EUROPEAN COMMISSION

View in the context of the Performance Evaluation Consultation Procedure (PECP)

Expert panels on medical devices and *in vitro* diagnostic devices (Expamed)

Contents

Scope of this expert view

This scientific view reflects the opinion of independent experts (MDR Article 106.1) on the performance evaluation report (PER) of the manufacturer. The advice is provided in the context of the performance evaluation consultation procedure (PECP), which is an additional element of conformity assessment by notified bodies for specific high-risk *in vitro* diagnostic devices (IVDR Article 48.6).

When making its conformity assessment decision, the notified body is obliged to give due consideration to the opinions expressed in the scientific view of the expert panel, where applicable (Annex IX, Section 4.9 or, as applicable, Annex X, Section 3, point (j)).

For class D devices, the notified body must provide a full justification in the case of divergent views between the notified body and the experts. This justification shall be included in the notification to the competent authority (IVDR Article 50; mechanism for scrutiny of class D devices).

1 ADMINISTRATIVE INFORMATION

Date of reception of the dossier	24/11/2021
Notified Body number	0123
Internal PECP dossier #	IVD-2021-000011
***In vitro* diagnostic medical device**	This assay is intended to be used as an aid in the diagnosis of *Trypanosoma cruzi* infection and as a screening test to prevent transmission of *T. cruzi* to recipients of blood, blood components, cells, tissue and organs.

2 INFORMATION PROVIDED BY THE NOTIFIED BODY

When consulting the IVD expert panel, the notified body provided the below information on the type of device in accordance with MDCG 2021-22.

Intended purpose (P)		
P1	what is detected and/or measured *please specify the analyte(s) or marker(s), e.g. SARS-CoV-2 spike protein, Kel1 (K)*	Antibodies to Trypanosoma cruzi
P2	function of the device *e.g. diagnosis, aid to diagnosis, monitoring, determining the infectious load, tissue typing etc*	• Aid in the diagnosis of T. cruzi infection • As a screening test to prevent transmission of T. cruzi to recipients of blood, blood components, cells, tissues, and organs
P3	the specific disorder, condition or risk factor of interest that it is intended to detect, define or differentiate *e.g. hepatitis C infection, exposure to SARS-CoV-2, risk of HIV transmission in blood transfusion etc.*	Chagas disease or American Trypanosomiasis
P4	whether it is automated or not	Automated
P5	whether it is qualitative, semi-quantitative or quantitative	Qualitative
P6	type of specimen(s) *e.g. whole blood, serum, saliva etc*	• Human Serum and Plasma • Serum and Plasma specimens from Cadaveric (non-heart beating) donors

P7	where applicable, the testing population *e.g. persons with specific health conditions, persons with specific symptoms, children in a certain age range*	• Volunteer blood donors of whole blood and blood components • Organ donors when specimens are obtained while the donor's heart is still beating • Cadaveric (non-heart-beating) donors • Individuals suspected to have T. cruzi infection
P8	intended user	For Laboratory Professional Use Only
Technology (T)		
T1	principle of the assay method or principles of operation of the instrument *e.g. real-time PCR, qualitative PCR, digital PCR, sandwich immunoassay, competitive immunoassay, immunoturbidimetric assay etc.*	Chemiluminescent microparticle immunoassay (CMIA) technology

3 VIEWS OF THE EXPERT PANEL

3.1 Information on panel and sub-group

Date of views	26/01/2022
Expert panel name	IVD expert panel
Sub-group of expert panel	IVD sub-group 2021-11

3.2 Summary of expert panel views

Device description:

The device is an assay in an automated system used for the qualitative detection of antibodies to *Trypanosoma cruzi* (the causative agent of Chagas disease) in human serum and plasma, including specimens collected post-mortem (non-heart-beating). The assay is intended to be used as an aid in the diagnosis of *T. cruzi* infection and as a screening test to prevent transmission of *T. cruzi* to recipients of blood, blood components, cells, tissue and organs. The technology on which is based is an automated two-step immunoassay for the qualitative detection of antibodies to *T. cruzi* in human serum and plasma using chemiluminescent microparticle immunoassay (CMIA) technology.

Views on the performance evaluation report:

a) The scientific validity report.

The scientific validity report supports the use of antibodies to *T. cruzi* as a marker to aid in the

diagnosis of *T. cruzi* (Chagas) infection and in screening to prevent the transmission of *T. cruzi* to recipients of blood, blood components, cells, tissues, and organs as per the requirements of the *In Vitro* Diagnostic Device Regulation (EU) 2017/746 (IVDR).

A comprehensive literature review focusses on different aspects of the assay performance, including reference from Europe where following reports of *T. cruzi* positive cases emerged in early 2000 in people of South America origin. No description on the European epidemiology is provided and thus the rational for using this diagnostic and blood screening test in the EU setting is undefined.

b) The analytical performance report.

The manufacturer has determined the analytical performance parameters based on the intended purpose of the device. The manufacturer demonstrates that the test shows acceptable performance and it is suitable for its intended purpose with sufficient accuracy and precision. The analytical performance report gives a short overview of the analytical performance studies with reference to IVDR requirements. The analytical studies were performed based on guidance from CLSI EP05-A2.

The manufacturer has evaluated all the parameters described in the Performance Evaluation Report, which support the claims and performance data included in the device instructions for use. The manufacturer has compiled comprehensive evidence on the analytical performance of the assay in relation to different parameters, such as cut-off, analytical sensitivity, analytical specificity, trueness, precision, specimen type, specimen storage, sample and reagent onboard storage and calibration stability.

c) The clinical performance report.

Clinical performance parameters were determined based on the intended purpose of the device. Overall analyses sensitivity and specificity are high and acceptable for the intended purpose of the test as diagnostic and screening assay.

The clinical performance of the assay was demonstrated through internal studies using specimens from random blood donors, specimens from a hospitalized/diagnostic population, pre-selected anti-*T cruzi* positive specimens, and by comparison to an on market assay approved for the same analyte and intended uses. The clinical performance demonstrates that the assay has state of the art performance and is suitable for use as an aid in the diagnosis of *T. cruzi* (Chagas) infection and as a screening test to prevent the transmission of *T. cruzi* to recipients of blood, blood components, cells, tissues, and organs.

Given the expected low prevalence of positive samples in the EU setting, the risk of false positivity increases. If not observed in clinical studies, such data should come from post market experience. Post market data are not included in the PER since the manufacturer did not recognise the need. This position is not acceptable since post market and risk management plans are essential to evaluate the benefits and risks of implementing the screening assays in European countries.

Views on the specific aspects of the performance evaluation report:

The manufacturer has provided clinical evidence based on scientific validity, analytical performance, and clinical performance data. Literature search strategy and the literature protocol are acceptable;

however, the number of articles used for the literature report should be higher.

The appropriateness of the technology to reach the intended purpose of the device and the manufacturer's claims about the performance and safety of the device is in agreement with IVDR. The use of this technology assay is fit for purpose.

Views on the adequacy of the approach chosen by the manufacturer:

The overall risk associated with the assay is comparable to the state of the art, and the overall medical benefits of the product outweigh and justify the overall residual risk acceptability. The approach chosen by the manufacturer has been evaluated and is adequate to ensure performance and safety of the device.

Overall conclusions and recommendations on the performance evaluation report:

In summary, overall, the experts were positive about the content and extent of the submitted dossier. There was however a concern regarding the general use of the test in European settings. Also, a number of recommendations for improvement of the assay evaluation are summarized in section 3.5.

3.3 Views on the specific reports included in the performance evaluation report (PER)

(IVDR, Annex XIII, Section 1.3.2, first paragraph)

Views of the expert panel on the performance evaluation report of the manufacturer (PER)
1. Expert views on the scientific validity report[1]
The scientific validity report supports the use of antibodies to *T. cruzi* as a marker to aid in the diagnosis of *T. cruzi* (Chagas) infection and in screening to prevent the transmission of *T. cruzi* to recipients of blood, blood components, cells, tissues, and organs as per the requirements of the *In Vitro* Diagnostic Device Regulation (EU) 2017/746 (IVDR). The manufacturer has carried out a review of existing literature and available study data to collect evidence to establish the use of antibodies to *T. cruzi* marker as stated above. The manufacturer uses an acceptable literature search strategy to ensure both positive and negative research studies. Besides, they are included articles from different geographical locations. The literature review of the peer-reviewed scientific literature uses keywords relevant for the subject and comparison to one other device measuring the same marker. The search literature covers the period from 2015 to 2020 in order to obtain the most current information on Chagas disease, the diagnosis of Chagas, and screening for Chagas in blood donors and cell, tissue and organ donors. Data which support the safety, effectiveness, and scientific validity of the assay. Collectively, the evidence supports that the assay is consistent with the generally acknowledged state of the art for its intended purpose. Additionally, the medical value and public health benefit outweigh the potential risks of the product.

[1] Annex XIII, Section 1.2.1 of Regulation (EU) 2017/746 - Demonstration of the scientific validity

However, the scientific validity report does not include the literature based on European data. They omitted them because they did not include it in search of the literature. In the background of the disease state that "Chagas Disease/American Trypanosomiasis Chagas disease is found mainly in the 21 continental Latin American countries where *T. cruzi* is endemic. However, due to population mobility, urbanization and immigration Chagas disease is also found in Canada, the United States of America, European, African, Eastern Mediterranean and Western Pacific countries. An estimated 6 million to 7 million people globally, mostly in Latin America, are infected with *T. cruzi* (Chagas disease). The clinical manifestations of Chagas disease lead to approximately 10,000 deaths every year.

The manufacturer misses the opportunity to focus on European situation where non-vector transmission is the only one possible. In Europe Chagas disease is an emerging infectious disease in several European countries receiving Latin American immigrants. It is highly prevalent among Bolivian migrants across different European countries. Chagas disease is the most common infective cause of cardiomyopathy and it is observed in 11–19% of patients in Europe. Public health policies are needed to avoid non-vectorial transmission of Chagas disease in Europe (Spinello A et al, 2017, *European Journal of Internal Medicine*). Manufacturer should also explain the ways of transmission of the disease in Instruction for Use where situation in Europe is not mentioned.

2. Expert views on the analytical performance report[2]

The manufacturer has determined the analytical performance parameters based on the intended purpose of the device. The manufacturer demonstrates that the test shows acceptable performance and it is suitable for its intended purpose with sufficient accuracy and precision. Common specifications (CS) for this assay do not exist. Specifications are described in the Analytical Performance Requirements and Clinical Performance Requirements of the manufacturer reports.

The manufacturer has evaluated all the parameters described in the Performance Evaluation Report, which support the claims and performance data included in the device instructions for use. The manufacturer has compiled comprehensive evidence on the analytical performance of the assay in relation to different parameters, such as cut-off, analytical sensitivity, analytical specificity, trueness, precision, specimen type, specimen storage, sample and reagent onboard storage and calibration stability.

In regard to parameters that were omitted, such the limit of detection, measuring range, linearity and limit of quantitation, studies were not performed, the manufacturer arguing that they are not applicable as the assay is qualitative with result interpretations of non-reactive or reactive. Since the reported result is not quantitative in nature, studies to determine analytical performance for limit of quantification, measuring range, and linearity were not conducted.

The manufacturer evaluates the suitability of the most common sample collection tubes type, obtaining that 14 different blood collection tubes were acceptable for this assay.

The studies conducted to evaluate the effect of specimen handling under various storage conditions and time periods when testing serum and plasma specimens show acceptable results, and samples can be stored 2 to 8°C for up to 14 days, 30°C for up to 7 days, up to 6 freeze/thaw cycles and also at -20°C or colder for up to 12 months. The specimen storage is acceptable if, when comparing samples

[2] Annex XIII, Section 1.2.2 of Regulation (EU) 2017/746 - Demonstration of the analytical performance

stored at 2 to 8°C for ≥ 7 days, samples stored at 15 to 30°C for ≥ 3 days, samples stored at –20°C or colder for ≥ 4 weeks, or samples subjected to ≥ 6 freeze/thaw cycles to samples tested within 24 hours of draw.

The sample on board storage is acceptable if, when comparing samples stored on board the instrument for a minimum of 3 hours to samples tested immediately upon loading on the instrument. Samples can be stored on board up to 10 hours in primary tubes or up to 3 hours in sample cups.

The accuracy and precision of the assay is considered acceptable and was checked in different settings: within-run, between-day, and between-instrument. The reproducibility was demonstrated using different instruments and reagent, calibrator, and control lots on at least 5 different days.

The analytical sensitivity of assay was determined using the WHO 1st International Standard for Chagas (anti-*Trypanosoma cruzi* II) antibody in human plasma NIBSC code: 09/186, 2011 and WHO 1st International Standard for Chagas (anti-*Trypanosoma cruzi* I) antibody in Human Plasma NIBSC code: 09/188, 2011. The analytical sensitivity was 15.6 mIU/mL for the WHO 09/186 standard and 6.6 mIU/mL for the WHO 09/188 standard.

The analytical specificity was carried out evaluating the susceptibility of the assay to potentially interfering endogenous substances, such as conjugated and unconjugated bilirubin, hemoglobin, triglycerides, and total protein. The results show that the assay is considered not susceptible to the potentially endogenous interfering substances. Potential interfering substances (exogenous) were tested in samples with high levels of biotin (> 3510 ng/mL). Trueness presented as % agreement has been calculated from clinical specificity (blood donor and diagnostic) and clinical sensitivity data.

The manufacturer also has demonstrated the performance of the assay when used to test specimens from patients with medical conditions unrelated to *Trypanosoma cruzi* infection. Also, the assay is not susceptible to within-assay sample carryover.

The cut-off is set to demonstrate optimal discrimination between true positive and true negative results. Manufacturer presented cut-off studies which were analysed by performing receiver-operating characteristic (ROC) analysis on data from internal clinical studies. The ROC analysis allows for the simultaneous evaluation of negative and positive populations and the effect that various cut-off values have on assay specificity and sensitivity. Cut-off multiplier factor varied from 0.7 to 1.2.

Other additional studies include reagent on board storage, and the results show that reagents can be stored for 15 days on board and a calibration can be stored on the system for 14 days.

Assay performance was tested also on cadaveric samples. The results show that all parameters tested are considered acceptable.

No seroconversion panels were evaluated. There appear to be commercially available panels that could have been evaluated, but very few. On the other hand, 25 parasite-containing samples were evaluated, as required by the draft CS, which can thus be considered acceptable to challenge the assay's claimed suitability for blood screening. Since this is an IgG test, perhaps it could have been compared to a test that detects total antibodies and thus detect a possible IgM phase earlier during seroconversion.

In conclusion, the analytical performance data demonstrates the state of the art performance of the assay and demonstrates that the assay is suitable for use as an aid in the diagnosis of *T. cruzi* (Chagas) infection and as a screening test to prevent the transmission of *T. cruzi* to recipients of

blood, blood components, cells, tissues, and organs.

3. Expert views on the clinical performance report[3]

Clinical performance parameters were determined based on the intended purpose of the device. The manufacturer's clinical performance report provides sufficient data for assessment of clinical performance. Some parameters were assessed in accordance to the draft of CS.

The clinical sensitivity was considered acceptable if the clinical sensitivity point estimate was greater than or equal to the lower limit of a two-sided 95% confidence interval of an expected sensitivity estimate of 100% when testing a confirmed positive population. For the sample size used in this study (421), the lower limit of the two-sided 95% CI for an expected sensitivity estimate of 100% was 99.13%.

The clinical specificity of the donor population was considered acceptable if the specificity point estimate was ≥ 99.5% and the initial reactive rate point estimate was ≤ 0.29%. The overall % agreement was 99.98% with a 95% CI of 99.89%-100.00%. The initial reactive rate (not reactive on retest) was 0.02% with a 95% CI of 0.00%-0.11%. The clinical specificity was 100.00% with a 95% CI of 99.93%-100.00%.

The clinical specificity of the diagnostic population was considered acceptable if the specificity point estimate was greater than or equal to the lower limit of the two-sided 95% confidence interval of the assay on the same population of diagnostic specimens. The overall % agreement was 99.50% with a 95% CI of 97.25%-99.99%. The initial reactive rate (not reactive on retest) was 0.00% with a 95% CI of 0.00%-1.83%. The clinical specificity was 100.00% with a 95% CI of 98.17%-100.00%.

There were cross-reacting samples (*T. brucei*, Plasmodium spp., *Leishmania* spp. samples) positive in the Chagas assay with a corresponding slightly (about 5%) lower specificity. In this context, diagnostic specificity was assessed with over 5000 samples in Europe only. This is in line with the requirements for a CE-marked test. However, it would have been interesting to see how the specificity performed in countries where the above mentioned cross-reacting samples are endemic, to see to what extent this cross-reactivity may influence the diagnostic specificity.

The manufacturer has evaluated the positive predictive value, negative predictive value and likelihood ratio from clinical specificity (blood donor and diagnostic) and clinical sensitivity data. The results provide the PPV, NPV, LR+, and LR- of the assay when used to test a combined population of blood donors, diagnostic specimens, and preselected positive specimens.

Positive Predictive Value: 421/421 = 100.00%; 95% CI: [99.13%, 100.00%]
Negative Predictive Value: 5280/5280 = 100.00%; 95% CI: [99.93%, 100.00%]
Likelihood Ratio + : Infinity
Likelihood Ratio - : 0.00

The clinical performance of the assay was demonstrated through internal studies using specimens from random blood donors, specimens from a hospitalized/diagnostic population, pre-selected anti-*T cruzi* positive specimens, and by comparison to an on market assay approved for the same analyte and intended uses. The clinical performance demonstrates that the assay has state of the art performance and is suitable for use as an aid in the diagnosis of *T. cruzi* (Chagas) infection and as a

[3] Annex XIII, Section 1.2.3 of Regulation (EU) 2017/746 - Demonstration of the clinical performance

screening test to prevent the transmission of *T. cruzi* to recipients of blood, blood components, cells, tissues, and organs.

3.4 Views on specific assessment aspects of the performance evaluation report (PER)

(IVDR, Annex XIII, Section 1.3.2, second paragraph)

Views of the expert panel on the specific aspects included in the performance evaluation report of the manufacturer (PER)
1. The justification for the approach taken to gather the clinical evidence
The manufacturer has provided clinical evidence based on scientific validity, analytical performance, and clinical performance data. The manufacturer has provided a Performance Evaluation Plan (PEP) to define the requirements and activities to determine the clinical evidence that supports the intended use in order to demonstrate conformity with the relevant general safety and performance requirements. However, the manufacturer has not developed more clinical studies that provide evidence as other sources of clinical performance data, and only has compared the assay to only one on-market assay approved for the same analyte and intended uses, which belongs to the own manufacturer. The manufacturer's approach to gather the clinical evidence is sufficient for screening of blood donors. However, the chosen clinical evidence approach is not adequate to demonstrate that the device will achieve the intended clinical benefits and safety, when used as diagnostic assay. Manufacturer should include more diagnostic samples from people with cardiomyopathy that is most common presentation of chronic infection. Manufacturer did not perform studies on pregnant women that are also important to prove benefit of the assay to prevent congenital infections.
2. The literature search methodology, protocol and report
In the Scientific Validity Report the manufacturer has developed a suitable literature search methodology and has compiled a lot of publications (105) to support the scientific validity of the assay. However, selection of the literature was evaluated first by the title and abstract of the article, and after, if selected, the literature was then evaluated by the full article content. After applying inclusion and exclusion criteria, the manufacturer has excluded 104 articles and only has included 1 article for the report. In conclusion, although the literature search strategy and the literature protocol are acceptable, the number of articles used for the literature report should be higher. Besides, the literature search methodology is appropriate for the endemic situations but for non-endemic European situation. IFU and Scientific Validity Report do not include articles based on European data, although they exist and European epidemiological situation is not described. The protocol of the performance studies was not designed in light of European perspective. Reports did not include data from Europe in a way that European non-endemic situation would be reflected.

3. The technology on which the device is based, the intended purpose of the device and any claims made about the device's performance or safety

Current diagnostic approaches for Chagas disease fall into three primary areas: parasitological methods, serological detection of antibodies to parasite antigens, and molecular detection of the parasite. Serological detection of antibodies to *T. cruzi* antigens is the most common method to evaluate for chronic infection, since after acute infection the parasites migrate preferentially into muscle tissue of the heart and gastrointestinal tract and may no longer be found in the bloodstream, and it is the methodology recommended according to PAHO and WHO guidelines.

The technology on which the assay is based consists in an automated two-step immunoassay for the qualitative detection of antibodies to *T. cruzi*, in human serum and plasma using chemiluminescent microparticle immunoassay (CMIA) technology. *T. cruzi* recombinant antigen coated paramagnetic microparticles and assay diluent, are combined and incubated; the antibodies to *T cruzi* present in the sample bind to the recombinant antigen coated microparticles, and then anti-human IgG acridinium-labeled conjugate is added to create a reaction mixture. The resulting chemiluminescent reaction is measured as relative light units (RLU), existing a direct relationship between the amount of antibodies to *T. cruzi* in the sample and the RLU detected by the system optics.

Due to this technology, reported sensitivities and specificities have been between 99%-100%. Nevertheless, there is the question whether a single test on an automated immunoassay platform like this devices is sufficient to diagnose and confirm Chagas disease.

In conclusion, technology is appropriate to reach the intended purpose of the assay and the manufacturer's claims about the performance and safety of the device are appropriate. Assay has no innovative aspects but the technology on which the assay is based proved to give good results in non-European settings for particulate parasite but also with other microorganisms like *T. gondii* that that can also be transmitted in similar way as *T. cruzi* and causes chronic infection with lack of specific symptoms.

The intended purpose of the device is the qualitative detection of antibodies to *Trypanosoma cruzi*. The assay is intended to be used as an aid in the diagnosis of *T. cruzi* infection and as a screening test to prevent transmission of *T. cruzi* to recipients of blood, blood components, cells, tissue and organs. The device is intended to screen individual human donors, including volunteer donors of whole blood and blood components, and other living donors for the presence of antibodies to *Trypanosoma cruzi*. Also, the device is intended for use in testing serum and plasma specimens to screen organ donors when specimens are obtained while the donor's heart is still beating, and in testing serum specimens to screen cadaveric (non-heart-beating) donors.

Finally, the general safety and performance characteristics are based on the intended purpose of the device and will be maintained throughout the product lifecycle.

The manufacturer has made a Post Market Performance Follow-up (PMPF) Plan in order to confirm the safety, performance and scientific validity throughout the expected lifetime of the device, to ensure the continued acceptability of the benefit-risk ratio and to detect emerging risks on the basis of actual evidence. Risk assessment will be conducted over the lifecycle of the device per the risk management plan. Risk analysis will be performed and include user needs, product requirements and associated performance criteria as potential sources of hazards or hazardous situations.

The manufacturer has defined the risk acceptability criteria in the risk management plan and residual

risk is assessed against the risk acceptability criteria. A benefit risk assessment has been performed to assess whether the benefits of the device outweigh the risk. The manufacturer assures that this is documented in the risk management report. However, the manufacturer has not included the risk management report in the dossier to check it.

The manufacturer has carefully evaluated the benefits of using the assay as a screening and/or diagnostic assay against any potential risks to donors, patient, operator and environment or property. Any risks were eliminated or reduced as far as possible based on design features incorporated into the assay, protection and/or labelling.

In summary, the overall risk associated with the assay is comparable to the state of the art, and the overall medical benefits of the product outweigh and justify the overall residual risk acceptability.

4. Acceptability of clinical evidence (clinical data and performance evaluation results) against state of the art in medicine

The assay is intended to be used as an IVD assay. State of the Art should be assessed for the assays with the same intended purpose as this device.

The evidence included and summarized in this report supports the use of the antibodies to *Trypanosoma cruzi* (*T. cruzi*) in clinical applications as an aid in the diagnosis of *T. cruzi* infection and as a screening test to prevent the transmission of *T. cruzi* to recipients of blood, blood components, cells tissues, and organs.

The evidence provided in this report includes a comparison of the test to another device measuring the same analyte/marker which belongs to the own manufacturer, raising the question of related design. Besides, European situation is not appreciated so it is hard to validate sufficiency of the clinical evidence for the intended clinical benefits and safety to be achieved in European situation.

Findings from the scientific peer-reviewed literature establishing acceptable analytical and clinical performance, in general supports that the assay is consistent with the generally acknowledged state of the art for its intended purpose.

3.5 Overall conclusions and recommendations

Overall conclusions and recommendations on the performance evaluation report

The assay has been developed for the qualitative detection of antibodies of *Trypanosoma cruzi* when Chagas disease or American Trypanosomiasis is suspected.

The assay is intended to be used as an aid in the diagnosis of *T cruzi* infection and as a screening test to prevent transmission of *T. cruzi* to recipients of blood, blood components, cells, tissue and organs. It is automated, qualitative assay, for laboratory professional use only.

According to IFU assay can be used with following samples: Human Serum and Plasma, Serum and Plasma specimens from Cadaveric (non-heart beating) donors, Volunteer blood donors of whole blood and blood components, Organ donors when specimens are obtained while the donor's heart is still beating, Cadaveric (non-heart-beating) donors, individuals suspected to have *T. cruzi* infection.

The manufacturer has compiled comprehensive evidence on the clinical performance of the assay to support its intended use. The assay's analyte is well documented within scientific literature. The draft Common Specifications have been addressed by the manufacturer though not yet binding.

Overall, it was concluded that the device achieves the intended clinical benefit and safety when used as intended, although the general opinion of the reviewers was that this assay to analyse donors has probably limited benefit in the EU setting.

An estimated 75 million individuals live in areas that put them at risk for having Chagas disease. Given the high cost of the complications of chronic Chagas disease, screening programs have been shown to be cost-effective, even in non-endemic settings with a medium prevalence. In Europe, the prevalence is very low, so the benefit is moderate.

Generally, the experts were positive about the content and extent of the submitted dossier. However, there are several recommendations for evaluation of the assay and for improvement of the dossier.

Recommendations:

- The absence of any discussion on the usability of the test in EU settings is of some concern. Scientific background to use the test in Europe is not described well, even if the test is used only on subsets of donors, e.g. originating from *T. cruzi* endemic regions. The lack of European references is obvious especially in IFU. The manufacturer is recommended to provide a comprehensive discussion on this issue.
- Because of the problem with cross reactivity and low prevalence of the disease in Europe, the IFU should include warning that all results of the test should be compared with epidemiological data and clinical picture.
- Manufacturer should specify the intended use of the assay (e.g. target groups) in European low prevalent settings. Good described intended use and rational behind it (e.g. use of the assay in pregnant women that spend many years in rural part of South America to protect offspring) would be beneficial for end user of the assay.
- Manufacturer should define which laboratories may use the assay. Professional use only definition in IFU is much broader than definition in product overview "*The Chagas assay is intended to be used by hospital and commercial reference laboratories requiring routine testing for Trypanosoma cruzi and by blood banks and plasma centers screening blood for Trypanosoma cruzi. The Chagas assay is for laboratory professional use only*." If it is decided to keep the IFU definition, additional warnings should be included or explanations in which settings assay can be used and what kind of competences is needed to be able to perform the test.
- The manufacturer has made a Post Market Performance Follow-up (PMPF) Plan to ensure the continued acceptability of the benefit-risk ratio and to detect emerging risks on the basis of actual evidence. However, the manufacturer has not included the risk management report in the dossier, and the absence of post market data is not acceptable. Given the expected low prevalence of positive samples in the EU setting, the risk of false positivity increases. If not observed in clinical studies, such data could come from post market

experience. It is recommended to request post market and risk management plans from the manufacturer to better evaluate the benefits and risks of implementing the screening assays in EU countries.

- The manufacturer only has compared the assay to one other platform, which belongs to the own manufacturer, potentially reflecting similar assay design. Comparative data against other platforms which are used in the market are encouraged, since the clinical performance may differ from analytical performance with respect to sensitivity and specificity, depending on internal and external factors. Benchmarking against other assays of competitors is important to gain a more robust and objective insight into the relative clinical performance. Such data may originate either from comparative studies, ring trials and external quality assessment and literature.

3.6 Stakeholder information, where available

Relevant information provided by stakeholders, if applicable[4]
Has the Secretariat provided information from stakeholders?
☐ YES ☒ NO
If yes, please summarise the information and how it was taken into account.

3.7 Divergent positions in case no consensus can be reached

In case no consensus on the views can be achieved[5], please summarise divergent positions
There were no divergent views.

Please indicate how many of the experts of the panel had divergent views

[4] According to Article 106.4 of Regulation (EU) 2017/745, expert panels shall take into account relevant information provided by stakeholders including patients' organisations and healthcare professionals when preparing their scientific opinions.

[5] According to Article 106.12 of Regulation (EU) 2017/745, when adopting its scientific opinion, the members of the expert panels shall use their best endeavour to reach a consensus. If consensus cannot be reached, the expert panels shall decide by a majority of their members, and the scientific opinion shall mention the divergent positions and the grounds on which they are based.