COVID-19 Diagnostic Testing

NAT Technical Screening

Name of the device	**ALINITY M SARS-COV-2 AMP KIT, ALINITY M SARS-COV-2 CTRL KIT**
Manufacturer	**ABBOTT MOLECULAR INC.**
Application #	316848
Technology	**PCR**
Test Setting	**Lab**
DED Screener	**Ian Aldous**

Notes to reviewer	

	Guidance	Acceptable	Comment
Device Description	**Type of Technology** **Instrumentation required** **Sample type/collection methods** **Testing setting:** Laboratory / Point of Care **Extraction methods** **Targeted sequence** **Sequences of Probes and primers** **Controls** (value assignment, supplied with kit) **Detection method**: potential for Biotin interference **Intended use assessed during review**	Y	
Limit of Detection	Spiking RNA / inactivated virus into clinical (preferred) or artificial matrix. The matrix should represent the most challenging clinical matrix. **Initial study** Dilution series including 3 replicates for each concentration. **Confirmatory study** 20 replicates of the final concentration. Acceptance criteria: 19/20 positive	N	Summaries only
Inclusivity	• Provide results of in silico analysis including the % identity to published COVID19 sequences. • 100% of the published sequences should be detectable.	N	Summaries only
Cross-Reactivity (Exclusivity)	• Provide results of in silico analysis of primers and probes against: common respiratory flora, other viral infections • Wet testing is recommended • Cross-reactivity is defined as greater than 80% homology • Matrix-specific cross-reactivity should be assessed, • Exogenous/Endogenous interferents: these depend on sample type (blood, sputum, stool). The interfering substances studies are not required for the classic/well established PCR (RT-PCR) using respiratory specimens, however for newer molecular type of assays, such as various isothermal methods, testing of potential interferents will be required even for respiratory specimens. Can reference CLSI EP07.	N	Summaries only
Precision	Conduct internal precision testing (i.e., at the manufacturer's site) in accordance with CLSI, EP5-A2. In the context of SAP, the 3x5x5 (3 instruments x 5 days x 5 replicates) design is acceptable to provide preliminary estimates of the repeatability (within run) and reproducibility of the assay. Full assessment of repeatability using the 20x2x2 (20 days × 2 run per day × 2 replicates) is expected at time of licensing.	N	Summaries only
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	N	Summaries only

Clinical Evaluation	Known clinical samples Minimum of 30 reactive and 30 non-reactive specimens • Other concentrations and non-reactive (100% agreement)	N	A total of 40 contrived positive specimens at approximately 1X to 2X LOD and 20x LOD were tested.
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	
Quality	• QMS certificate provided? • Evidence of lot release programme	Y	

Standard Questions (Round #1):

- Select appropriate preamble and questions for the application.
- Email questions to Admin screener

You are asked to reply to this email with the requested information within 10 calendar days. If you do not reply to this email within 10 calendar days, we will consider the non-response as a formal withdrawal of your application. In such an instance, Health Canada will not follow-up with any additional communication regarding your application and will mark the application as withdrawn in our database.

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. Please ensure that the actual study reports are provided when requested; it is not considered sufficient to simply state performance characteristics without providing the scientific results. Failure to provide a complete and comprehensive response may result in refusal of the application.

Extensions may be granted for a maximum total of 30 days. If you require more than 30 days (for example, to run a new study) please withdraw your current application and resubmit when the new, complete application is prepared. To request an extension, please reply to this email and provide a date within the next 30 days by which you will be able to submit the required information.

For many of the questions below, statements have been made in the Instructions for Use, but evidence (scientific reports) were not provided.

For some of the questions below, very brief summaries were provided, but these summaries lacked adequate level of detail for review.

Ensure that actual study reports are provided when requested. It is generally not sufficient to state performance characteristics without providing supporting scientific evidence. Failure to provide the requested information may result in refusal of your application.

As a guide, the expected format for study summaries has been provided below the questions.

Questions:

1. Provide a complete device description, with details and rationale for its design, and for your selection of all reagents. Include a detailed description of all components, including their composition and source.
2. Describe all instruments required to perform the test, from sample collection to result. Provide details on the reaction settings required (temperature, time).
3. Provide a clear description outlining the specimen types that can be used with the device, the extraction methods that are to be used for each, and the specimen volume required. Note that the evidence you

provide in support of your device must include all labelled sample types, or you must provide evidence that these sample types are equivalent.

4. Describe the sample extraction methods required for all claimed specimen types, including specific commercial kits and instrumentation, if relevant to be used with the test device. Include the study report which provides evidence that the extraction methods work with the test device.
5. Provide a detailed description of all controls used with the kit (e.g. negative control, positive control, internal control), including a rationale for their selection, and their source. Identify the specific sequences of targets, primers and probes, where relevant. Describe the recommended frequency of use, thet results expected and the acceptance criteria. Ensure you identify the concentration of the positive control relative to the LoD
6. Describe the targeted sequences of the SARS-CoV-2 genome. Provide a list of all primers and probe sets and briefly describe what they detect, and include their nucleic acid sequences. Indicate if biotin-streptavidin/avidin chemistry is used in any steps of the test. You may include relevant supporting literature.
7. Provide a study report, or a detailed summary of methods and results, to support the claimed Limit of Detection (LoD)/analytical sensitivity. LoD can be determined by spiking RNA or inactivated virus into a clinical (preferred) or an artificial matrix. The matrix selected should represent the most challenging clinical matrix. The initial study requires a dilution series including 3 replicates for each concentration. The confirmatory study with 20 replicates of the final concentration is needed. Include in your responses a detailed description of the samples (live or inactivated virus, viral RNA) used in these studies, including their source.
8. Provide a description of your *in silico* analysis of inclusivity, including the database search parameters, the number of SARS-CoV-2 sequences analyzed, the date the analysis was performed, etc. Provide a summary of the results, including the % identity to current published COVID19 sequences, a description of any mismatches and a discussion of their effect on the results of your assay..
9. Provide results of matrix-specific cross reactivity studies demonstrating that the following pathogens are not cross-reacting with the assay. *In silico* analysis and all currently available results of wet testing should be submitted.
   Note: For wet testing, concentrations of 10^6 CFU/ml or higher for bacteria and 10^5 pfu/ml or higher for viruses is recommended.
   Note: If *in silico* analysis reveals ≥ 80% homology between the cross-reactivity microorganisms and your test primers/ probe(s), we recommend that you perform a microbial interference study with SARS-CoV-2 and the microorganisms that your test primers/ probe(s) have homology to, or provide an appropriate scientific rationale which supports the clinical utility of your test given your results.

High priority pathogens from the same genetic family	High priority organisms likely in the circulating area
Human coronavirus 229E	**Adenovirus (e.g. C1 Ad. 71)**
Human coronavirus OC43	**Human Metapneumovirus (hMPV)**
Human coronavirus HKU1	**Parainfluenza virus 1-4**
Human coronavirus NL63	**Influenza A & B**
SARS-coronavirus	**Enterovirus (e.g. EV68)**
MERS-coronavirus	**Respiratory syncytial virus**
	Rhinovirus
	Chlamydia pneumoniae
	Haemophilus influenzae
	Legionella pneumophila
	Mycobacterium tuberculosis
	Streptococcus pneumoniae
	Streptococcus pyrogenes
	Bordetella pertussis
	Mycoplasma pneumoniae

	***Pneumocystis jirovecii* (PJP)**
	Pooled human nasal wash - *to represent diverse microbial flora in the human respiratory tract*
	Candida albicans
	Pseudomonas aeruginosa
	Staphylococcus epidermis
	Staphylococcus salivarius

10. Provide the study reports for interference testing all proposed endogenous, and of exogenous substances (common medications).
11. Provide study reports for precision testing. Conduct internal precision testing (i.e., at the manufacturer's site) in accordance with CLSI EP5-A2. In the context of the Interim Order, the 3x5x5 (3 instruments x 5 days x 5 replicates) design is acceptable to provide preliminary estimates of the repeatability (within run) and reproducibility of the assay. Full assessment of repeatability using the 20x2x2 (20 days × 2 run per day × 2 replicates) is expected at time of authorization.
12. Stability (Shelf life and Shipping/transport stability)
    Provide all evidence currently available supporting the stability of test kit, including sample stability. Alternatively, submit a plan for stability studies. 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 the reports for any Clinical Performance Studies using known positive clinical samples. **(Note: contrived samples are not acceptable)** A minimum of **30 reactive and 30 non-reactive specimens** is needed. Validation of the reactive and non-reactive samples using a reference standard is needed, and details on the reference standard used must be provided (name and manufacturer). For reactive samples, 20 samples at 1x-2x LoD demonstrating 95% agreement is needed. Other concentrations and non-reactive samples should demonstrate 100% agreement. A statistical rationale for the sample size of the study should also be provided.

<u>Guide to study reports/summaries format</u>

a) Study Title
b) Objectives
   - Provide a short description of the objective
c) Methodology
   - Sample type: description of the matrix
   - Number of samples tested (pos & neg)
   - Sample characterization: Name of assay or method used to characterize the samples
   - Testing algorithm: time-point, replicates, run, days, site, etc
d) Results
   - Tabular format whenever possible
   - Statistical analysis
   - Discrepant results (explanation and resolution)
   - Results for each setting and/or sample type
e) Conclusion
   - Clear conclusion supporting the performance claim
   - Rationale for any method deviations

Review of Responses / New Questions (Rounds #2 etc., as deemed appropriate):

Note: As per discussion with Rosslynn on June 17 2020, questions will be repeated a second time only in subsequent rounds.

<< Date >>
<< Screener >>
<< Insert Responses/HC Comment to Screening Deficiency Questions >>

Copy/Paste this section as needed, depending on the number of rounds of questions.
Resave/re-upload to dB new file as "IO Technical Screening application #xxxxxx #2, #3, etc.

File Disposition:

1. **Background/*Antécédents***
   The applicant has requested authorisation for the above named device under the ***Interim order respecting the importation and sale of medical devices for use in relation to COVID-19.***

   In their original application, the applicant did not provided adequate evidence to allow for a full assessment the safety, effectiveness and quality of the subject device. As a result, additional information was sought, as documented above.

2. **Evaluation/*Évaluation***
   <Provide a short description of the type of information that was requested, and what is still either missing or inadequate.

3. **Conclusion**
   The applicant has not provided the required level of scientific evidence to allow for an assessment of device safety, effectiveness and quality, as required under the IO, and as outlined in the ***Guidance on Requirements for serological antibody tests submitted under the COVID-19 Interim Order***. No further review is possible at this time.

4. **Recommendation**

   Recommend for Review…… ☐
   Recommend for Rejection…… ☐

   The applicant should be notified that their application cannot be evaluated further based on the evidence provided to date.

Chose one of the 4 choices below as applicable; delete others:

< The application is recommended for rejection because the evidence submitted does not meet the requirements set out in Section 5(a) of the Interim Order respecting the importation and sale of medical devices for use in relation to COVID-19, to enable us to issue the authorization. >

< The application is recommended for rejection because Health Canada did not receive a response to the questions sent on [xxx]. The lack of a response therefore did not satisfy Section 5(b) of the Interim Order respecting the importation and sale of medical devices for use in relation to COVID-19. >

< The application is recommended for rejection because the evidence submitted was not sufficient to allow Health Canada to conclude the benefits of this product outweigh the risks to the general public. This is a requirement of Section 5(c) of the Interim Order respecting the importation and sale of medical devices for use in relation to COVID-19, to enable us to issue the authorization. >

< The application is recommended for rejection because the evidence submitted was not sufficient to allow Health Canada to conclude that the health or safety of patients, users or other persons will not be unduly affected. This is a requirement of Section 5(d) of the Interim Order respecting the importation and sale of medical devices for use in relation to COVID-19, to enable us to issue the authorization. >

The following deficiencies remain:
<List deficiencies here, as they are to appear in the letter to the applicant. For example: Missing or deficient cross-reactivity testing, etc>

OR

<insert technical assessment, if necessary for explaining our conclusion>