Instructions and requirements for Emergency Use Listing (EUL) Submission:

In vitro diagnostics detecting antibodies to SARS-CoV-2 virus

Emergency Use Listing of IVDs

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1 Introduction

The global spread of COVID-19 has dramatically increased the number of suspected cases and the geographic area where COVID-19 testing is needed to identify infected individuals. In order to do this, in vitro diagnostics (IVDs) of assured quality, safety and performance are required. The World Health Organization (WHO) revised the Emergency Use Listing (EUL) Procedure (previously referred to as the Emergency Use Assessment and Listing Procedure (EUAL)) on 8 January 2020, to be used primarily during a Public Health Emergency of International Concern (PHEIC). The EUL process is based on an essential set of available quality, safety and performance data. It is intended to expedite the availability of IVDs needed in PHEIC situations and, in that context, to assist interested UN procurement agencies and Member States in determining the acceptability of using specific products for time limited procurement.
The EUL procedure includes the following:

- **Quality Management Systems Review and Plan for Post-Market Surveillance**: review of the manufacturer's Quality Management System documentation and specific manufacturing documents;
- **Product Dossier Review**: assessment of the documentary evidence of safety and performance.

2 Intended Audience

This document has been prepared to assist manufacturers in correctly compiling the documentary evidence for the purposes of WHO EUL review of IVDs to detect SARS-CoV-2 specific antibodies (IgM, IgG) and describes the required information to support submissions to WHO. This document should be used together with WHO document "Emergency Use Listing (EUL) Procedure" [1] for candidate IVDs for use in the context of a public health emergency of international concern and the document "Invitation to manufacturers of in vitro diagnostics for SARS-CoV-2 to submit an application for EUL by WHO".[2] Manufacturers[3] who wish to submit the documentary evidence for an IVD should read these documents carefully and fully adopt the guidance therein to compile a successful submission.
Note: Manufacturers interested in applying for immunoglobin A (IgA) detection assays are requested to contact WHO as different requirements may apply.

[1] This document may be accessed through the following website:
https://www.who.int/diagnostics_laboratory/eual/200110_new_eul_procedure_final.pdf?ua=1
[2] This invitation may be accessed through the following website:
https://www.who.int/diagnostics_laboratory/EUL/en/
[3] For the purposes of the EUL, the following definition applies: "**Manufacturer** means any natural or legal person with responsibility for design and/or manufacture of a diagnostic with the intention of making the diagnostic available for use, under his name; whether or not such a diagnostic is designed and/or manufactured by that person himself or on his behalf by another person(s)".

3 The Submission

3.1 Submission clarity

Manufacturers should make every effort to ensure that their product documentary evidence is clear and well-organized (see section 4.2) to help make the WHO review procedure as efficient and timely as possible.

Note: Clarification of specific data requirements will require discussion between the applicant and WHO. Applicants are strongly encouraged to contact WHO as early as possible to discuss specifics of the application.

3.2 Confidentiality

All information submitted in the product dossier is confidential. WHO assessors will treat all information to which they will gain access during the assessment, or otherwise in connection with the discharge of their responsibilities as confidential and proprietary to WHO or parties collaborating with WHO with respect to the SARS-CoV-2 PHEIC.

3.3 EUL submission requirements – Important guidance on documents to be submitted

All items preceded by the symbol "➢" in each section below are required to be submitted as part of the EUL submission.

The instructions and feedback we provide are subject to change as more is learnt about COVID-19 and its risk-benefit profile. Any updates will be published on our website as they become available and applicants will be notified.

4 EUL Submission Format

4.1 EUL submission format

- The EUL submission is required to be submitted electronically. Further information will be provided to the manufacturer when their application is accepted for review.

4.2 Layout and order

WHO requires the following format for the dossier submission:

- Use the format page *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.
- Ensure that the files are identified appropriately. The names should link directly with the sections of the dossier as outlined in this document.
- Font sizes for text and tables are of a style and size (at least font size 12) that are large enough to be easily legible, when provided electronically.
- For sections where information is not available, the manufacturer should provide an explanation/justification for not providing the requisite information.

Submissions should be compiled according to the WHO requirements described above. However, in order to expedite review WHO may accept submissions previously prepared for National Regulatory Authorities if all the information required by WHO is incorporated in such a submission. Manufacturers should contact WHO to determine if a prior regulatory authority submission is appropriate to substitute for the specific sections of the submission.

4.3 Electronic copy requirements

- A searchable 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.
- The file name should be descriptive of its content and meaningful to the reviewers. The name can be up to 125 characters and can have spaces, dashes (not elongated dashes), underscores, and periods. However, the name of the file must not contain any of the following special characters or it will fail the loading process:
  - tilde (~)
  - vertical bar (|)
  - asterisk (*)
  - forward slash (/)
  - elongated dash (–)
  - colon (:)
  - double quotation marks (“)
  - hash sign (#)
  - backward slash (\)
  - apostrophe (’)
  - greater than sign (>)
  - single quotation mark (‘)
  - less than sign (<)
  - various other symbols (e.g., →,*, β , α ,∞,±,™)
  - question mark (?)
- All PDF files should be created directly from the source documents whenever feasible (such as sending the document to “print” and selecting to save the print prepared document as a PDF file which should be available in a drop-down menu in the print preview box) 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.
- If submission of a scanned document is unavoidable, we highly recommend that you perform optical character recognition (OCR) so that the text is searchable and clearer. 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.

4.4 Language and units of measurement

- 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.
- All measurements units used must be expressed in the International System of Units (SI) unless otherwise specified.

5 Quality Management System (QMS)

IVDs submitted for the WHO EUL procedure must be manufactured under a suitable, adequate and effective quality management system (QMS).

An assessment of the manufacturer's QMS documentation is a critical step in the reviewing of a SARS-CoV-2 EUL submission. Based on this assessment, WHO decides either to continue with the review of the submission or to request further documentation, or to terminate the application at this point.

The decision to proceed with the review process will be made only if there is sufficient objective evidence that the applicant is the manufacturer, that there is evidence of an adequate QMS in place and that the required manufacturing capacity exists.

The quality management standard *ISO 13485 Medical devices — Quality management systems — Requirements for regulatory purposes* is considered a benchmark in quality management for manufacturers of IVDs by regulatory authorities throughout the world. WHO base their requirements on those identified in this internationally-recognized quality management standard.

The following documentation is required to be submitted for review:

- Evidence of implementation and maintenance of an adequate QMS (e.g. current ISO 13485:2016 certificate or equivalent, together with the most recent regulatory (or certification body) inspection report).
- A copy of the quality manual.
- A list of current quality management documentation.
- Quality control (QC) and batch release procedures.
- Procedure(s) for the control of design and development changes.
- Procedure(s) relevant to the identification and the control of non-conforming goods, including, but not limited to, procedures for corrective and preventive action, recalls, field safety notices, etc.
- The most recent management review report.
- Details of the production workflow including QC points (in process and final release activities).
- A flow chart of the entire manufacturing process. If design and manufacture is carried out at different sites, or by external suppliers, this should be indicated on the flow chart. Only refer to sites of suppliers of raw materials involved in critical design and manufacturing activities.
- List of critical supplier(s) including supplied products (components/raw materials) and services.

- If the critical supplier holds a certificate issued by a conformity assessment body, and it is related to the quality management system, annex copies to the application document. If there are no such certificates, state this.
- When was the product developed and when was it first placed on the market or the planned timeline for placing on the market.
- Provide a list of all countries in which the product under assessment is intended to be marketed. For manufacturers submitting to WHO EUL, it is expected that the product under assessment is intended to be distributed globally, and particularly in low and middle-income countries.
- If the product has ever been distributed, please detail the manufacturer's experience with the product (including research-use-only products), especially (but not limited to) number of products distributed, number of customer complaints (if any), type(s) of complaint(s) and customer feedback.
- Details on the manufacturing output and capacity (existing inventory, current output, minimum time to provide finished product, maximum batch size, scale up capacity in percentage of current output and required time).
- Address(es) of all manufacturing site(s) including warehouse(s) and other facilities used in the manufacturing process.

The manufacturer's quality management system must cover all sites currently used to manufacture this product. WHO is required to be notified if any new sites are added.

6 Product Dossier

The product dossier submission should include product descriptive information and documentary evidence of safety and performance. Based on the submitted documentation, a risk-based judgement will be made on whether there is a favorable benefit-risk profile. Applicant are expected to provide the following product information:

6.1 Product information

6.1.1 Regulatory versions

Different regulatory requirements apply to different international markets for IVDs. Manufacturers who market their IVDs to multiple countries often alter some aspects of their products to comply with regional regulatory requirements and marketing needs (e.g., differences in design, information within the instructions for use (IFU), intended use statements, batch release procedures, sites of manufacture, information on package labels). If such various versions of a product exist, WHO must have a clear understanding of precisely for which version of the product the manufacturer is seeking EUL.

- Identify if there are multiple regulatory versions of the product.
- If the product has multiple regulatory versions, **clearly indicate which regulatory version of the product the manufacturer is submitting for EUL assessment**.
- Ensure for any of the documents submitted in the product dossier, that the regulatory version to which it relates is identified. Where the document is not the version associated with the specific product version submitted for EUL, a justification for its inclusion in the product dossier should be provided.

6.1.2 Product description including variants (configurations) and accessories

The dossier should include product descriptive information sufficient to allow a dossier reviewer to understand the design applied to the product and how it functions. The IFU may be used to provide some of this information on the condition that it is clearly indicated in the dossier what information can be found in the IFU. The following information is required:

- Legal manufacturer
- Product name and product code(s)/catalogue number(s)
- Overview and intended use of the IVD
    - Type of IVD (e.g. immunochromatographic (lateral flow), immunofiltration (flow through) rapid diagnostic test, enzyme linked immunosorbent assay (ELISA), chemiluminescence immunoassay (CLIA), electrochemiluminescence immunoassay (ECLIA) etc).
    - What the product detects (e.g. IgG, IgM, antibodies against SARS-CoV-2 virus in human blood, serum or plasma).
    - The function of the product (e.g., screening, monitoring, aid to diagnosis, staging or aid to staging of disease).
    - The specific disorder, condition or risk factor of interest that the product is intended to detect, define or differentiate.
    - Whether the test is qualitative or quantitative.
    - The type of specimen(s) required (e.g. human serum, plasma, venous whole blood, capillary whole blood, etc.).
    - The target population (dependent on intended use).[4]
    - Any limitations to the intended use.
    - The intended user (e.g. trained laboratory professionals, health professional, trained lay users).
    - The intended environment of use (e.g. point-of-care, laboratory).
- A general description of the principle of the assay method (including a full description of the ligands and reactions that take place at the "Test" and "Control" regions).
- For control material(s) to be used with the assay, include a description of what they are, whether they are included with the IVD, 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 materials provided with the product for specimen collection and transport or a description of the specifications of such materials recommended for use.
- If applicable, a description of any accessories, e.g. reader.
- 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.

[4] https://www.who.int/news-room/commentaries/detail/advice-on-the-use-of-point-of-care-immunodiagnostic-tests-for-covid-19 This information may be updated as more information becomes available.

- If applicable, a description or complete list of the various configurations/variants of product that will be made available.

6.1.3 Testing capabilities

- Briefly describe the 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.

6.1.4 Risk analysis

A risk analysis should be undertaken to identify and quantify all known or foreseeable hazards[5] for the product, taking into account such aspects as the user(s) of the device, and the technology involved. Provide the following

- A summary report of the risks identified during the risk analysis process, including, but not limited to:
    - Risk of false positive and false negative results occurring based on the technology used (e.g. through the reagents used or a high dose hook effect)
    - Risk to the patient/community arising from false positive or false negative results.
    - Risk of false results based on erroneous use of the product.
    - Indirect risks that may result from product-associated hazards, such as instability, which could lead to erroneous results.
    - User-related hazards, such as reagents containing infectious agents.
- A description of how these risks have been controlled to an acceptable level.
- Measures to inform users of any residual risks.
- A conclusion with evidence that the remaining risks are acceptable when compared to the benefits. This statement must be signed by senior management.
- Evidence that the risk analysis is part of the manufacturer's risk management plan (e.g. submission of the manufacturer's risk management documentation).

6.2 Product design and manufacturing information

6.2.1 Product Design

6.2.1.1 Formulation and composition

- For each of the ingredients, provide formulation/composition information.
- Provide a description of the components of the assay (e.g., reagents, assay controls, membranes).
- Include a detailed description of any capture antigens and antibodies used in the test, how they were designed and purified, e.g.:
    - antigen: which antigen/protein, full length or partial/truncated (specify protein domain selected and any fusion, linkers or purification constituents),

[5] Examples of possible hazards and contributing factors associated with IVDs are given in ISO 14971:2019

which expression system was used, how they were purified and QC of purity; if commercial products, is there a certificate of analysis, etc.;
- antibodies: are monoclonal or polyclonal antibodies used, are they manufactured in house or purchased commercially, what species they are derived in, what epitope is targeted by the antibodies used in an assay, if commercial products, is there a certificate of analysis, etc.;
- conjugates: components of the conjugate (antigen, immunoglobulin binding agent such as protein A, G, L or anti-antibody, and the nature of the colour probe or development system) and conjugation method.

6.2.1.2 Biosafety & biohazard

In this section, the applicant is required to provide evidence demonstrating that correct use of the product is safe; and any information relating to the design, use and disposal of the product that assures safe use under conditions where the product is likely to be used in the current outbreak setting.

- Provide evidence that risks associated with the following aspects (as applicable) have been considered and means taken to minimize the risks identified and to inform the user of any residual risk:
  - Specimen type.
  - Specimen collection.
  - Specimen processing.
  - Inactivation of specimen.
  - Safe disposal.
  - Safety of any control materials provided, including descriptions of inactivation methods and their validation.

6.2.1.3 Documentation of design changes

Have any design changes been applied to the product?

- If so, provide records of each design change for the product submitted including:
- The reasons that each change was made.
- References to validation/verification data to support the change.

6.3 Product performance specification and associated validation and verification studies

The manufacturer should 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, site where study performed and by whom, product identifier (e.g. product code), lot numbers, IFU version used, the date of initiation and the date of completion).
- Clearly defined acceptance criteria and an explanation as to how they were derived.
- A summary of the study findings including a conclusion that clarifies how the study objectives have been met.
- The study protocol and full report.

When studies are still in progress or plans to commence such studies are in place, the manufacturer should provide the study protocol and the study plan along with anticipated dates of completion and submission to WHO.

6.3.1 Analytical performance

Please note: in the absence of knowledge of the limit of detection (LOD), weak reactive and medium reactive specimens can be manufactured as described below if naturally occurring specimens of appropriate analyte concentrations are not available:

- Prepare a doubling dilution series of a strongly positive serum/plasma specimen using the appropriate specimen matrix as diluent.
- Test all members of the dilution series in duplicate in the device.
- Determine the cut-off dilution described as the highest dilution at which the specimen's reactivity is < ± (visually read RDT) or negative (reader assisted RDT or immunoassay).
- A low reactive specimen will be one constructed with reactivity 2-3 x the cut-off dilution; a medium concentration will be one with 5-7 x the cut-off dilution.

6.3.1.1 Stability of specimen(s)

This section contains information on the collection, storage and transport of specimens to be used:

- Identify the different specimen types that can be used with the product, including detailed information for each matrix and anticoagulant where applicable (e.g. capillary or venous whole blood, serum, plasma, use of different anticoagulants, etc.).
- For whole blood, serum and plasma, provide the studies/published data in support of specimen stability claims, storage claims including number of allowable freeze-thaw cycles and, where applicable, claims for transport conditions for each applicable specimen type.
- For other specimen types, contact WHO for specimen stability requirements.

6.3.1.2 Validation of specimens – matrix equivalence studies

If a manufacturer can demonstrate equivalency between two or more matrices or specimen types as described below, only one representative specimen type/matrix needs to be tested in the following analytical studies: section 6.3.1.4 precision, 6.3.1.6 analytical specificity, 6.3.1.11 robustness, and 6.3.1.12 stability of the IVD. If the manufacturer chooses to test only one representative specimen type or matrix in these analytical studies, the following study is required to be submitted.

- A matrix equivalency study should be conducted to establish the relationship between specimen type and IVD performance.
- The following conditions should be met in the matrix equivalence study:
  - If the product differentiates IgG and IgM, matrix equivalency should be evaluated for each Ig class separately.
  - The test should include a minimum of four reactive specimens; one low reactive (e.g. approx. 2 – 3 x cut-off dilution) and the rest across the dynamic range and one negative specimen for each claimed specimen type.
  - Each matrix set (e.g. venous whole blood, capillary blood, serum, plasma) should preferably be from the same donor (paired specimens).
  - Contrived specimens obtained by spiking negative specimens with the appropriate amount of analyte (IgG and IgM) may be used.

- The panel of five specimens should be tested in duplicate and the results compared between the matrices.
- For visually read tests, blinding and randomization of the specimens should be included in the experimental design.

6.3.1.3 Metrological traceability of calibrators and control material values (when reference material is available)

At present, no validated reference materials are available for SARS-CoV-2 assays. Once an International Standard (IS) has been established, all materials used in the validation of the assay must be calibrated against the established IS.

6.3.1.4 Precision (repeatability and reproducibility)

Note: This information can be submitted to WHO as a commitment to EUL.

a) <u>Repeatability</u>

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

b) <u>Reproducibility (intermediate precision)</u>

This section includes information about the study used to estimate, as appropriate, variability between-days, runs, sites, lots, operators and instruments.

- Both repeatability and reproducibility studies should include a minimum of one negative specimen, one low reactive specimen (e.g. approx. 2 – 3 x the cut-off dilution) and 1 moderately positive specimen (e.g. approx. 5 – 7 x the cut-off dilution).
- The studies can be combined into a single study with an appropriate study design which will allow for robust statistical analysis of repeatability and reproducibility.
- All claimed specimen types must be tested unless matrix equivalency has been demonstrated.
- If lay users are claimed as an intended user, this factor is required to be addressed in the study.

6.3.1.5 Analytical sensitivity

In the absence of an international standard and scarcity of well characterized sero-conversion panels, an interim analytical sensitivity should be estimated by dilution of positive clinical specimens as described in section 6.3.1.

- Five specimens from early (within four weeks after symptom onset) and five convalescent specimens (> 4 months after symptom onset) of infection should be selected. The specimens should be collected from individuals whose SARS-CoV-2 infection was confirmed by PCR.
- These specimens should be tested in the product and a comparator assay and the results compared.
- The justification for the choice of comparator assay must be provided (use of an RDT is not acceptable). The choice of assay can be discussed in advance with WHO.
- The positive agreement (%) must be evaluated on three different lots

A SARS-CoV-2 interim IS for serology assays is expected to become available later in 2020.[6] This interim standard may be used by assay developers before final status of the IS attained. WHO may request the manufacturer to perform additional testing if appropriate material to estimate analytical sensitivity becomes available.

- In case National Regulatory Authorities (NRAs) or other entities have made reference material available, please provide a detailed description of such material and studies undertaken, provide the following:
    - A description of specimen type and preparation including matrix, analyte (measurand) levels, and how levels were established
    - The number of replicates tested at each concentration.

6.3.1.6 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 to be detected, in the presence of other substances/agents in the specimen or antibodies to a potentially confounding infection in the individual being tested.

a) Interfering substances

Testing of potential interferents is required. 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. The interferents to evaluate depend on the specimen type. Please note the following requirements:

- Endogenous substances should be spiked into the appropriate negative matrix at the highest levels found in individuals.
- Each endogenous and exogenous specimen must be tested unspiked and spiked with the analyte at a concentration near the cut-off dilution (e.g. approx. 2 – 3 x the cut-off dilution).
- Specimens must be tested in triplicate.
- If equivalency between specimen matrices has been demonstrated in 6.3.1.2 only one claimed specimen type/matrix is required to be included in these studies. However, note that if whole blood is a claimed specimen type, it must be included in this study (whether or not it has shown equivalency with other specimen types).
- The tables below indicate the potentially interfering substances that may be found in blood/plasma/serum specimens.
- If non-blood clinical specimen types are claimed, (e.g., oral fluid, urine etc.), additional substances may need to be considered. Contact WHO for further information.
- Where significant interference is observed, provide a plan to address these issues.

See the table below for evaluation of interfering substances that may generate false positive or false negative results:

[6] https://www.nibsc.org/science_and_research/idd/cfar/covid-19_reagents.aspx

Table 1: Potential interfering substances

Potential Interfering Substance
Blood Specimens
Haemoglobin
Bilirubin Conjugated
Bilirubin Unconjugated
Serum proteins (e.g., Human Serum Albumin)
Triglycerides
Cholesterol
Antibodies against the expression systems used to generate recombinant antigens (e.g., E. coli, yeast, insect cells)
Human anti-mouse antibody (HAMA) (if applicable)
Biotin (if applicable)
Rheumatoid Factor
ANA anti-nuclear antibodies

b) <u>Cross reactivity</u>

Cross-reactivity should be evaluated by testing specimens containing high titred antibodies to microorganisms that could potentially cause false positive results (table 2).

Note I: If, as part of the clinical specificity study **section 6.3.2.b),** the required number of anti-SARS-COV-2 negative specimens are tested from populations with high prevalence of infections with the micro-organisms listed in part a) of table 2 below, the data can be accepted in lieu of individual testing required in table 2. Appropriate evidence of prevalence must be provided, and clinical specificity must be > 95% (lower bound of the 95% confidence interval).

Note II: Specimens with antibodies to the micro-organisms listed in part b) of table 2 below must be tested (independent of the clinical study).

Note III: For intended use settings in which a high prevalence is present of any of the organism listed in part c of table 2) testing of specimens with antibodies to each of those organisms is recommended.

The following information is required:

- Testing of near-neighbour species/strains and of organisms whose infection produces symptoms similar to those observed for COVID-19 and are therefore relevant for differential diagnosis. Depending on the intended use setting, other highly prevalent organisms might need to be considered, e.g. parasites.
- Cross-reactivity must be evaluated at a minimum against organisms listed in parts a & b of table 2 (see note I and note II above).
- Cross-reactivity should be evaluated with high titred specimens.
- Evidence of the presence/titre of IgM and IgG in the test specimens should be provided. Please provide information on the methods used to characterize these specimens as positive (in-house, commercial assays, commercial vendors, etc.).

- For pathogens where serology testing is not routinely performed, convalescent samples (collected four to six weeks after onset of symptoms) may be considered. This method can be discussed with WHO.
- A minimum of at least **5 specimens** should be tested for each organism listed
- Omissions from actual laboratory testing should be supported by a well-documented justification that includes a due diligence attempt to obtain the relevant specimens
- Where cross-reactivity is observed, provide a plan to address the associated issues.
- Please provide summary results in the table format below.

Table 2: Cross-Reactivity: List of Organisms

Specimens positive for antibodies to the following microorganisms	*Number of specimens tested*	*Assay equivocal or positive results*	*% Cross reactivity*
a) Coronaviruses & common pathogens relevant for differential diagnosis (required if only a total number of 500 specimens have been tested in the clinical specificity study section 6.3.2.b)			
Human coronavirus 229E			
Human coronavirus OC43			
Human coronavirus HKU1			
Human coronavirus NL63			
SARS-coronavirus (optional)			
MERS-coronavirus (optional)			
Adenovirus (e.g. C1 Ad. 71)			
Human Metapneumovirus (hMPV)			
Parainfluenza virus 1-4			
Influenza A virus			
Influenza B virus			
Haemophilus influenzae			
Rhinovirus			
Respiratory syncytial virus			
b) Other organism (mandatory testing independent of clinical studies)			
Epstein-Barr virus (infectious mononucleosis)			
Human Immunodeficiency virus (HIV)			
Plasmodium falciparum			
Plasmodium ovale			
Dengue virus (type 1-4)			
c) Other organisms (optional, depending on prevalence)			
Enterovirus (e.g. EV68)			
Chlamydia pneumoniae			
Legionella pneumophila			
Mycobacterium tuberculosis			
Streptococcus pneumoniae			
Streptococcus pyrogenes			
Bordetella pertussis			

Mycoplasma pneumoniae			
Pneumocystis jirovecii (PJP)			

6.3.1.7 Immunoglobulin class specificity (if applicable):

The manufacturer should evaluate the potential for human IgG to cross-react and therefore produce false positive results with the IgM assay test line and vice versa for the IgG test line.

- Please provide data or the rationale used to determine if cross-reactivity with IgG/IgM (as applicable) is a potential assay interferent.
- Approaches to evaluate class specificity may depend on the assay format.
- It should include what method was used to determine that the IgG positive specimens were COVID-19 IgG positive and COVID-19 IgM negative and vice versa.

6.3.1.8 Validation of the cut-off value for RDTs with a reader (instrument) or other immunassays

This section provides information on how the assay reader cut-off was established.

- Provide the relevant studies and rationale for the chosen cut-off;
- Analytical data with the description of the study design, including methods for determining the cut-off;
- The population(s) studied (demographics/selection/inclusion and exclusion criteria/number of individuals included/excluded);
- The method and mode of characterization of specimens;
- The statistical methods (e.g. Receiver Operator Characteristics (ROC)) to generate results.

6.3.1.9 High Dose Hook Effect

- If the manufacturer does not consider that the assay has a potential for high dose hook effect, provide the rationale to support this.
- If the potential risk of a false negative result has been identified (see 6.1.4 risk assessment) the respective analytical study must be provided e.g. using dilution experiments of relevant patient specimens or spiking negative patient specimen with high concentration analytes.
- The mitigation steps taken by the manufacturer should be described.
- A remaining risk of false negative results through high dose hook effect must be described in the IFU.

6.3.1.10 Validation of assay procedure: quality control accessories and within-device procedural control band (dot)

- The product should include a procedural control band (dot) or the IFU should include instructions to achieve reasonable quality control.
- Where an IVD uses a within-device procedural control band (or dot), the extent to which the presence or absence of this band (or dot) corresponds to a valid test (identification of and traceability to a suitable reference should be demonstrated).
- ***For immunoassays (not RDTs),*** please indicate what failure modes the control indicates (e.g. insufficient volumes used, incorrect timing, instability of the system, incorrect specimen used) and provide the corresponding evidence".

6.3.1.11 Flex and robustness studies

This section provides information to demonstrate that the product design is robust, e.g., insensitive to environmental and usage variation. Robustness (flex) studies are designed to challenge the system under conditions of stress to identify potential device deficiencies, including failures, and determine the robustness of the product. The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small but deliberate variations in procedural parameters listed in the procedure documentation and provides an indication of its suitability during normal usage. The values chosen (e.g. variance from nominal IFU required times, volumes, orientation of devices) should be decided by risk assessment as to how likely an intended user is to err and by how much.

- The manufacturer must consider multiple skill levels of users, as well as potential instrument and reagent problems. Below is a list of factors that need to be considered.
- Evidence is required to demonstrate that the testing conditions recommended in the IFU are validated and how they were verified.
- The influence of the following factors on expected results (both positive and negative) must be considered
    - Specimen and/or reagent volume
    - Operating temperature (i.e. incubation temperature) and humidity
    - Reading times and illumination (visual readings)
- The robustness of the instrumentation that is part of the IVD should be considered relating to
    - Ruggedness (including the effect of vibration from other instruments)
    - Impact of dust and mold on componentry (e.g. optics)
    - Impact of power/voltage fluctuation
- Studies investigating the impact of specimen volume should be conducted in one claimed specimen type. **However, if whole blood is claimed, the studies need to be conducted in this specimen type in addition.**
- For all other flex studies, the most common specimen type used for the clinical studies should be tested.
    - The test panel should include one negative specimen and one low reactive specimen (e.g. approx. 2 – 3 x the cut-off dilution).
    - Provide a summary of the evidence collected to date and a plan for further testing if such studies are not complete.

6.3.1.12 Stability of the IVD

Shelf-life, in-use stability and shipping stability information provided under this section must be consistent with the instructions for use and product labels provided within the submission.

a) <u>Shelf life of the IVD including shipping stability</u>

WHO acknowledge that not all studies will have been completed when submitting to the EUL. In this case, please provide a study protocol and plan for completion of the studies. Accelerated studies or extrapolated data from real time data are acceptable for initial shelf life claim provided sufficient evidence is provided to support the claim, however, it is a requirement that real time stability studies will be finalized.

Stability studies are required to be undertaken to determine and validate the shelf life of the product. The products must firstly be subjected to real time or simulated shipping conditions prior to placing into the shelf life study. The following shipping conditions should be investigated (reflecting the range of environmental conditions of the countries to which the product is/ will be supplied):

- Conditions to mimic extremes of conditions (temperature, humidity, pressure) exposed to during transport/shipping.
- Storage temperature and humidity range.
- When accelerated studies have been performed in anticipation of the real time studies, identify the method used for accelerated studies and the calculations and their validation employed to extrapolate findings to projected real time stability.

b) <u>In-use stability</u>

- Provide a report on in-use stability (open pack or open vial stability) for each assay component.
- All labile components (e.g., buffer) are required to be evaluated.
- The studies should reflect actual routine use of the device (real or simulated), this includes open vial stability.
- Consideration should be given to multiple access of reagent bottles (opened several times during its use) as well as to different vial sizes, 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 impact of temperature and humidity (particularly on open test cassette pouches).

6.3.2 Clinical evidence

WHO acknowledges that not all studies will have been completed when submitting to the EUL. When studies are still in progress or plans to commence such studies are in place, the manufacturer should provide the study protocol and an update of progress or the study protocol and plan along with anticipated dates of completion. If more clinical data becomes available at a later time, this should be submitted to WHO. It is a requirement that such studies described below will be finalized.

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.

- Specimens from all sections of the population for which claims are made in the IFU are required to be tested.
- The clinical performance in general should be ideally evaluated for **each claimed clinical specimen type. If matrix equivalence has been demonstrated between plasma (anticoagulants), serum and venous whole blood, then not all specimen types are required in the clinical study. However, if capillary blood is a claimed specimen type, clinical performance on capillary blood is required to be demonstrated.**

- Specimens should be tested in a blinded fashion, e.g., positive and negative specimens in the testing panel should be interspersed (i.e. not presented in any discernable order) and blinded to the end user; the end user should also be blinded to the results of any comparator method testing.
- Performance data should be stratified according to the time interval between date of onset of symptoms and date of specimen collection date (0-7 days, 8-14 days, ≥15 days post symptom onset).
- Small sample sizes are vulnerable to selection bias. Criteria for the selection of specimens are required to be explained (e.g. testing of consecutive patients). In addition, archived samples should be randomized and tested in a blinded fashion.

a) <u>Clinical / diagnostic sensitivity</u>

- A minimum of 200 positive specimens from individual patients should be tested.
    - A minimum of 100 prospective positive specimens from individual patients confirmed positive for COVID19 infection by PCR,
    - a minimum of 100 prospective specimens from individual patients with signs and symptoms suggestive of COVID-19 (unknown etiology at the time of specimen collection).
    - At least 30 specimens should be PCR positive at time of specimen collection and within a week of symptom onset.
- However, if a prospective study is not feasible for the 100 positive patients confirmed positive for COVID19 infection by PCR, an acceptable alternative would be to test at least 100 retrospectively collected SARS-CoV-2 positive specimens.
- Each specimen must be accompanied by basic information such as,
    - the specimen type,
    - the specimen collection date,
    - date of onset of symptoms (if present),
    - date of PCR testing,
    - severity or absence of symptoms,
    - tests used to identify COVID19 patients, etc.

(**Comment**: When studies are still in progress or plans to commence such studies are in place, then at least 50 % of data are requested to be provided in the initial submission. The remaining data may be supplemented during the dossier assessment).

b) <u>Clinical/ diagnostic specificity</u>

- 200 specimens from individual symptomatic patients that tested negative by PCR (no evidence of exposure to SARS-CoV-2).
- 600 individual specimens from the general population collected before November 2019; if the manufacturer has performed analytical specificity testing with all micro-organism listed in Table 2 a & b, it is acceptable to test only 300 specimens from the general population.

(**Comment**: When studies are still in progress or plans to commence such studies are in place, then at least 50 % of data are requested to be provided in the initial submission. The remaining data may be supplemented during the dossier assessment)

All claims made by the manufacturer must be validated statistically. WHO may require the number of specimens examined to be increased to provide sufficient statistical confidence to the intended performance claim.

c) Recommended comparator method/ assigning clinical truth to specimens

- A PCR based assay must be used as the primary comparator assay to ensure that the collected specimens tested are compatible with a true positive status of the patient.[7]
- In addition, a validated immunoassay (not RDT) detecting the respective anti- SARS-CoV-2 antibodies (e.g. IgM, IgG) should be used to characterize the specimens tested (secondary comparator test). The choice of the immunoassays needs to be justified and clinical performance data must be provided. It is not acceptable to use only immunoassays as the comparator assay for the estimation of clinical sensitivity.

d) Resolution of discrepant results:

- The procedure to resolve discrepant results must be described and applied to each of the respective specimens and can include immunofluorescence, virus neutralization assays, Western blot, and PCR techniques as applicable.

7 Plan for Post-Market Surveillance

Post-market surveillance, including monitoring all customer feedback, detecting and acting on adverse events, product problems, non-conforming goods and processes is a critical component of minimizing potential harm of an IVD listed for emergency use. Certain adverse events should be reported to regulatory authorities in the relevant jurisdiction(s). In the PHE settings this EUL procedure serves, it cannot be assumed there are sufficient resources in place to support consistent and effective post-market surveillance but manufacturers must make all efforts possible.

The manufacturer is required to ensure that should the EUL be granted, activities are in place to monitor product safety, quality and performance post-EUL. It is expected that post-market surveillance activities will be in accordance with WHO guidance "WHO guidance on post-market surveillance of in vitro diagnostics".[8]

8 Labelling

Where possible, the submission should contain a complete set of labelling associated with the product. This includes labels and Instructions for Use (IFU) as well as instrument manual (if applicable) and other instructional materials provided to the user.

8.1 Labels

- Include copies of all packaging labels for the assay. This includes:
    - outer labels (secondary packaging)

[7] U.S Food and Drug Administration Emergency Use Authorization (FDA EUA) PCR test[7] or a WHO EUL listed PCR test

[8] Available on the web page https://www.who.int/diagnostics_laboratory/postmarket/en/

- 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 instrumentation, the above requirements also apply to the instrument.
- The instrument should clearly display information regarding its status as a new or reprocessed product.

8.2 Instructions for use (IFU)

- The IFU will be reviewed for clarity, correctness, consistency with the information submitted in the dossier, and suitability for the target user group. The following must be submitted in the dossier:
- A copy of the current IFU.
- The IFU should, where possible, comply with the Principles of Labelling for Medical Devices and IVD Medical Devices of IMDRF/GRRP WG/N52 FINAL:2019.

8.3 Instrument manual

- If the product requires associated instrumentation, include a copy of the instrument manual and/or associated operator manuals.

8.4 Any other instructional materials provided to the user

- Provide copies of any other instructional materials that are provided to the user.

9 Contact Information

Any inquiries regarding the EUL should be addressed to: *diagnostics@who.int*