

**FIRST INVITATION TO SUBMIT AN EXPRESSION OF INTEREST
FOR THE WHO EVALUATION OF
IN VITRO DIAGNOSTIC DEVICES FOR THE DETECTION OF
ANTIBODIES TO YELLOW FEVER VIRUS**

DEADLINE FOR SUBMISSION: 01/06/2021



1. Introduction

The Immunization Analysis and Insights, Surveillance and Risk Assessment Team of the World Health Organization (“**WHO**”) invites manufacturers of in vitro diagnostic devices (**IVDs**), being either enzyme immunoassays (**EIAs**) and/or rapid diagnostic tests (**RDts**) to detect IgG and/or IgM antibodies to Yellow Fever virus to submit an expression of interest for product evaluation in accordance with this Invitation to Submit an Expression of Interest (this “Invitation”). Manufacturers of IVDs meeting the minimum requirements set forth in Invitation are invited to respond in the form required by WHO and to submit their products, as and when directed by WHO, for evaluation and testing under the WHO Evaluation Programme of IVDs for the Detection of Antibodies to Yellow Fever virus (the “**Evaluation Programme**”).

For consideration under the Evaluation Programme, manufacturers must complete, in its entirety, the form in Annex 1 and must return the completed and signed form together with the required documentation to WHO by the deadline stated on the first page of this Invitation. Any missing or unclear information, or failure to submit by the deadline, may be grounds for WHO to exclude a product for consideration for this first invitation. Such Expression of Interest will not be binding on either WHO or the manufacturer but should be received by WHO by 01/06/2021 at the latest.

Participation in the Evaluation Programme means acceptance by the applicant of the terms and conditions of this Invitation (including the annexes).

WHO reserves the right to cancel this Invitation or not to select any application at any time, without thereby incurring any liability or any obligation to inform the applicants of the grounds for WHO’s action.

Any information considered by interested entities as confidential must be clearly marked as “confidential”.

Participation in the Evaluation Programme, publication by WHO of the testing results and/or inclusion of the IVDs in WHO’s list of evaluated products may not be used by the manufacturers and suppliers concerned for commercial or promotional purposes. Under no circumstances is a manufacturer or supplier authorized to refer to WHO, the manufacturers’ or suppliers’ participation in the Evaluation Programme, the publication of the testing results by WHO and/or inclusion of the IVDs in WHO’s list of evaluated products, in any statement or material of an advertising or promotional nature, press release and/or similar public statement and/or other material aimed at promoting the manufacturer or supplier and/or its products.

Publication of the testing results and/or inclusion in WHO’s list of evaluated products does not furthermore in any way imply an endorsement, certification, warranty of fitness or recommendation by WHO of any company or product for any purpose and does not imply preference over products of a similar nature that are not mentioned. WHO will not accept any liability or responsibility whatsoever for any injury, death, loss, damage, or other prejudice of any kind that may arise as a result of, or in connection with the procurement, distribution and use of any product, as to which WHO has published the testing results and/or which is included on the aforementioned list.

2. Intended Audience

This Invitation is only intended for manufacturers¹ of IVDs detecting antibodies to Yellow Fever virus. Submissions by distributors/agents and/or re-branders will not be eligible for participation in the Evaluation Programme.

3. Background

Yellow fever is a severe disease transmitted by a mosquito borne virus which can cause major outbreaks in unvaccinated population with significant morbidity and mortality with major social and economic disruption. Since its symptoms can resemble those of multiple other diseases, including hepatitis and other hemorrhagic fevers like Ebola viral disease, accurate diagnostic testing is essential for distinguishing Yellow fever from other diseases. Besides the nucleic acid testing (NAT) the serology analysis for specific anti- Yellow fever IgM is so far is the only diagnostic possibility to confirm a case of a suspected Yellow fever case as recommended by the WHO. The availability of accurate, reliable tests for Yellow fever specific IgM will contribute to Yellow fever virus surveillance and will facilitate the detection of outbreaks and the assessment of risks. These in turn will aid timely Yellow fever virus outbreak responses and planning of preventive mass vaccination campaign and routine immunization activities.

4. Product Specifications for assessment under the Evaluation Programme

This Invitation is limited to products that meet the following specifications and requirements:

1. If the product is an EIA, it should comply with the following minimum product specifications:
 - Assay is preformed 96 well microtitre plate format*
 - Assay can be performed within one working day (i.e. within 8 hours, with no overnight incubations required)
 - Kit contains all necessary reagents and buffers to perform testing (supplemental reagent kits or ancillary kits/reagents are acceptable)
 - Kit contains positive and negative controls
 - 96 well formatted plates can be washed with standard microtitre plate washer
 - The assay readout is optical density which can be measured with standard EIA microtitre plate readers (e.g. absorbance 405 nm or 450 nm)
 - Kit storage at 4-8°C
 - Minimum shelf life of 12 months

*NOTE: If you have an EIA with a different format, you may still submit an Expression of Interest. However, WHO reserves the right to prioritize products that meet all requirements outlined above.

¹ "Manufacturer" means any natural or legal person or legal entity with responsibility for the design and/or manufacture of a medical device with the intention of making the finished medical device available for use, under his name; whether or not such a medical device is designed and/or manufactured by that person himself or on his behalf by a third party(ies).

2. If the product is an RDT, it should comply with the following minimum product specifications:
 - Presence of a control line
 - Able to detect antibodies or antigens from all geographically and genetically diverse YF virus strains
 - No more than 3 operator steps
 - Time to result < 45 minutes

*NOTE: If you have an RDT with a different format, you may still submit an Expression of Interest. However, WHO reserves the right to prioritize products that meet all requirements outlined above.

3. If and when the application is considered by WHO to meet the product specifications set out in this Invitation, WHO will request via email that the relevant manufacturer: (i) submit to WHO a duly signed Confidentiality Agreement (as per the form attached in Annex 2); (ii) submit to the documentation requested in Annex 3; (iii) accept the terms and conditions of WHO performance evaluation according to a protocol communicated by WHO at this stage, (iv) submit to the WHO reference laboratory sufficient material to complete the WHO performance evaluation (see below), and (v) consent to the publication of the evaluation and testing results by WHO, subject to the terms of the Confidentiality Agreement.
4. The manufacturer shall agree to the free supply and delivery of 382 tests derived from 2 independent lots² and related supplies (including instrumentation, quality control material and any other material specific to the testing of this product, if applicable) to the WHO evaluating laboratory designated by WHO. The manufacturer will take responsibility for ensuring all supplies arrive in the evaluating laboratory by a given deadline (to be communicated by WHO) in a condition suitable for assessment. If the deadline cannot be met, there can be no guarantee that the evaluation will proceed.]. The manufacturer may provide training if deemed necessary, before the start of any testing if this is part of routine service delivery.

5. The Evaluation Process

The process of the Evaluation Programme consists of the following steps:

- Preliminary Stage: Receipt of the Expressions of Interest in response to this Invitation and relevant instructions for use;
- Stage 1: WHO review/screening of Expressions of Interest received from manufacturers in response to the Invitation, including assessment against the product specifications and other requirements noted in Section 4 of this Invitation. Each applicant will be notified in writing by WHO (by e-mail) whether their application has been rejected or selected. If the product is deemed by WHO to meet these requirements, the manufacturer will be

² For the purposes of WHO performance evaluation, a lot is defined as “The amount of material that is uniform in its properties and has been produced in one process or series of processes. The material can be either starting material, intermediate material or finished product.” Furthermore, the two lots must be sourced from a representative production run and not produced especially for the purposes of the WHO performance evaluation

requested by WHO in writing to submit all the documentation referenced in Annexes 2 and 3 within WHO-established timeframes. It is recommended that this technical documentation be prepared in advance; however, it should only be submitted upon specific request from WHO.

- Stage 2: Desktop assessment of quality management system (QMS) certification and associated audit reports;
- Stage 3: Desktop assessment of verification/validation studies for specific performance claims as well as product stability;
- Stage 4: Performance evaluation of the submitted product at a laboratory designated by WHO;

WHO may decide, at any time and at its sole discretion, to exclude an application or a product from the Evaluation Programme. WHO reserves the right to freely decide on the acceptance or not of the IVD, and WHO will not in any circumstances reimburse any costs or expenses associated with the submission of an application or product (and associated equipment/accessories) in response to this Invitation (including possible complementary information and documentation), nor any costs associated with possible further discussions and/or possible submission of a more detailed information.

6. Outcome of the assessment process

Once WHO is satisfied that the assessment process under the Evaluation Programme is complete for the relevant IVD and that such IVD meets the Evaluation Programme's requirements, the product [the product bearing a specific product name, product code(s) and regulatory version, as manufactured at the specific manufacturing site(s) inspected] will be included in the WHO list of evaluated EIAs/RDTs. The list will be published on the WHO website. The manufacturer will receive a letter of evaluation from WHO informing it of the outcome of the overall WHO evaluation assessment of the IVD.

The WHO list of evaluated EIAs/RDTs may be used as a reference to provide guidance to interested United Nations Agencies (including WHO) and national health authorities of WHO Member States in their procurement decisions. In addition, the list of evaluated EIAs/RDTs will be used for any potential procurement process for Yellow Fever virus EIAs/RDTs issued by UNICEF supporting GAVI for procurement and distribution of Yellow Fever diagnostics.

7. Checklist

7.1 The only action necessary for a manufacturer interested in participating in the Evaluation Programme is to send the details of the products considered for submission by completing, in its entirety, the form in Annex 1 and returning the completed and signed form together with the supplementary information described in Annex 1 (relevant instructions for use) to WHO by the deadline stated on the first page of this EOI. Participation in the Evaluation Programme means acceptance of the terms and conditions of this EOI (including the annexes).

WHO may, in its sole discretion, request at any stage, further information from the manufacturer

to clarify or revise one or more aspects (more detailed description of the materials, etc.). A deadline for a response will be provided, and must be adhered to for continuation of the evaluation

7.2 Only upon specific request via email from WHO, the following should be submitted:

- Signature and submission of a Confidentiality Agreement (as per the attached sample in Annex 2);
- Documentation supporting the performance, and the effectiveness of the manufacturer's quality management system, as described in Annex 3.

NOTE: Submission of this documentation must comply to the formatting described in Annex 3. WHO reserves the right to reject documentation received in other formats.

- Product and associated supplies and instrumentation. Two separate production lots (with different lot numbers and different expiry dates) in quantities defined by WHO, according to the following definition of a lot: "The amount of material that is uniform in its properties and has been produced in one process or series of processes. The material can be either starting material, intermediate material or finished product." Furthermore, lots must be sourced from a representative production run and not produced especially for the purpose of this Evaluation Programme.

NOTE: All products will be stored according to the manufacturer's stated storage conditions from time of receipt until actual testing occurs (the evaluation laboratory designated by WHO will determine the order in which testing will be conducted).

No evaluation will take place unless the manufacturer has fulfilled the above conditions by the dates set by WHO and in accordance with WHO's instructions.

8. Additional documents to be read in conjunction with this Invitation

ANNEX 1	EXPRESSION OF INTEREST SUBMISSION FORM
ANNEX 2	WHO STANDARD CONFIDENTIALITY AGREEMENT
ANNEX 3	INSTRUCTIONS FOR SUBMISSION OF DOCUMENTARY EVIDENCE

9. Further Information

Any enquiries associated with this Invitation and the Evaluation Programme should be directed to Dr Mick Mulders (muldersm@who.int).

ANNEX 1
EXPRESSION OF INTEREST SUBMISSION FORM
IVDs TO DETECT YELLOW FEVER VIRUS ANTIBODY

PLEASE COMPLETE A SEPARATE FORM FOR EACH PRODUCT YOU ARE SUBMITTING FOR ASSESSMENT

CONTACT INFORMATION

Company details

Please indicate address of each site if more than one site in the manufacture of the tests to be assessed.

Name of manufacturer		
Address	Street Name and No	
	City	
	Postcode	Country
Postal Address	Street Name and No	
	City	
	Postcode	
Telephone		
E-mail		
Web address		
Address/s where test is assembled i.e. from raw materials through to finished product		
Address where quality control testing is performed prior to release to customers.		
Name of parent or legal organization if relevant		

Authorized contacts for the company

Name of FIRST authorized contact		
Authorized contact	Department	
Postal Address		
	Street Name and No	
	City	
	Postcode	
Authorized Contact Telephone	Fixed Line:	Mobile
Authorized Contact E-mail		
Name of SECOND authorized contact		
Authorized contact	Department	
Postal Address		
	Street Name and No	
	City	
	Postcode	
Authorized Contact Telephone	Fixed Line:	Mobile
Authorized Contact E-mail		

PRODUCT INFORMATION

Product name	
Product code(s)/Catalogue number(s) and number of tests per kit	
Format of EIA	<input type="checkbox"/> Microtitre plate <input type="checkbox"/> Bead <input type="checkbox"/> Other <input type="checkbox"/> Not applicable
Format of RDT	<input type="checkbox"/> Lateral Flow <input type="checkbox"/> Other
Level of automation	<input type="checkbox"/> Fully (undiluted specimen added and results calculated) <input type="checkbox"/> Partially (all reagent addition etc) <input type="checkbox"/> Not automated
Sensitivity (with 95% confidence intervals) N.B. If confidence intervals not available, please provide absolute numbers tested.	
Specificity (with 95% confidence intervals) N.B. If confidence intervals not available, please provide absolute numbers tested.	
Quality control	<input type="checkbox"/> Provided with the kit <input type="checkbox"/> Available supplementally <input type="checkbox"/> For lateral flow devices, control line
Result output	<input type="checkbox"/> Qualitative <input type="checkbox"/> Quantitative
Specimen type	<input type="checkbox"/> Serum

	<input type="checkbox"/> Plasma (If yes, please provide details of validated anticoagulants) <input type="checkbox"/> Capillary Blood <input type="checkbox"/> Venous blood (If yes, please provide details of validated anticoagulants)
Shelf Life Stability (time and temperature range)	
Transport conditions (temperature and any other relevant information)	
In-use stability (Please note if all reagents have the same in-use storage or provide details of all differences)	<input type="checkbox"/>
On instrument stability (if applicable) (time and temperature range)	<input type="checkbox"/>
Operating conditions (temperature and humidity range)	
Incubation temperatures (deg C)	
Time to a result (minutes)	
Reagent reconstitution required. If yes, please provide details.	
List of items required but not provided, including any equipment	

Patient identification capability Please describe if there is the ability to track electronic identification of the patient either manually or by bar code.	
Training requirements	
Target list price USD	
Quality systems certification (ISO 13585, ISO 9001, MDSAP etc)	
Any other information that you feel is important for WHO to know	

ATTACHMENTS

Please provide a copy of the current Instructions for Use (IFU) for each device you are submitting. If these are not provided with the product to the end customer in paper format, please provide information on how these can be obtained.

SUBMISSION OF THE EOI FORM AND ATTACHMENTS

One electronic copy of the completed EOI Submission Form and the above listed attachments must be emailed before 01 06 2021 to:

Dr Mick Mulders, Global VPD Laboratory Networks, IVB/IAI/Surveillance and Risk Assessment, World Health Organization, 20 Avenue Appia, CH-1211 Geneva 27, Switzerland

Disclaimer

This Request for Expression of Interest is not a solicitation and replying to it does not guarantee that a vendor will be invited to any solicitation by WHO. No further details of the planned solicitation will be made available to vendors prior to the issuance of solicitation documents. In the event of a solicitation for the subject matter described herein, any Request for Proposal and any subsequent purchase order or contract will be issued in accordance with WHO's rules and procedures. Any and all costs and expenses incurred in relation to, or ensuing from, the submission of an Expression of Interest will exclusively be borne by the applicant. The application and selection process set forth in this document will not be subject to claims for financial compensation of any kind whatsoever.

WHO is acting in good faith by issuing this Request for Expression of Interest, however, this Request for Expression of Interest does not entail any commitment on the part of WHO, either financial or otherwise. WHO reserves the right to send solicitation documents to vendors identified by WHO through means other than this Request for Expression of Interest; reject any or all Expression(s) of Interest, without incurring any obligation to inform the affected applicant(s) of that decision or the grounds thereof; and/or change or cancel the procurement process at any time, including during the Request for Expression of Interest or formal solicitation processes.

AUTHORISED REPRESENTATIVE DECLARATION

The undersigned key authorized representative of the company makes the following declarations on behalf of the company and, in signing this form, declares that he/she has the power and authority to bind the Manufacturer and to establish working agreement with WHO.

I declare that

- I am authorized to represent the manufacturer specified in this EOI Submission form (the "Manufacturer") for the purposes of an assessment allowing eligibility for procurement by WHO of the product specified in this EOI Submission form (the "Product").
- The Instructions for Use have been submitted as attachment/s.
- All the information provided in this form and its attachment/s is current, complete and correct.

Name of key authorized representative of the Company: _____

Signature: _____

Date: _____

ANNEX 2
WHO STANDARD CONFIDENTIALITY AGREEMENT

SAMPLE

NOT FOR SIGNATURE

Between

.....having its principal offices at

.....(hereinafter referred to as "the Company");

and

The World Health Organization, Avenue Appia, 1211 Geneva 27, Switzerland, (hereinafter referred to as "WHO").

The Company has developed (a) Yellow Fever virus IVD, known under the trademark WHO is interested in having the Product(s) evaluated by the WHO Expanded Programme on Immunization ("EPI") (hereinafter referred to as the *"WHO Evaluation Programme of IVDs for the Detection of Antibodies to Yellow Fever Virus"*) so that such Product(s) may be used as a reference by WHO, other UN Agencies and national health authorities for future procurement of these molecular assays.

Therefore, the Parties have agreed as follows:

1. The Company shall disclose and furnish to WHO the Information and sufficient quantities of the Product(s) in order to enable WHO to assess the Information and arrange for such evaluations of the Product(s), as WHO may determine are reasonably necessary to assess the performance of the Product(s) and (its)(their) suitability for use by any laboratory conducting testing for Yellow Fever virus. At the conclusion of the testing and evaluation process, WHO will report the results thereof to the Company and, at the Company's request and cost, return or destroy the Information and any unused quantities of the Product(s). For the avoidance of doubt, "Information" as used herein does not include the data and information resulting from the testing and evaluation process. Such data and information shall belong to WHO (subject always, however, to the other provisions of this Agreement).

2. If and to the extent the Information has been marked by the Company as "Confidential", WHO shall treat such Information as confidential and proprietary for a period of 5 years after disclosure to it. In this connection, WHO shall take all reasonable measures to ensure that the Information in question is not used for any purpose other than the aforementioned evaluation and testing activities and is not disclosed or provided to any person who is not bound by similar obligations of confidentiality and restrictions on use as contained in this Agreement.
3. WHO shall not be bound by any obligation of confidentiality or restriction on use to the extent it is clearly able to demonstrate that any part of the Information:
 - a) was known to WHO prior to any disclosure by the Company to WHO; or
 - b) was in the public domain at the time of disclosure by the Company to WHO; or
 - c) becomes part of the public domain through no fault of WHO; or
 - d) becomes available to WHO from a third party not in breach of any legal obligations of confidentiality to the Company.
4. Except as provided in paragraph 6 below, each Party furthermore undertakes to abide by similar obligations of confidentiality and restrictions on use as contained in paragraphs 2 and 3 above with regard to the testing results and reports generated as a result of this Agreement (regardless of whether or not such results and reports have been marked as "confidential").
5. The provision of Product(s), Information, testing results and reports hereunder shall not in itself be construed as conveying rights under any patents or other intellectual property which either Party may have or may hereafter obtain.
6. Subject to the protection of each Party's confidential information and the provisions of this paragraph 6, testing results generated under this Agreement may be published by either Party. In order to avoid prejudicing confidential information of the other Party, the submitting Party will transmit to the other Party for its review, the material intended to be published at least 60 (sixty) working days before a proposed publication is submitted to any editor, publisher, referee or meeting organizer. In the absence of an objection by the other Party within that 60-day period concerning prejudice to its confidential information, and provided that all other conditions of this paragraph 6 have been met, the publication may proceed.

In connection with the foregoing, it is understood and agreed that notwithstanding any other provisions in this Agreement, WHO shall be entitled to evaluate and publish the evaluation results, and to exclusively control this evaluation and the content of the aforesaid publication, provided that in order to avoid prejudice to the Company's confidential Information disclosed to WHO pursuant to paragraphs 1 and 2 above, WHO shall submit any proposed publication to the Company for review in accordance with the provisions of this paragraph 6. For the avoidance of any doubt, the Company shall only be entitled to object to a proposed publication if and to the extent it contains any confidential Information of the Company, and not on the grounds that the Company is not satisfied with the evaluation results and/or does not agree with WHO's evaluation thereof. Similarly, the Company shall not proceed to the publication of the testing results without having first submitted its proposed publication to WHO for review in accordance with the provisions of this paragraph 6, it being agreed furthermore that the Company's publication (or other public disclosure) shall be placed under embargo until WHO has been able to publish the testing results.

All publications of the results of any evaluation and testing activities carried out under this Agreement shall include the following statement:

"This evaluation was carried out as part of the WHO Evaluation Programme of IVDs for the Detection of Antibodies to Yellow Fever Virus".

Other than as provided hereinbefore, neither Party shall, in any statement or material of an advertising or promotional nature, refer to the relationship of the Parties under this Agreement or to the relationship of the other Party to the Product(s).

7. The Company shall provide the Information and sufficient quantities of the Product(s) to WHO, or WHO's designee(s), free of charge. In the event that WHO, or its designee(s), do not receive the Information and/or sufficient quantities of the Product(s), WHO shall be under no obligation to arrange for the performance of any evaluation or testing activities in relation to the Product(s).
8. The Company hereby furthermore confirms that it has taken good note of, agrees with and to the extent applicable, shall abide by, the provisions contained in the document, entitled "First Invitation to Submit an Expression of Interest for *WHO Evaluation Programme of IVDs for the Detection of Antibodies to Yellow Fever Virus*".

9. Any dispute relating to the interpretation or application of this Agreement shall, unless amicably settled, be subject to conciliation. In the event of failure of the latter, the dispute shall be settled by arbitration. The arbitration shall be conducted in accordance with the modalities to be agreed upon by the Parties or, in the absence of agreement, with the rules of arbitration of the International Chamber of Commerce. The Parties shall accept the arbitral award as final.

On behalf of WHO:

Signature:

Name:

Title:

Date:

On behalf of the Company:

Signature:

Name:

Title:

Date:

ANNEX 3

INSTRUCTIONS FOR SUBMISSION OF DOCUMENTARY EVIDENCE

WHO EVALUATION OF IN VITRO DIAGNOSTIC DEVICES FOR THE DETECTION OF ANTIBODIES TO YELLOW FEVER VIRUS

Table of Contents

1.	The Submission	3
2.	Submission Format	3
3.	Product Information	4
4.	Product Performance Specifications and Associated Validation and Verification Studies	5
5.	Labelling	10
6.	Quality Management System	11

1. The Submission

1. Submitting Documentary Evidence

The documentary evidence to be submitted is described in this Annex. It includes the evidence to substantiate specific claims of product performance, product stability, that a suitable set of instructions are available with the product for the user, as well as the existence of a relevant quality management system.

2. When to Submit the Documentary Evidence

You will be invited to submit this information if WHO has favorably reviewed your Expression of Interest, according to the criteria described in Section 4 (*“Product Specifications for Entry in the Evaluation Programme”*) of the *First invitation to Submit Expression of Interest for WHO Evaluation Programme of IVDs for the Detection of Antibodies to Yellow Fever Virus*. In such cases, you will be informed by email to submit this and other information.

DO NOT SUBMIT THIS INFORMATION UNTIL YOU HAVE RECEIVED AN EMAIL INFORMING YOU TO SO.

3. Submission Clarity

Manufacturers should make every effort to ensure that their documentary evidence is clear and well-organized to help make the WHO review procedure as efficient as possible.

Submission Requirements – Important guidance on documents to be submitted
All items in each section below are required to be submitted as part of the submission (or, when indicated, as applicable).

Where information does not exist, e.g. certain studies, please provide a justification.

Note: All information submitted in the documentary evidence is CONFIDENTIAL.

2. Submission Format

1. Submission Format

Submit one electronic copy of the entire submission.

2. Layout and Order

WHO encourages the following format for the required documentation:

- Use the format *1 of 2, 2 of 2*, etc.
- Clearly divide the submission into sections, as prescribed in this document, and number all pages of each section so that they are easily identified.
- Include a table of contents.
- The physical pages of the submission and the page numbers should correspond.
- Ensure that there are appropriately named tab identifiers. The names should link directly with the sections of the dossier as outlined in this document.
- Standard A4 paper is used for all submissions. Text and tables should be prepared using margins that allow the document to be printed on A4 paper. The left-hand margin should be sufficiently large that information is not obscured through binding.
- Font sizes for text and tables are of a style and size that are large enough to be easily legible, even after photocopying or when provided electronically. Fonts smaller than 12

points should be avoided whenever possible, except in tables and footnotes where a font size of 10 points is acceptable.

3. Electronic copy requirements

- PDF is the primary file format used for the electronic copy. However, you must not include any PDF that requires a password to open it.
- When the source document (e.g. Microsoft Word document), please consider when using Adobe® plug-ins to create PDF files and/or capture or display data, there is a risk that information may not display correctly because reviewers may not have access to certain plug-ins to review content being displayed by a plug-in.
- All PDF files should be created directly from the source documents whenever feasible rather than creating them by scanning. PDF documents produced by scanning paper documents are far inferior to those produced directly from the source document, such as a Microsoft Word document, and, thus, should be avoided if at all possible. Scanned documents, particularly tables and graphs, are more difficult to read. For any scanned document, we highly recommend that you perform optical character recognition (OCR) so that the text is searchable. Check to see that the content has been correctly converted by: (1) highlighting an area of text and (2) searching for a word or phrase. If the word or phrase is not returned in the search, then the OCR did not recognize the text. WHO recognizes that use of OCR may not be feasible in some cases for documents with figures and images. Hence, there may be cases in which it is appropriate to have scanned documents in the electronic copy.

4. Language and Units of Measurement

For the purposes of this evaluation, the following requirements are highly recommended:

- Submit all documents presented in the dossier in English (unless other arrangements have been made with WHO prior to submission of the dossier).
- Any translations of documents must be carried out by a certified translator. Provide an official document attesting to the accuracy of the translation and details on the credentials of the translator. Provide both the original and the translated documents.
- All measurements units used must be expressed in the International System of Units (SI).

3. Product Information

1. Product description including variants (configurations) and accessories

The submission should include product descriptive information sufficient to allow the reviewer to understand the product and how it functions. The instructions for use may be used to provide some of this information. Provide the following information:

- The intended use of the IVD
- What the product detects (the measurand).
- The function of the product e.g., screening, monitoring, diagnostic or aid to diagnosis, surveillance).
- Whether the product is automated or manually operated.
- Whether the test is qualitative or quantitative.
- The type of specimen(s) required (e.g. serum, plasma, whole blood, etc.).
- If an EIA, whether the assay is in 96 well format or not (if not, please describe) or if an RDT, if the assay is a lateral flow format or not (if not, please describe).
- The intended testing population (e.g. antenatal women, symptomatic

individuals, etc.).

- The intended setting of use (e.g. laboratory, point-of-care).
- A general description of the principle of the assay method or instrument principles of operation.
- For control material to be used with the assay, include a description of what they are, how they are expected to work, and where in the testing process they are used. If a control is commercially available, provide the supplier's name and catalogue number or another identifier.
- A description of the specimen collection and transport materials that are provided with the product or descriptions of specifications recommended for use.
- For instruments of automated assays: a description of the appropriate assay characteristics or dedicated assays.
- For automated assays: a description of the appropriate instrumentation characteristics or dedicated instrumentation.
- If applicable, a description of any software to be used with the product.
- If applicable, a description or complete list of the various configurations/variants of product that will be made available.
- A description of the accessories, and other products that are intended to be used in combination with the IVD but are not provided. Please give details regarding any specifications required associated with microplate readers (including wavelength/s necessary for reading the assay), and microplate washers, instrumentation for specimen and reagent distribution.

2. Product design - Formulation and composition

A description of the components of the assay (e.g., reagents, assay controls and calibrators), and, where appropriate, a description of the reactive ingredients of relevant components (e.g., antibodies, antigens).

Include a brief description of any capture antigens and antibodies used in the test, how they were designed and purified (e.g., are monoclonal antibodies used, are they manufactured in house or purchased commercially, what species they derive from, what epitope is targeted by the antibodies used in an assay, if commercial products, is there a certificate of analysis, etc.).

3. Product workflow

Briefly describe current specimen throughput capacity, total time required to perform the test (from clinical specimen collection to result), and number of tests that can be performed per instrument run and per day.

4. Product Performance Specifications and Associated Validation and Verification Studies

The manufacturer shall submit, where available, evidence of relevant investigations to support the intended use. For each study to be submitted, the following must be provided:

- Study description, study identifier, product identifier (for example, lot numbers), IFU version used, the date of initiation and the date of completion.
- A summary of the study findings including a conclusion that clarifies how the study objectives have been met; and
- The study protocol and full report. Where the following studies are not complete or not yet available, the manufacturer shall provide timelines for completion and submission to

WHO.

- Where the studies are not considered relevant based on the design of your assay, please provide a justification.

1. Precision of measurement

This section describes repeatability and reproducibility studies.

1.1. Repeatability

This section includes repeatability estimates and information about the studies used to estimate, as appropriate, within-run variability.

Provide the studies undertaken to establish within-run variability. Such studies should include the use of specimens that represent the full range of expected analyte (measurand) concentrations that can be measured by the product, as claimed by the manufacturer.

1.2. Reproducibility

This requirement contains reproducibility estimates and information about the studies used to estimate, as appropriate, variability between-days, runs, sites, lots, operators and instruments. Such variability is also known as intermediate precision.

Provide the studies used to establish intermediate precision as appropriate:

Include the use of specimens that represent the full range of expected analyte (measurand) concentrations that can be measured by the product, as claimed by the manufacturer.

2. Analytical sensitivity

This section includes detailed information about the study design and results to determine the analytical sensitivity of the IVD. Analytical sensitivity may be defined as limit of detection, limit of the blank or limit of quantification.

Provide the studies undertaken with available reference material. WHO requires each assay to be calibrated/tested against biological reference material when and where available and if relevant. Provide a description of specimen type and preparation including matrix, analyte (measurand) levels, and how levels were established, and the number of replicates tested at each concentration.

If this performance characteristic is not considered applicable, please provide a rationale for not providing the results of testing.

3. Analytical specificity

This section describes interference and cross-reactivity studies to determine the analytical specificity, defined as the ability of a measurement procedure to detect or measure only the analyte (measurand) to be detected, in the presence of other substances/agents in the specimen. Note that any related studies should be derived from a comprehensive risk assessment of the test and its intended setting of use. The choice of analytes should be directly linked to the outcomes of such a risk assessment.

3.1. Cross-Reactivity

Cross-reactivity should be evaluated by testing specimens from patients with antibodies to

other microorganisms which could potentially cause false positive results.
Please provide summary results in the table format and information related to the methods used to characterize these specimens as positive for the analytes listed.

Cross-Reactivity: Example table below for IgG or IgM assays

Disease/Infectious agent Positive Sera	Number of specimens N	Assay Equivocal or positive results	Cross- reactivity
Hepatitis C	10		
Dengue	10		
Zika virus	10		
TBE virus	5		
Malaria	10		
HIV	10		
EBV (acute infection)	10		
Hepatitis A (acute infection)	10		
.....		

3.2. Interfering Substances

The impact of potentially interfering substances must be evaluated. The evaluation is conducted to demonstrate that the potential interferents do not generate false positive results in known negative specimens, and do not lead to false negative results in known positive specimens.

Please provide summary results in the table format below.

Interfering Substances: Example table below for evaluation of interfering substances for the ability to generate **false positive results**:

Potential interfering substance	Concentration	Results (Detected X/3)
Haemoglobin		
Bilirubin		
Serum proteins		
Anti-nuclear antibodies		

Interfering Substances: Example table below for evaluation of interfering substances for the ability to generate **false negative results**.

Potential interfering substance	Concentration	Results (Detected X/3)
Haemoglobin		
Bilirubin		
Serum proteins		
HAMA		
Rheumatoid Factor		
HLA (for assays constructed using viral lysate, if cell line of human origin is used)		
Anti-nuclear antibodies		

3.3. Hook Effect:

If the potential exists for high titre positive clinical specimens which may lead to false negative results, please evaluate and establish at what titre the hook effect is observed.

If this potential does not exist, please provide a rationale for not testing for the presence of a hook effect.

3.4. Immunoglobulin class specificity:

You should evaluate the potential for human IgG to cross-react and therefore produce false positive results with your IgM assay (and vice versa for an IgG assay).

Please provide data or the rationale used to determine if cross-reactivity with IgG/IgM (as applicable) is a potential assay interferent.

4. Traceability of Calibrators and Control material

Please provide evidence that supports the metrological traceability of values assigned to calibrators and trueness control materials. This should include a description of all calibrators and trueness control materials associated with the system. OR a statement of why this category of study is not applicable to this case

NOTE: Precision control materials used during analytical studies to establish the reproducibility of a measurement procedure do not require the assessment of metrological traceability to a reference material or a reference method

5. Stability (excluding specimen stability)

This section describes claimed shelf life of the IVD in use stability and shipping stabilities. Information provided under this section must be consistent with the instructions for use and product labels provided within the submission.

5.1. Claimed Shelf Life

This section provides information on stability testing studies to support the claimed shelf life. Testing should be undertaken on at least three different lots manufactured under conditions that are equivalent to routine production conditions (these lots do not need to be consecutive lots).

The study protocol must specify acceptance criteria and testing intervals.

5.2. In-use Stability

This section provides information on the in-use stability for the IVD.

Provide the studies for each assay component (for example, EIA plate, lateral flow device, buffer vial, conjugate, substrate, acid).

- For each component, testing is required on a minimum of one lot.
- The studies should reflect actual routine use of the device (real or simulated). This would include open vial stability and/or, for automated instruments, on-board stability.
- Consideration should be given to multiple access of reagent bottles (opened several times during its use) as well as to different vial size, depending on the presentation in the final kit (e.g. where there may be a 5 mL buffer vial and a 10mL buffer vial, depending on number of tests), in-use stability must be performed on each vial configuration.
- The study protocol must specify acceptance criteria and testing intervals.
- In the case of automated instrumentation, if calibration stability is claimed, then supporting data should be included.

5.3. Shipping Stability

This section provides information on shipping stability studies.

- Provide the information identified in the introduction to Section 7, from studies of one lot to evaluate the tolerance of products to the anticipated shipping conditions.
- Shipping studies can be done under real and/or simulated conditions and should include variable shipping conditions such as extreme temperature (heat and/or cold), humidity, light and/or pressure.
- These studies must reflect the environmental conditions of the countries of supply. The information provided must include a justification for the anticipated conditions.
- The study protocol must specify acceptance criteria and testing intervals.
- If simulated conditions are used, the methods used must be identified.
- The results and conclusions must clearly demonstrate that the product will be effective at the end of its claimed shelf life after being subjected to the anticipated shipping conditions. As such, it is necessary that after the product has been subjected to the stressed conditions, that there is testing at the end of the claimed shelf life to demonstrate stability.

6. Clinical evidence (clinical or diagnostic sensitivity and specificity)

Clinical evaluation is the assessment and analysis of data generated from the clinical intended use of the product in order to verify the clinical safety and performance of the device. Clinical evidence is the combined information from the clinical data and its evaluation. A manufacturer must have clinical evidence to support any clinical claims. This will include claims for clinical or diagnostic sensitivity and specificity.

When assigning clinical truth for all specimens, optimally specimens obtained from patients with data demonstrating seroconversion should be used i.e. from patients with a pattern of only nucleic acid detectable for early bleeds with results of serial bleeds demonstrating the rise of both IgM and IgG antibodies. Acute and convalescent phase specimens should be chosen and ideally tested in parallel.

The specimens should ideally be collected from the intended use population and undertaken by user's representative of the intended user group.

Manufacturers should attempt to demonstrate performance against the different strains, if

possible, by using specimens sourced globally.

The specimens may be collected prospectively or retrospectively for each claimed type.

5. Labelling

The submission should contain a complete set of labelling associated with the product. This includes

- labels
- instructions for use (IFU)
- if applicable, the instrument manual
- any other instructional materials provided to the user

1. Labels

Include copies of all packaging labels for the assay. This includes:

- outer labels
- component labels

These labels must minimally include the following information:

- The product name and product identification number (product code/catalogue number)
- The name and contact details of the manufacturer, or an authorized representative of the manufacturer, on the outer package labels
- The name of the reagent/ingredient
- The expiry date
- An indication of any special storage and/or handling conditions that apply
- The warnings and precautions
- The lot/batch and/or serial number
- The information regarding particular product conditions such as product sterility
- The names of all included reagents in each box on the outer package label, where possible

Where a component is too small to contain all the above information, it must at a minimum contain name, lot number expiration date, volume, and storage conditions.

If the product requires associated dedicated instrumentation, the above requirements also apply to the instrument.

2. Instructions for use

The instructions for use will be reviewed during assessment Stage 3 for clarity, correctness, consistency with the information submitted in the documentation, and suitability for the target user group. The following must be submitted in the documentation:

- A copy of the current instructions for use (for the product)
- The instructions for use should, where possible, comply with the requirements of IMDRF document “Principles of Labelling for Medical Devices and IVD Medical Devices” IMDRF/GRRP WG/N52 FINAL:2019.
- Labels for the kit and all components.

3. Instrument manual

If the product requires associated instrumentation, include a copy of the instrument manual and/or associated operator manuals. If the instrument manual is large, an electronic version (CD or DVD) may be included instead of a hard copy.

4. Any other instructional materials provided to the user

Provide copies of any other instructional materials that are provided to the user for instance, if applicable, a copy of the instructions for use of any QC material required but not supplied by the manufacturer.

6. Quality Management System

An effective quality management system is a key consideration for all manufacturers of diagnostics. Therefore, IVDs submitted for WHO evaluation should be manufactured under an appropriate quality management system. The manufacturer's quality management system should cover all sites used to manufacture this product.

The quality management standard *ISO 13485 Medical devices — Quality management systems — Requirements for regulatory purposes* is considered to be a benchmark in quality management for manufacturers of IVDs by regulatory authorities throughout the world. WHO bases their requirements on those identified in this internationally recognized quality management standard. Alternatively, an MDSAP certificate is considered equivalent¹.

Provide evidence of the implementation of a manufacturing quality management system including;

- ISO 13485:2016 certificate or an MDSAP certificate;
- the most recent related quality management system (QMS) audit report;
- a copy of the quality manual;
- a list of valid quality management documentation;
- QC and batch release procedure/s;
- procedure/s for the control of design and development changes;
- procedure/s relevant to control of non-conforming goods, including but not limited to procedures for corrective and preventative actions, recalls, field safety notices etc.;
- a recent management review report;
- details of the production workflow including quality control (QC) points (in process and final release activities);
- critical supplier list including supplied products (components / raw materials) and services;
- details on the experience with the product (when was the product developed and when was it first placed on the market);
- details on the manufacturing capacity (existing inventory, minimum time to provide finished product, maximum batch size);
- information on outsourcing or contract manufacturing for any of the components.

END OF REQUIREMENTS

¹ <https://www.fda.gov/medical-devices/cdrh-international-programs/medical-device-single-audit-program-mdsap>