Consultation: Review of the regulation of certain self-testing IVDs in Australia

Therapeutic Goods Administration

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2nd December 2019

Executive Summary

Ellume Ltd (Ellume) develops, manufactures and commercialises digital diagnostic products for clinicians and consumers. Ellume's focus is on the accurate diagnosis of common infectious diseases with an aim to improve healthcare outcomes for individuals, their families and their communities.

Ellume has developed and validated an influenza IVD intended for self-test purposes. That is, the product has been specifically designed to meet the requirements of a home-use, self-test diagnostic that would be available to consumers over-the-counter (OTC). It is anticipated that having an OTC influenza diagnostic available to the nation's population would bring numerous benefits including:

- Reductions in morbidity through earlier and more appropriate treatment (of influenza or other illness) with the consequential economic benefits of,
    - Reduced healthcare costs
    - Reduced absenteeism
- Significant reduction in transmission with individuals self-testing within the isolation of their homes (especially important in times of pandemic)
- More targeted and appropriate distribution of the nation's anti-viral therapy stockpiles during pandemics
- Reduction in inappropriate use of antibiotics
- More accurate and current public health surveillance data capture

Ellume appreciates the opportunity to respond to this consultation. Having dedicated significant resources to developing a self-test influenza IVD, Ellume can provide insights into the mechanisms that can successfully be deployed to mitigate risk of self-test IVDs delivering false results. Ellume can also provide insights into design features that can be implemented to maximise benefits of having self-test IVDs available to the Australian public.

Ellume is confident that the IVD regulatory framework within which all other IVDs are assessed in Australia adequately scrutinizes quality, safety and performance, and ultimately that the TGA will make an appropriate decision as to whether or not the benefits outweigh the risks of making an IVD available to the Australian population. Ellume believes that:

- There is not a sound reason for the Excluded Purposes Specification to be remade in October 2020 when it is due to be automatically repealed.
- There should be no prohibition on IVD Sponsors being able to make an ARTG entry application to the TGA for any IVD. The TGA will assess, on a case-by-case basis through mandatory application audit the safety and performance of tests and ultimately whether the benefits of having the self-test IVD available to the Australian public outweigh the risks. This is the mechanism by which the availability of all IVDs are decided and hence the Therapeutic Goods (Excluded purposes) Specification 2010, amended 2014 is redundant and serves only to restrict the potential availability of life-saving IVDs.
- There are some infectious diseases for which the ability to perform self-testing would be of greater benefit than others. The disease must be reasonably common, highly infectious such that there is a significant risk to either the individual, the community or both and there is a specific treatment available and/or preventive measures are easily administered.
- When considering benefit versus risk the TGA should ensure risks and benefits to both the individual and the Australian public are taken into account as was assessed when the first self-test HIV IVD was included on the ARTG.

- In the case of infectious disease self-tests the benefits/risk analysis would take into consideration the benefits as they apply to the community primarily and the benefits as they relate to the individual secondarily.
- In the case of consumer genetic and serious disease self-tests the benefits/risk analysis would primarily take into consideration the risks as they apply to the individual and much less so as they relate to the community (converse situation to infectious disease self-tests).

Consultation Questions & Responses

1. SHOULD SELF-TESTS FOR OTHER INFECTIOUS DISEASES BE ALLOWED?

1a) Considering the experience with HIV self-testing, should self-tests for other infectious diseases be supplied and used in Australia subject to appropriate risk mitigation strategies?

Yes.

Ellume considers self-tests that have been evaluated and approved by the TGA as capable of offering significant benefit compared to the risks for individuals and the broader Australian population, should be legally supplied in Australia. Given that there has been success with HIV testing then it would stand that testing should be extended to other infectious diseases.

The example given of influenza testing is pertinent. Influenza is a disease with a significant burden on morbidity and for some of the population who are more at risk of severe disease there is a mortality associated with influenza infection.

Reasons justifying the value of allowing access to TGA regulated self-tests for infectious diseases are listed below.

- *Regulated self-tests can deliver appropriate performance and safety in the context of favourable benefits versus risk profiles.*
  The probability and severity of risks associated with self-tests would be key considerations of the TGA assessment. It is expected that tests which do not achieve acceptable performance and safety standards relative to the benefits they would provide would not be approved for inclusion on the ARTG. Overall, TGA assessment would ensure that available self-tests deliver acceptable benefits versus risks profiles.

- *Regulated self-tests can increase testing which in turn can reduce transmission.*
  Regulated self-tests can promote testing by individuals that would not have been otherwise tested. This includes individuals who are not comfortable accessing current health services or do not have ready access to health services. Evidence collected from HIV self-testing in Australia reported that self-testing was responsible for an increased rate of testing for HIV and a reduced number of undiagnosed cases [1].
  Considering the example of influenza detection IVDs, the ability to diagnose influenza infection early and accurately at home would have a beneficial effect on community burden. Patients including those in remote communities or some who would be reluctant to seek medical care would be able to perform self-testing at home. There would need to be mechanisms in place for the patient to access health care in the event of a positive result (e.g. telemedicine) and education provided to the patient with regards to preventive measures to restrict the spread of the disease (e.g. through product labelling).
  In addition, the risk of an influenza pandemic is certainly another good reason to have the ability to diagnose the disease at home. In the event of a pandemic, patients would be able to

diagnose themselves at home, instigate preventive measures (such as self-quarantine, hand-washing etc) and in the case of patients at high-risk of severe disease (such as children, pregnant women, the elderly, those with extensive co-morbidities) being able to present to their GP with a diagnosis to obtain antiviral treatment early in the time course of their disease.

- *Regulation of self-tests ensures consumer safety.*
  There is an increasing trend for consumers to utilize the exemption in the Therapeutic Goods (Medical Device) Regulations 2002 for importation of self-tests for personal use and avoidance of the Excluded Purposes Specification. This trend is likely to continue growing and without regulatory oversight can lead to the use of self-tests that do not meet the TGA's performance and safety standards. Regulated self-test IVDs provide a trusted and viable alternative to those currently self-testing using tests ordered via the internet.

- *Self-tests facilitate early and effective responses to reduce burden on healthcare services.*
  Self-testing for infectious diseases may allow for early testing and for healthcare services to be employed when necessary. For example, viral infections such as influenza which have seasonal peaks can lead to overwhelming demand on healthcare services particularly Emergency Departments (EDs) and general practitioners (GPs). The demands on EDs and GPs during these seasonal peaks could be reduced if reliable self-testing devices for influenza could be legally supplied in Australia, allowing consumers with flu-like symptoms to be tested at home before deciding whether to seek medical treatment.

  Self-tests can also support rapid and accurate intervention decisions which can reduce the severity of a disease and in turn reduce the burden on healthcare services as well as reduce absenteeism. For example, rapid diagnosis of influenza can facilitate the effective use of antiviral therapy, reduce inappropriate use of antibiotics and also minimise the likelihood of hospitalisations due to influenza.

- *Data capture from self-tests can promote accurate and timely health surveillance.*
  Interventions and their impacts can only be evaluated with use of an effective means of data capture. Self-tests can facilitate more widespread testing and collection of data for health surveillance which can be used to inform decisions for effective distribution of the nation's anti-viral therapy stockpiles.

It is noted that on page 8, dot-point 3 the following statement is made in relation to risk mitigations being put in place to ensure benefits outweigh risks.

'Mitigations could include ensuring……that the sensitivity and specificity of the test is suitable to minimise the risk of false negative and false positive results'

Care must be taken to review the sensitivity and specificity of the test in the context of the risk versus benefit equation. For all IVDs the default should not be to a certain minimum sensitivity or specificity but rather should take into account the following:

- risks of false negatives and false positives (risk being a combination of likelihood of false results as determined by sensitivity and specificity, and impact of those false results taking into account risk mitigations designed into the IVD product and associated service offering), and should,
- also consider those risks in the context of the degree of benefits to the individual and the overall Australian population.

For example, in some cases a sensitivity of 85% may be sufficient to support a favourable benefits / risk analysis and in other cases a sensitivity of 95% may be required. As no IVD has perfect sensitivity and specificity there will always be a certain percentage of users that will receive a false result. In that respect in the case of infectious disease, an epidemiological modelling exercise can be very helpful in quantifying benefits (e.g. number of deaths avoided, number of hospitalisations avoided, etc) to put the residual risks of an infectious disease IVD into context hence allowing an appropriate final decision by the TGA on allowing ARTG entry. It is recommended that the TGA has access to epidemiological modelling experts to assist with this assessment or that the TGA requires developers to submit evidence to support the benefits of the test.

1 b) Are there any tests for particular infectious diseases that should not be available as a self-test? Please provide reasons why not.

No.

Ellume proposes that no particular self-tests should be prohibited from being submitted to the TGA for mandatory audit. Whether the self-test IVD is then made available in Australia can only be decided on a case-by-case basis by the TGA with the input from specialists and subject-matter-experts to assess the relative benefits versus the risks posed by making the self-test IVD available to the Australian public. When assessing risks and benefits it is important that risks and benefits to both the individual and to the broader Australian public are considered. In some cases, a self-test IVD may not present significant benefits to the individual however may introduce quite significant benefits to the Australian public (e.g. in reducing the spread of an infectious disease through self-quarantine and also early and appropriate treatment to limit viral burden/shedding therefore greatly reducing the burden of disease on the Australian healthcare system).

However, there are some diseases for which the ability to perform self-testing would be of greater benefit than others. The disease must be reasonably common, highly infectious such that there is a significant risk to either the individual, the community or both and that there is a specific treatment available and/or preventive measures are easily administered. In addition, having the correct diagnosis is important such that the incorrect treatment could be detrimental to the patient or community. In addition, the sampling required for the test needs to be taken into consideration – it must be easily performed and accessible for the lay person and must not cause further harm to the patient. The ability to detect certain diseases may be limited by the ability for a lay person to perform the sampling correctly.

1c) Do you have any additional suggestions on how potential risks to consumers could be mitigated if self-tests for other infectious diseases were allowed to be supplied in Australia?

Yes.

The main mitigations concentrate on ensuring that, as much as possible, a user will receive a test error output rather than a false result in the event of misuse or due to a test being faulty. Additionally, any risk control measures that facilitate education of the user and their Healthcare

Professional (HCP) and easy access by consumers to a HCP and support (technical as well as counselling) are highly desirable.

Various suggestions for reducing potential risks to consumers are listed below:

- To ensure that appropriate samples are used it is recommended that automatic checks are incorporated into self-test products. E.g. A design feature to detect the presence of human sample to confirm adequate/correct sample collection and/or sample loading.
- In many cases the reagents used in IVD assays are biological in nature and therefore robustness to environmental conditions (temperature, humidity), whilst a desirable attribute and to be considered when selecting reagents through the design and development process, cannot always be guaranteed. As self-tests may be exposed to conditions that exceed intended storage conditions it is recommended that a self-test automatically verify the integrity of key reagents and provide feedback to users if the self-test is compromised and block use of the test.
- To avoid the risk of misuse it is essential that self-tests are based on a user-driven design process. It is suggested that the TGA's assessment of a self-test product include evaluation of how human factors have informed the design and development of the product.
    - To validate the usability of a self-test with lay users it should be required that usability conclusions are based on data from summative human factors testing.
    - To validate the understanding of intended users of key communication concepts (including appropriate self-selection), label comprehension studies should be completed.
    - User environment(s) should be well considered for design requirements for the operation of a self-test IVD. Self-test IVDs may be used in environments that are quite different and more challenging than those encountered even in POC locations. Some examples include the following aspects of operating the IVD:
        - Surrounded by the noise and distractions of a busy household/job site
        - Operation of the IVD under vibration (e.g. as experienced in a mobile vehicle)
        - Operation of the the IVD at high altitudes
        - Potential contamination from household agents (e.g. hand creams, detergents, water, etc)
        - Designed to withstand dropping (e.g. mishandling when unwrapping components)
- In case a user experiences issues completing a self-test or would like to report a safety concern it is recommended that users can access a customer support helpline.
- Design should facilitate connectivity to HCPs and labelling should include clear messaging with respect to follow-up with a HCP.
- To promote correct operation by lay users it is suggested that the user interface is intuitive and that instructions for use are provided in multiple formats to cater for different ways in which users prefer to process information – digital step-by-step instructions and an instruction video delivered via an App, for example.
- Performance claims must be based on clinical performance evaluations undertaken in the intended user population (lay users in the actual or simulated intended environment).
- Design with in-built fail-safe mechanisms, for example:
    - Blocking use of expired tests;
    - Blocking use of used tests;
    - Interlocked critical user steps. I.e. cannot move onto next step until current one is completed satisfactorily.

- Digital result output rather than relying on the user to visually identify presence or absence of a coloured line(s).
- Novel sample collection devices designed to minimise harm from self-collection and to maximise quality sample collection.

Other considerations:

Maximizing/enhancing benefits

Whilst design features of the self-test IVDs can greatly mitigate risks and are very important, thoughtful design of a self-test IVD will also take into consideration how the potential benefits of the self-test IVD can be enhanced. For example:

- The opportunity to educate the Australian public on the disease state that the self-test is detecting through relevant information supplied in labelling. A good example is the promotion of influenza vaccination and self-isolation as two of the most important ways to limit spread of Flu and loss of life and productivity during an influenza season.
- Designing the IVD with connectivity so that results can be captured for the purposes of timely disease surveillance and/or to facilitate integration of test results into Electronic Health Records (with appropriate privacy regulations in place). This is particularly important for notifiable infectious disease results. Positive results brought to a health care professional will be notified however there may be some who do not seek medical assistance. Tests that are linked digitally to data storage will have the advantage of being accessible by public health authorities. This may have implications on which tests are approved for use in the Australian market.

Healthcare Professional Awareness

As self-tests for various diseases and conditions become available on the Australian market for the first time, the benefits can only be realised if HCPs are alert to the tests that are available and are familiar with the clinical performance and limitations of each. HCPs will then be prepared to provide appropriate advice when individuals present with the self-test IVD result – avoiding unnecessary retests. In that regard, it would be beneficial to include a HCP awareness communication programme pre-launch and during the initial stages of commercialisation as a condition of approval. This would aim to provide HCPs with all the information about the IVD they would normally receive in a POC product insert.

There may be benefit in including the Sponsor's ARTG entry identifier on the outer packaging of self-test IVDs (as required for medicines) so that the Australian public, and the HCPs they interact with, have confidence that the test they have purchased and used has undergone rigorous TGA assessment.

2. SHOULD DIRECT TO CONSUMER GENETIC TESTS BE ALLOWED?

2a) Should Direct to Consumer Genetic Tests be permitted in Australia (following evaluation by the TGA) to provide consumers with an alternative to overseas testing which has not been evaluated by the TGA for its quality and performance?

In principle Ellume proposes that no particular self-tests should be prohibited from being submitted to the TGA for mandatory audit. Whether the self-test IVD is then made available in Australia can only be decided on a case-by-case basis by the TGA with the input from specialists and subject-matter-experts to assess the relative benefits versus the risks posed by making the self-test IVD available to the Australian public. In the case of consumer genetic self-tests the benefits/risk analysis would primarily take into consideration the benefits and risks as they apply to the individual and much less so as they relate to the community (converse situation to infectious disease self-tests).

Whilst it is suggested that no particular self-tests should be prohibited from being submitted to the TGA for mandatory audit, it is recognised that significant resources are spent by both the developer and the TGA in preparing and reviewing technical files submitted, hence it would be beneficial for the TGA to release guidance documents describing criteria to consider when determining potential benefits and potential risks for a specific disease/condition. These will assist the developer in determining whether there is merit in submitting the self-test for mandatory application audit and should avoid wasting the developer's and the TGA's time.

Ellume does have some reservations regarding the use of self-testing for genetic diseases and this also qualifies for serious diseases (next section). The quality of the tests and their accuracy would need to be heavily scrutinized. The potential for harm from inaccurate tests could be great. As outlined in the discussion argument the background or scientific basis for these tests is more poorly understood by the general public and thus counselling by medical professionals or genetic counsellors is of great help in interpreting results. Counselling should be mandatory prior to undertaking these tests – there may be benefits in regards to lifestyle modifications (in the cases of diabetes or cardiovascular disease) and preparedness if using the tests but there is also the extra stress and concern that the patient may now experience, particularly if they are not counselled appropriately. There is also great concern regarding private health information being made available to third parties such as insurance companies and the effect this may have on a patient's ability to obtain insurance in the future.

Given the stringent regulation of marketing and advertising by the TGA there is also concern that patients may still access overseas testing (easier to find on internet searches, etc) with the same issues outlined in the background information regarding unregulated tests.

It is noted that genetic tests are performed for certain hereditary diseases (breast cancer as an example) by medical practitioners in Australia (in the case of a positive family member) however they are not currently used as a general screening tool. The reasons for this should be explored further - If medical practitioners are not particularly using these tests (What are the validity of these tests? Is this a supply issue within Australia also?) should the consumer be given the opportunity to use these?

2b) Are there any particular genetic tests that should not be available as a self-test? Please provides reasons why not.

As already stated, in principle Ellume proposes that no particular self-tests should be prohibited from being submitted to the TGA for mandatory audit. Whether the self-test IVD is then made available in Australia can only be decided on a case-by-case basis by the TGA with the input from specialists and subject-matter-experts to assess the relative benefits versus the risks posed by making the self-test IVD available to the Australian public. In the case of consumer genetic self-tests the benefits/risk analysis would primarily take into consideration the benefits and risks as they apply to the individual and much less so as they relate to the community (converse situation to infectious disease self-tests).

2c) Do you have any suggestions on how potential risks to consumers could be mitigated if genetic self-tests were allowed to be supplied in Australia?

All of the mitigations suggested for infectious disease self-test IVDs would also apply to these genetic self-tests. The tests would need to be highly regulated with good clinical evidence to support the use of the tests. In addition, counselling should probably be mandatory and as a suggestion, the tests could only be made available on prescription after visiting the GP.

3. SHOULD SELF-TESTS FOR OTHER SERIOUS DISEASES OR CONDITIONS BE ALLOWED?

3a) Should self-tests for serious diseases be able to be supplied in Australia following evaluation by the TGA to determine their safety and performance?

In principle, Ellume proposes that no particular self-tests should be prohibited from being submitted to the TGA for mandatory audit. Whether the self-test IVD is then made available in Australia can only be decided on a case-by-case basis by the TGA with the input from specialists and subject-matter-experts to assess the relative benefits versus the risks posed by making the self-test IVD available to the Australian public. In the case of self-tests for serious disease the benefits/risk analysis would primarily take into consideration the benefits and risks as they apply to the individual and much less so as they relate to the community (converse situation to infectious disease self-tests).

Whilst it is suggested that no particular self-tests should be prohibited from being submitted to the TGA for mandatory audit, it is recognised that significant resources are spent by both the developer and the TGA in preparing and reviewing technical files submitted, hence it would be beneficial for the TGA to release guidance documents describing criteria to consider when determining potential benefits and potential risks for a specific disease/condition. These will assist the developer in determining whether there is merit in submitting the self-test for mandatory application audit and would avoid wasting the developer's and the TGA's time.

As above with genetic testing, counselling would be required before testing for diseases such as cancer or diabetes to make sure that the patient understands the implications of results from such a test. The accuracy of these tests would need to be heavily regulated as the potential for harm from a false result could be great. Education of both the patient and health care professionals with regards to what test results mean, when to use them, when to seek medical care are required. Interpretation of some tests for serious disease (such as myocardial infarction) can be difficult to interpret even for physicians and dependent on multiple factors as to how to manage the result.

However, the potential for benefit from early diagnosis (such as in cancer or diabetes) could be great.

3b) Are there any particular tests for serious diseases that should not be available as a self-test? Please provide reasons why not.

As already stated, in principle Ellume proposes that no particular self-tests should be prohibited from being submitted to the TGA for mandatory audit. Whether the self-test IVD is then made available in Australia can only be decided on a case-by-case basis by the TGA with the input from specialists and subject-matter-experts to assess the relative benefits versus the risks posed by making the self-test IVD available to the Australian public. In the case of self-tests for serious diseases the benefits/risk analysis would primarily take into consideration the benefits and risks as they apply to the individual and much less so as they relate to the community (converse situation to infectious disease self-tests).

3c) Do you have any suggestions on how potential risks to consumers could be mitigated if self-tests for serious diseases were allowed to be supplied in Australia?

All of the mitigations suggested for infectious disease self-test IVDs would also apply to these self-tests for serious diseases. In addition, counselling should probably be mandatory and as a suggestion, the tests could only be made available on prescription after visiting the GP.

References

1. Australian Federation of AIDS Organisations 2019, AFAO Welcome HIV self-testing device, Australian Federation of AIDS Organisations, viewed 19th November 2019, <https://www.afao.org.au/media-release/afao-welcome-hiv-self-testing-device/>