COVID-19 Diagnostic Testing

Technical Screening Serological Assays (ELISA, antigen and antibody tests)

Name of the device	ANTI-SARS-COV-2 ELISA (IGG)
Manufacturer	EUROIMMUN MEDIZINISCHE LABORDIAGNOSTIKA AG
Application #	**313727**
DED Screener	**Catherine Milley**

	Guidance	Acceptable	Comment
Device Description	**Type of technonology:** ELISA, Lateral-Flow, antigen detection, antibody detection. **Intended use:** qualitative, quantitative **Sample type / collection methods**: fingertip sample type data need to be removerd from IFU if not for POC **Testing setting:** Laboratory / Point of Care **Instrumentation required** **Calibrator and controls** (value assignement) **Detection method**: Biotin interference? **Antigen source:** what it is and what is the source. **Patient serum used to validate the tests:** number and variety of sera (assessed during review). **Intended use statement assessed during review**	Deficient	ELISA Semi-quantitative IgG Samples: serum and plasma (citrate, EDTA, heparin) Overall, limited information provided beyond IFU. Additional information will be requested.
Analytical Sensitivity	There is no requirement for LoD for serological assay. Diagnostic Sensitivity demonstrated in clinical studies is more relevant. For antigen tests, LoD is required. Relative analytical sensitivity of ELISA can be assessed by end-point dilution analysis which indicates the dilution of serum in which antibody is no longer detected. Should be requested at screening only if nothing is provided (quality of information assessed during review)	Deficient	Relative analytical sensitivity of ELISA can be assessed by end-point dilution analysis which indicates the dilution of serum in which antibody is no longer detected
Cut Off	How the cutoff was established	Deficient	Provide a detailed summary of the cutoff validation study supporting the claimed cutoff.
Hook effect	Applicable for sandwich immunometric assays	Deficient	
Sample matrix	• **Equivalence between sample types/Matrix equivalency studies :** POC needs data for fingertip sample type. If no data for each sample type, a specimen equivalency study is requested • **Validation of anticoagulants** • **For antigen test**: Equivalency between swabs recommended if all the studies were done with one swab (This may be too much for an IO?)	Deficient	

Interference	• **Endogenous substances** including : Hb, bilirubin, Proteins, TG, HAMA, RF, Total IgG, Total IgM. For antigen tests, either naturally present in respiratory specimens or artificially introduced into the nasal cavity or nasopharynx
	
	• **Exogenous:** Common medication
	
	• Cross-reactivity with non-targeted commensal and pathogenic microorganisms
	  • **Human coronavirus 229E**
	  • **Human coronavirus OC43**
	  • **Human coronavirus HKU1**
	  • **Human coronavirus NL63**
	  • **SARS-coronavirus**
	  • **SARS-CoV-2 IgG or SARS-CoV-2 IgM**
	  • **MERS-coronavirus (not essential)**
	  • Adenovirus (e.g. C1 Ad. 71)
	  • Human Metapneumovirus (hMPV)
	  • Parainfluenza virus 1-4
	  • Influenza A & B
	  • Enterovirus (e.g. EV68)
	  • Respiratory syncytial virus
	  • Rhinovirus
	
	Microbial interference by other common respiratory pathogens:
	  • Chlamydia pneumoniae
	  • Haemophilus influenzae
	  • Legionella pneumophila
	  • Mycobacterium tuberculosis
		Deficient	

	• Streptococcus pneumoniae • Streptococcus pyogenes • Bordetella pertussis • Mycoplasma pneumoniae • Pneumocystis jiroveci (PJP) • Candida albicans • Pseudomonas aeruginosa • Staphylococcus epidermis • Rhinovirus Staphylococcus salivarius **Antigen assay**: in silico analysis alone is not acceptable. If wet testing is also provided only wet testing results should be listed in package insert. **For antibody assays : Class specificity** : For IgM assays, to determine if reactivity with SARS-CoV-2 specific IgG is a potential assay interferent and viceversa for IgG assays. Detection of total Ab detection: no need for class specificity		
Precision	Evidence of repeatability	Deficient	
Seroconversion	Seroconversion panel testing, ***if available***. Please provide a complete test report, be sure to include details on the seroconversion panels themselves, such as source, validation of the samples including in the panel) including the time from infection each test sample represents (time to seroconversion). Describe the source of the panel.	Deficient	
Stability	• Description of stability test plan • reagent stability studies do not need to be completed at the time of IO issuance, however the study design should be agreed upon during review and the stability studies started immediately following authorization	Deficient	
Clinical Evaluation	• A minimum of 50 positive clinical samples and 200 negative clinical samples is required for clinical evaluation. • POC intended use: Performance data reuired for each sample type. • Timing of the collection of positive samples (infection time) if available: Positive samples should include infection times of 4-10 days and 11-24 days	Deficient	
Point of Care	Near patient studies performed in clinical setting by intended users. Minimum of 9 operators and questionnaire to assess IFU clarity.	n/a	
Labeling	Instructions for use Reagent labels Intended Use Statement will be assessed during review	Y	IFU provided

As COVID-19 a new disease, there are some unknowns regarding the antibody response and the optimal target proteins to be used in the design of serological assays. For many of the questions below, statements have been made in the Instructions for Use, but evidence (scientific reports) were not provided. Please ensure that you provide the following information:

1. A complete device description, with details and rationale for its design, and for your selection of any reagents and controls. Describe any antigens incorporated into the design, and provide information on their source. You may include relevant supporting literature.
2. Your labelling allows the use of different sample types (serum, and plasma with different anticoagulants). As such, the evidence you provide in support of your device must include all sample types allowed in your labelling, or you must provide evidence that these sample types are equivalent. Ensure that the evidence your provide supports the equivalency of each type of anticoagulant.
3. Limit of detection/analytical sensitivity report, or a detailed summary of methods and results
4. Hook effect study, or a rationale describing why it is not needed for your design
5. A detailed summary of the cutoff validation study supporting the claimed cutoff value.
6. Cross reactivity/analytical specificity studies report, or a detailed summary of methods and results. Please note that testing for cross reactivity with antibodies to human coronaviruses 229E, OC43, HKU1, NL63,as well as Adenovirus (e.g. C1 Ad. 71), Human Metapneumovirus (hMPV), Parainfluenza virus 1-4 , Influenza A & B , Enterovirus (e.g. EV68), Respiratory syncytial virus, and Rhinovirus is expected, and an assessment of common respiratory pathogens (Chlamydia pneumoniae, Haemophilus influenzae, Legionella

pneumophila, Mycobacterium tuberculosis, Streptococcus pneumoniae, Streptococcus pyogenes, Bordetella pertussis, Mycoplasma pneumoniae, Pneumocystis jiroveci (PJP), Candida albicans, Pseudomonas aeruginosa, Staphylococcus epidermis, Staphylococcus salivarius) is preferred.

7. Antibody Class specificity study report, or a detailed summary of methods and results . For example, for IgM assays, determine if reactivity with SARS-CoV-2 specific IgG is a potential assay interferent, and vice versa for IgG assays.
8. Interference testing of endogenous substances (Hb, bilirubin, Proteins, TG, HAMA, RF, Total IgG, Total IgM), and of exogenous substances (common medications)
9. Clinical Performance Studies Reports.
   Clinical accuracy should be established using human specimens from patients with microbiologically confirmed COVID -19 infection. You should:
   a. Include the name and manufacturer of the RT-PCR test used to characterize the samples.
   b. Show the clinical agreement to establish the diagnostic sensitivity (PPA) and specificity (NPA) of the test; 95% confidence intervals should be provided.
   c. Clearly identify the timing of the collection of positive samples (infection time) if available.
   d. Provide a breakdown of the assay sensitivity and specificity for each sample type. Alternatively, a sample equivalency study may be submitted.
   e. Provide a statistical rationale for the sample size of the study. A minimum of 50 IgG positive samples + 50 IgM positive samples and 200 negative samples should be tested. The positive sample set should include relevant samples from the targeted population to support the claimed intended use, for example:
      - Samples in early onset stage of the disease
      - Samples in intermediate onset stage of the disease
      - Samples in convalescence stage of the disease
      - Samples from patients with severe symptoms
      - Samples from patients with mild symptoms
10. Seroconversion panel testing, if available. Please provide a complete test report, being sure to include detail on the seroconversion kits themselves, including the time from infection that each test sample represents.
11. Evidence of repeatability should be provided. Provide detailed summaries for all precision studies available.
12. Stability (Shelf life, Shipping/transport, and In-use)
    Briefly describe your stability test plan. Note that reagent stability studies do not need to be completed at the time of IO issuance, however the study design will be assessed during review of your submission, and we will require that the stability studies be started no later than immediately following authorization. Provide the claim you are making for stability of your device and how you arrived to this claim.
13. Provide a description of the lot release program in place to ensure that each production lot meets the established specfications. The information required includes a detailed protocol, a description of the testing panel, and a clear description of the acceptance criteria