers of Class 4 IVDs prior to applying for inclusion in the ARTG. This involves an assessment of a manufacturer's quality management systems as well as an evaluation of the design and performance of each Class 4 IVD. Manufacturers are required to hold technical documentation to demonstrate that their device complies with the essential principles of *the Medical Device Regulations*.

For further information on overall technical documentation and clinical evidence requirements for in vitro diagnostics, please refer to the *Meeting clinical evidence requirements for 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 Act 1989

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 HBV and HCV. Any tests allowed under the *Excluded Purposes Specification 202*0 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

HBV and HCV have presented a significant public health issue in Australia for several decades and remain an ongoing challenge within priority populations. Current vaccination strategies for HBV have reduced the number of people being diagnosed with the infection and the advent of direct acting antiviral medications to treat hepatitis B and C viral infections have reduced the number of acute and chronic infections. However, there is an increasing burden of liver disease, liver cancer and premature death due to long-term chronic hepatitis infections. Chronic hepatitis B and C infection are a leading cause of liver damage, liver cancer, liver fibrosis and cirrhosis.

The Department of Health in 2018 published the *third National Hepatitis B Strategy 2018-2022* and the *fifth National Hepatitis C Strategy 2018 – 2022*. Outlined in these strategies are key areas of focus including increasing the proportion of people who are correctly diagnosed and improving access to testing for HBV and HCV, particularly for priority populations. The two strategies in combination with the *fifth*

National Aboriginal and Torres Strait Islander Blood Borne Viruses and Sexually Transmissible Infections Strategy 2018-2022 aim to increase accessibility to testing and treatment, as a number of people remain undiagnosed despite cures existing for both conditions.

The Excluded Purposes Specification 2020 allows manufacturers and sponsors to apply for inclusion of self-tests for HBV and HCV in the ARTG, allowing for the legal supply of these self-tests in Australia (subject to TGA evaluation and approval). Legal supply of self-tests for HBV and HCV may improve access for testing among priority populations, as well as the general population, 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 direct acting antiviral medications that could assist in the reduction of transmission rates and the severity of the complications associated with hepatitis B and C viral infection.

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 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., antibody or antigen test)
- 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).

Please note:

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).

The TGA is also guided by the European Union Common Technical Specifications (EU CTS) definitions and standards for self-tests, rapid detection tests and the testing of serious diseases. Manufacturers are expected to comply with these requirements but can adopt solutions of a level equivalent to the EU CTS for appropriately justified reasons. The EU CTS provides further guidance on other performance evaluation requirements such as appropriate specimen numbers and sample selection.

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 *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., HBV) or prohibited (e.g., HCV) 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.

Clinical requirements for HBV and HCV self-tests

HBV and HCV self-tests are rapid presumptive screening tests for HBV or HCV infection 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 performance requirements for HBV self-tests

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

- a clinical sensitivity of at least 99%[1, 2]; and
- a clinical specificity of at least 99%[3].

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

Clinical performance requirements for HCV self-tests

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

- a clinical sensitivity of at least 99.5%[4, 5]; and
- a clinical specificity of at least 99%[6] .

This also reflects the expected performance of the test with clinical specimens in comparison to the currently accepted reference standard (e.g., EIA or Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR)), as it is expected that the self-test shall have an overall performance equivalent to that of the established device.

Clinical characteristics for HBV and HCV self-tests

HBV and HCV self-tests are expected to demonstrate a high level of clinical sensitivity and specificity as discussed above.

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. Contrived samples would not be acceptable in determining clinical sensitivity and specificity.

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. In addition, a review of relevant literature that supports the performance of the device may be requested.

The TGA will be guided by the EU CTS with regard to appropriate specimen numbers and sample selection for the clinical evaluation of HBV and HCV self-tests (e.g., 400 positive specimens and 1,000 negative specimens for HBV and HCV). Testing must include use of samples from different stages of infection and reflect different subtypes, antibody and viral markers. Sensitivity testing must be conducted with true positive and seroconversion samples.

True positive HBV and HCV samples are expected to be characterised and discordant results investigated using testing algorithms in accordance with a well-established laboratory case definition for HBV and HCV[7, 8]. Where claims are made for multiple specimen types, the manufacturer will need to provide specimen equivalence studies. It is expected that sample stability will be demonstrated for all claimed specimen types intended for use with the test.

The manufacturer is not required to provide Australian specific usability studies for HBV and HCV self-tests, 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 for HBV and HCV self-tests are expected to address:

- **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%) 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 false 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%[11, 12] 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 HCV or HBV status of the individual as determined by laboratory testing (e.g., EIA, PCR or RT-PCR). Studies should include participants from high and

low prevalence settings and naïve populations (i.e., individuals that have not previously tested positive and know their status).

Preferably the user sensitivity should be ≥99% for HBV and HCV self-tests. A user sensitivity of <99% 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[13].

Risks

False negative results are more likely to occur for antigen tests if a test is performed before the period of increasing viral replication rate and viral shedding (e.g., antigen production peak for acute infection roughly 40 days for HBV and 50-60 days for HCV[14]).

False negative results are more likely to occur for antibody tests if the person has waning immunity from a past infection or if testing is performed during the 'window' (e.g., seroconversion) period for the device. 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.

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 be easily encouraged or

implemented.

Despite the limitations described above, the benefits gained from utilising HBV and HCV self-tests may outweigh the risks (i.e., a false positive or false negative result), especially for self-tests 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. The mitigation strategies for HBV and HCV 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); 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 HBV or HCV 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 testing vs. 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 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 for an antigen test if testing is performed if a person has a low level (i.e., antigen is present in a lower amount than the test can detect) chronic infection. Clear warnings on the risk of false negative results for a HCV antibody test if testing is performed in the 'window period' (and a clear explanation of what the window period is)
- warning that negative results obtained within three months of a high risk event should be repeated at two to three months to confirm the initial negative result[15]
- clear indication that HBV or HCV 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

- clear warnings on the risk of false negative results
- negative results may not mean that a person is not infectious and if symptoms persist to seek medical assistance
- information should be included to identify groups at high risk (i.e., priority populations)
- information on behaviour that may place an individual at an increased risk for HBV or HCV infection, the need to test frequently if there is an ongoing risk and be vaccinated for HBV
- 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; 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 safe sex and safe injecting practices and the need for individuals engaging in high risk behaviours to undergo testing for other sexually transmitted infections and blood borne viruses[16].

It is also recommended that the IFU contain information to promote good infection control procedures of individuals to reduce the spread of blood borne 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*.

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 (Therapeutic Goods Advertising Code) Instrument 2021*, 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
- 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; and
- provide the TGA with regular annual reports (more information is available on the annual reports page on the TGA website) 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.

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 additional post-market monthly reports on the number of self-tests supplied in Australia and any adverse events or problems with poor performance of the test; and
- 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 HBV and HCV 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)- guidelines on hepatitis B&C testing
2. WHO prequalification of in vitro Diagnostics - WHO performance evaluation acceptance criteria for HBsAg in vitro diagnostics in the context of WHO prequalification
3. EU common technical specification - guidelines for IVDs
4. Advisory Committee on Medical Devices (ACMD) - recommendation, Meeting 12 15 March 2013
5. WHO - guidelines on hepatitis B&C testing
6. ACMD - recommendation, Meeting 12 15 March 2013
7. Public Health Laboratory Network - hepatitis B laboratory case definition
8. Public Health Laboratory Network - hepatitis C laboratory case definition
9. WHO - HIV assays: operational characteristics
10. TGA - Following clinical performance and risk mitigation rules for HIV tests
11. WHO - HIV assays: operational characteristics
12. TGA - clinical performance requirements and risk mitigation strategies for HIV tests
13. The literature review may include data for devices used for similar intended purposes as the device under assessment
14. WHO - guidelines on hepatitis B&C testing
15. ASHM hepatitis B and C viruses - diagnostic strategy

16. Department of Health – hepatitis B and C viruses information

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Topics: In Vitro Diagnostic medical devices (IVDs)

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Updates to template.

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