COVID-19 Diagnostic Testing

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

Name of the device	SOFIA 2 SARS ANTIGEN FIA
Manufacturer	DIAGNOSTIC HYBRIDS, INC. - ALSO TRADING AS QUIDEL CORPORATION
Application #	**314994**
Technology	**Antigen**
Test Setting	**Both Lab and POC**
DED Screener	**Catherine Milley/26 May 2020**

Notes to reviewer	**Has FDA EUA, US-EUA200742**

	Guidance	Acceptable	Comment
Device Description	**Type of technology:** - ELISA, Lateral-Flow, antigen detection, antibody detection. - qualitative, quantitative - instrumentation required **Sample type / collection methods**: Fingerstick samples require additional validation for POC use (see below) **Testing setting:** Laboratory / Point of Care **Calibrator and controls** (value assignment) **Antigen source:** what it is and what is the source. **Intended use statement assessed during review**	deficient	- FIA (fluorescence immunoassay), sandwich design, lateral flow - used with Sofia 2 instrument (MDL 101571), and possibly Sofia (MDL 92830). Applicant's intent to be confirmed - No information provided on software for instruments - qualititative – reported as positive, negative, or invalid - detects nucleocapsid protein from SARS-CoV and SARS-CoV-2. T(does not differentiate, between the two) -nasopharyngeal (NPS), nasal (NS) and oropharyngeal (OPS) (IFU does not state this one, but quick reference does) swab specimens directly, or after transport in Viral Transport Media (specific types in amended IFU) -lab and point of care -kit includes nasal swabs, but not NPS swabs -kit includes positive and negative controls. Instrument has monthly calibration cassette (supplied with instrument)
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	Summary descriptions of LoD studies provided, for both Sofia and Sofia 2 instruments. However, additional detail is required regarding methods, swabs, and results. Full test reports to be requested Provide the complete study reports (Study 1 and Study 2) for Limit of Detection, as referenced in the "Analytical Sensitivity" section of your EUA Amendment document
Cut Off	How the cutoff was established	Deficient	Not provided
Hook effect	Applicable for sandwich immunometric assays	Y	Part of LoD study
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 • Patient serum used to validate the tests: number and variety of sera (assessed during review). • Validation of anticoagulants **For antigen test**: Equivalency between swabs recommended if all the studies were done with one swab	Deficient	Comparison between direct swabs and swabs in viral transport media is required.
Interference and Cross Reactivity	• **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. **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 vice versa for IgG assays. Detection of total Ab detection: no need for class specificity	Deficient	Summary level data on Cross reactivity with micro organisms and with negative sample matrices provided Exogenous and endogenous interferents statement provided – In original EUA application they appear to be leveraging previously collected data on other test kits, but same instrument. Amended EUA application appears to reference testing done on subject device. Study reports to be requested: Provide the complete study reports for Cross Reactivity and Endogenous Interferents, as referenced in the "Analytical Specificity" section of your EUA Amendment document

Precision	Evidence of repeatability	Deficient	To be requested
Seroconversion	Seroconversion panel testing, ***if available***.	n/a	
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	To be requested
Robustness	Use variation : sample and reagent volume, operating temperature and humidity, reading time and illumination (visual reading)	Deficient	To be requested
Clinical Evaluation	• A minimum of 50 positive clinical samples and 200 negative clinical samples is required for clinical evaluation. • **Comparator assay (RT-PCR) should be authorised**, either by HC, or EUA from US, or WHO EUL. • **ELISA:** reference range study with a minimum of 500 samples • **POC intended use**: Performance data required for each sample type. • **Timing of the collection of positive** samples (infection time)	Deficient	Clinical samples: using VTM samples Positive: 59 Negative: 84 Also, summary of a study of contrived samples: 20 positive, 47 unspiked. Complete clinical study reports to be requested: Provide both Study 1 and Study 2 referenced in the "Clinical Evaluation" section of your EUA Amendment document
Point of Care	**Near patient studies** performed in clinical setting by intended users. Minimum of 9 operators and questionnaire to assess IFU clarity.	Deficient	Not provided
Labeling	**Instructions for use** **Reagent labels** Intended Use Statement will be assessed during review	Y	IFU provided Labels provided
Quality	• **QMS certificate provided?** • **Evidence of lot release programme**	Y	Applicant states they have MDSAP certification

Questions:
You are asked to respond to all the questions in a single, comprehensive package, using a Question and Answer format with references to attachments, as needed. Your response should be submitted in a single e-mail communication; attachments can be included in a compressed zip file format.

1. Provide the following information:

- You have provided information that you submitted to the US FDA to amend your current EUA. Please clarify that the changes proposed there reflect the device labelling that you are seeking under Health Canada's Interim Order. This includes the updates to the allowed types of VTM, and the addition of the Sofia instrument.
- Clarify the sample types that you intend to include in your labelling for Canada. We note that the indications list nasopharyngeal (NPS), and nasal (NS) samples, but the Quick Reference also include oropharyngeal (OPS) samples.
- A description of any software changes required in order for the Sofia instrument(s) to run the proposed test. Identify the software version number.
- A detailed description of all controls and calibrators, where applicable;
- A detailed description of all reagents (e.g. chemical composition of buffer, reagent, positive and negative control swabs);
- A detailed description of antibodies used in the test, including how they were designed and purified;
    - Are monoclonal or polyclonal antibodies used?
    - Are the antibodies manufactured in-house or purchased commercially?
    - What species are the antibodies derived in?
    - What epitope is targeted by the antibodies used in the assay?
    - For commercial antibodies, identify the source, and provide a Certificate of Analysis;
- A detailed description of the conjugates: components of the conjugate (antibody and colour probe) and conjugation method.

2. The summaries provided for the following validation studies are not sufficient to allow an adequate assessment. Please provide the complete study reports for the following:
    a. Limit of Detection (Study 1 and Study 2), as referenced in the "Analytical Sensitivity" section of your EUA Amendment document
    b. Cross Reactivity and Endogenous Interferents studies, as referenced in the "Analytical Specificity" section of your EUA Amendment document

c. Study 1 and Study 2 referenced in the “Clinical Evaluation” section of your EUA Amendment document

3. Cutoff: Provide a detailed summary of the cutoff validation study supporting the claimed cutoff concentration and/or signal detection.

4. Provide a study on the test robustness. The influence of the following factors on expected results (both positive and negative) must be considered when designing these studies:
   - Recommended sample and reagent volume (if applicable);
   - Operating temperature and humidity; and
   - Reading times and illumination (visual readings).

5. Precision studies must be provided to demonstrate repeatability. Include a description of the panels used to assess repeatability, including the source, specifications, and the validation method. **If unavailable at time of submission, reproducibility studies will be requested as a condition to authorization.**

6. Stability (Shelf life, Shipping/transport, and In-use)
   Provide the claim you are making for stability of your device and the rationale for how you arrived at this claim. Provide all evidence currently available supporting the stability of your device. Alternatively, submit 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.

7. Provide a description of the lot release program in place to ensure that each production lot meets the established specifications. The information required includes a detailed protocol, a description of the testing panel, and a clear description of the acceptance criteria.

8. For tests intended to be use for point of care testing, a near patient study, performed in the intended use setting by intended users, is required. The study should be performed by a minimum of 9 operators, under the intended conditions of use. It should include a questionnaire to assess clarity of the instructions for use, the ability of the users to understand and interpret the result and to operate the device, as well as the robustness of the device.