CE59PT0402

Hangzhou Clongene Biotech Co., Ltd.

Risk Analysis Report

COVID-19 Antigen Rapid Test Cassette (Nasal Swab)

Revision	By	Date
1.0	Xingqiao Pang	29/01/2021

1. Summarize

This report is a risk analysis to the COVID-19 Antigen Rapid Test Cassette (Nasal Swab). The report would determine all potential hazards and the potential reason that each hazard would cause, and estimate the probability of hazard occurrences, and, simultaneously, estimate the damage level once hazards occur. If there are the measures to reduce the risk, expatiate it, and estimate the residual risk levels.

Conclusion: By taking the adaptable measures, all risk that would cause hazard would be reduced to the level that can be as low as reasonably practicable, that is to say, the potential risk would be reduced to the practicable levels.

2. Purpose

The purpose of risk analysis is to estimate the hazard, which is took place in the use of the COVID-19 Antigen Rapid Test Cassette (Nasal Swab).

3. Reference standard

a) EN ISO 14971:2019 Medical devices-Application of risk management to medical devices
b) EN 13641:2002 Elimination or reduction of risk of infection related to in vitro diagnostic reagents
c) 98/79/EC Directive 98/79/EC of the European Parliament and of the council of 27 October 1998 on in vitro diagnostic medical devices
d) EN ISO 13485:2016 Medical devices - Quality management systems - Requirements for regulatory purposes
e) ISO 17511:2020 In vitro diagnostic medical devices—Requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples
f) EN ISO 18113-1:2011 In vitro diagnostic medical devices - Information supplied by the manufacturer (labelling) - Part 1: Terms, definitions and general requirements
g) EN ISO 18113-2:2011 In vitro diagnostic medical devices - Information supplied by the manufacturer (labelling) - Part 2: In vitro diagnostic reagents for professional use
h) EN ISO 15223-1:2016 Medical devices - Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements
i) EN 13975:2003 Sampling procedures used for acceptance testing of in vitro diagnostic medical devices — Statistical aspects
j) EN 13612: 2002 Performance evaluation of in vitro diagnostic medical devices
k) EN ISO 23640:2015 In vitro diagnostic medical devices - Evaluation of stability of in vitro diagnostic reagents (ISO 23640:2011)
l) EN 62366-1: 2015 Medical devices – Part1:Application of usability engineering to medical devices

4. Production specification: Structure and principal

The COVID-19 Antigen Rapid Test Cassette (Nasal Swab) is designed to detect nucleocapsid antigen

from the SARS-CoV-2 in nasal swab from patients who are suspected of COVID-19 by their healthcare provider.

Principle: The COVID-19 Antigen Rapid Test Cassette (Nasal Swab) is a lateral flow immunoassay based on the principle of the double-antibody sandwich technique. SARS-CoV-2 nucleocapsid protein monoclonal antibody conjugated with color micro- particles is used as detector and sprayed on conjugation pad.

During the test, SARS-CoV-2 antigen in the specimen interacts with SARS-CoV-2 antibody conjugated with color microparticles making antigen-antibody labeled complex. This complex migrates on the membrane via capillary action until the test line, where it will be captured by the pre-coated SARS- CoV-2 nucleocapsid protein monoclonal antibody. A colored test line (T) would be visible in the result window if SARS-CoV-2 antigens are present in the specimen. Absence of the T line suggests a negative result. The control line (C) is used for procedural control, and should always appear if the test procedure is performed properly.

5. Risk analysis group

Risk analysis group is composed of members as follows:

Title	Name	Project
Project Team Leader	Xingqiao Pang	Whole plan of risk analysis
R & D Department Manager	Qingqing Chen	Evaluate the harm degree as a view of biological
Quality Department Manager	Xingqiao Pang	Evaluate the harm degree as a view of doctor
Manufacturing Department Manager	Jun Wu	Evaluate the harm degree as a view of chemist and mechanical performance
Marketing Department Manager	Guoqin Chen	Evaluate the harm degree as a view of users

6. Identification of qualitative and quantitative characteristics (acc. to EN ISO 14971:2019)

a) What is the intended use and how to be used?

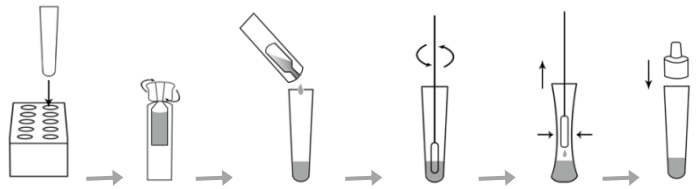
The COVID-19 Antigen Rapid Test Cassette (Nasal Swab) is a lateral flow immunoassay intended for the qualitative detection SARS-CoV-2 nucleocapsid antigens in nasal swab from individuals who are suspected of COVID-19 by their healthcare provider.

The COVID-19Antigen Rapid Test Cassette (Nasal Swab) is intended for use by medical professionals or trained operators who are proficient in performing lateral flow tests. The product may be used in any laboratory and non-laboratory environment that meets the requirements specified in the Instructions for Use and local regulation.

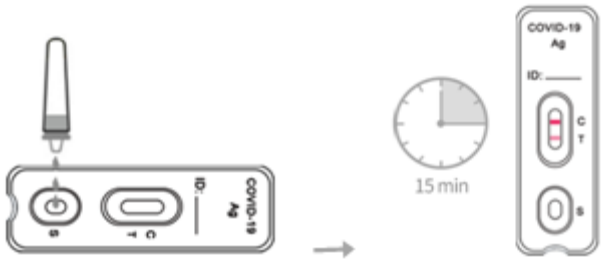
The method of using:

Note: Allow the test cassettes, reagents and specimens to equilibrate to room temperature (15-30℃ or 59-86℉) prior to testing.

1. Put an extraction tube on the work station.
2. Unscrew the lid of an extraction reagent. Add all of the extraction reagent into the extraction tube.
3. Sampling refers to section 'Specimen Collection'.
4. Insert the nasal swab specimen into the extraction tube which contains extraction reagent. Roll the swab at least 5 times while pressing the head against the bottom and side of the extraction tube. **Leave the nasal swab in the extraction tube for one minute.**
5. Remove the nasal swab while squeezing the sides of the tube to extract the liquid from the swab. The extracted solution will be used as test sample.
6. Cover the extraction tube with a dropper tip tightly.



7. Remove the test cassette from the sealed pouch.
8. Reverse the specimen extraction tube, holding the tube upright, transfer 3 drops (approximately 100μL) slowly to the specimen well (S) of the test cassette, then start the timer.
9. Wait for colored lines to appear. Interpret the test results **at 15 minutes**. Do not read results after 20 minutes.



b) Intended to be in contact with the patient or other persons?

The COVID-19 Antigen Rapid Test Cassette (Nasal Swab) which is intended for in vitro diagnostic use only will not contact the patient or other persons.

c) Materials/components used

All materials or components used in the reagents had been widely used in many IVD products, which have been used in clinical test for several years and proven on the safe side. And many of those IVD products have the CE certifications.

d) Is energy delivered to or extracted from the patient?

There is not any energy flowing in or out from the patient.

e) Are substances delivered to or extracted from the patient?

There are not any substances coming into the patients bodies. The nasal swab is the substance out from the patients. In general, the specimen will be collected by trained clinical laboratory personnel specifically instructed and trained in vitro diagnostic procedures following standard laboratory procedures, which would not make any hazard for patients.

f) Are biological materials processed by the reagent for subsequent re-use, transfusion or transplantation?

To prevent inaccurate test results due to improper specimen handling and/or transportation, after collecting specimens in accordance with routine clinical laboratory procedures, we need to store the swab in the extraction reagent provided with the kit, or immerse the swab head in the prescribed virus preservation solution to store. In addition, we need to extract the solution from the collected swab specimen as the test sample through the extraction tube with the extraction reagent added. Therefore, it is strongly recommended to train in specimen collection.

g) Is the reagent supplied sterile or intended to be sterilized by the user?

The reagents do not need the asepsis style or sterilization.

h) Is the reagent intended to modify the patient environment?

The reagents are not intended to modify the patient environment.

i) If the reagent has the measure function or analysis function?

The reagents have not measure function or analysis function.

j) Is the reagent intended for use in conjunction with other medical devices, medicines or other medical technologies?

The reagents do not use in conjunction with any medicines or other medical technologies.

k) Are there unwanted outputs of energy or substances?

The reagents have not any energy or matter output unexpected.

l) Is the reagent susceptible to environmental influences?

The condition for transporting and storing the reagents, which are not special requests, as follows: the temperature range is 4℃~30℃, the relative humidity is normal.

m) Does the reagent influence the environment?

All nasal swabs specimens and used reagents should be considered potentially infectious and avoided contact with skin.

n) Are there essential consumables or accessories associated with the reagent?

The accessories going with the reagents are dropper tip, extraction tube, work station and sterilized swab.

o) Is maintenance or calibration necessary?

Each reagent is used only once. So the reagents need not maintenance and/or calibration.

p) Does the reagent contain software?

The reagent does not contain software.

q) Does the reagent have a restricted shelf-life?

The reagents have the shelf-life of 24 months.

r) Are there any delayed or long-term use effects?

Test results of the reagent may be unauthentic if lingering and/or long-term used.

s) What determines the lifetime of the reagent?

The lifetime of the reagent is influenced by the environment temperature and the seal of the foil pouch. When the environment temperature exceeds 30℃, or the foil pouch was seal incompletely, the lifetime of the reagent will be reduced greatly.

t) Is the reagent intended for single use?

Yes.

u) Is safe decommissioning or disposal of the medical reagent necessary?

Discard the reagent in the bio-hazardous dustbin after single use.

v) Does installation or use of the reagent require special training or special skills?

The operator must be pre-trained specially before use the reagent.

w) How will information for safe use be provided?

The information for safe use included in the labels and IFU will be provided directly to the end user.

x) Will new manufacturing processes need to be established or introduced?

Any new manufacturing processes needn’t be established or introduced.

y) Is successful application of the medical device critically dependent on human factors?

The user should read “Test Procedure” in the IFU before performing the test.

7. Risk assessment of hazards

Severity

Ranking	Ranking (descriptive)	Description

1	Negligible	Temporary discomfort or inconvenience to user/operator
2	Marginal	Injury (usually requiring medical intervention) to user/operator
3	Critical	Severe injury or impairment to user/operator
4	Catastrophic	Life-threatening or death to user/operator

Probability of Occurrence

Ranking	Likelihood	Description	Probability
1	Improbable	Unlikely to occur	$<10^{-6}$
2	Remote	Unlikely but possible to occur	$10^{-4}\sim10^{-6}$
3	Occasional	Likely to occur sometime	$10^{-3}\sim10^{-4}$
4	Probable	Likely to occur several times	$10^{-1}\sim10^{-3}$
5	Frequent	Likely to occur frequently	$\geqslant10^{-1}$

Risk Assessment Table

		Severity			
		Negligible	Marginal	Critical	Catastrophic
Probability	Frequent				
	Probable				
	Occasional				
	Remote				
	Improbable				

Risk Assessment Levels

Level	Safety Risk	Description
Red	Unacceptable	Risk in this region is not tolerated. Resolution Required – redesign, do not release.
Green	Acceptable	Risk is considered to be negligible compared to the risk of other hazards.

Hazard	Risk Assessment before Mitigation					Risk Control Measure	Risk Assessment after Mitigation		
	Cause	Adverse Effect	Risk Estimation		Risk Evaluation		Risk Estimation		Risk Evaluation
			Severity	Probability of Occurrence			Severity	Probability of Occurrence	
False Results	The quality of the antibodies does not produce the expected performance.	Users requires medical attention	3	3	Unacceptable	Design control phase 3 & 4 reports require verification and validation. Incoming QC inspection documents -Specification For 101005001 (QC-2050) -Specification For 101005301 (QC-2053) -Specification For 101000401 (QC-2004)	3	1	Acceptable
False Results	Critical raw material (mouse- anti-goat IgG polyclonal antibody, SARS-CoV-2 nuclenocapsid protein monoclonal antibody, SARS-CoV-3 nuclenocapsid protein monoclonal antibody) is non-conforming.	Users requires medical attention	3	3	Unacceptable	Design control phase 3 & 4 reports require product testing, verification & validation; incoming QC inspection must be done. -Specification For 101005001 (QC-2050) -Specification For 101005301 (QC-2053) -Specification For 101000401 (QC-2004)	3	1	Acceptable
False Results	Inadequate stability of the raw material	Users requires medical attention	3	3	Unacceptable	Qualification of alternate suppliers if possible, appropriate QC inspection criteria. Stability testing should be done. -Specification of QC -Procurement Specification	3	1	Acceptable
False Results	The sample pad does not conform to specifications.	Users requires medical attention	3	3	Unacceptable	Sample pad inspection procedure -Inspection Criterion For Fiberglass (QC-3003)	3	1	Acceptable

Hazard	Risk Assessment before Mitigation					Risk Control Measure	Risk Assessment after Mitigation		
	Cause	Adverse Effect	Risk Estimation		Risk Evaluation		Risk Estimation		Risk Evaluation
			Severity	Probability of Occurrence			Severity	Probability of Occurrence	
False Results	Packaging materials do not conform to specifications.	Users requires medical attention	3	3	Unacceptable	Packaging materials Inspection and testing control procedure -Inspection Criterion For Carton (QC-3023) -Inspection Criterion For Foil Bag (QC-3026)	3	1	Acceptable
False Results	The storage conditions of raw material are not correct.	Users requires medical attention	3	3	Unacceptable	The shelf life of the raw material should be defined in COA from vender and validated by R&D during the product development; Manufacturing SOPs -Raw Material Warehouse Management System (QMS-P01)	3	1	Acceptable
False Results	Operator not following manufacturing procedures.	Users requires medical attention	3	3	Unacceptable	manufacturing & QC inspection documents; training procedures -Specification of QC -Procurement Specification -Standard Operating Procedures -Control Procedure of Manufacturing Process(QMS-L00) -Training Management System (QMS-D02)	3	1	Acceptable
False Results	Lack of reagent integrality (e.g. the desiccant is missing)	Users requires medical attention	3	3	Unacceptable	QC inspection documents -Standard Practice for assembly of drop reagent (MF-2021) - Functional Testing Procedure	1	1	Acceptable

Hazard	Risk Assessment before Mitigation					Risk Control Measure	Risk Assessment after Mitigation		
	Cause	Adverse Effect	Risk Estimation		Risk Evaluation		Risk Estimation		Risk Evaluation
			Severity	Probability of Occurrence			Severity	Probability of Occurrence	
						For COVID-19 Semi-Finished Product - Preparation Of COVID-19 Control Standards - Final Testing Procedure For COVID-19 Product			
False Results	Improper package	Users requires medical attention	3	3	Unacceptable	Packaging SOP and finished product QC - Final Testing Procedure For COVID-19 Product	3	1	Acceptable
False Results	Incorrect QC Samples used, inappropriate QC procedure	Users requires medical attention	3	3	Unacceptable	Manufacturing & QC inspection documents; training procedures QC inspection documents; training procedures -Specification of QC -Procurement Specification - Functional Testing Procedure For COVID-19 Semi-Finished Product - Final Testing Procedure For COVID-19 Product -Training Management System (QMS-D02)	3	1	Acceptable
False-positive	The nature/ characteristic of the sample gives interference	Can have extremely devastating psychological effects on the person tested ,or damage to the reputation, even lead to unemployment and	3	3	Unacceptable	Interferences substances were tested during development and field trials The IFU indicates which samples to use. -Instruction for use of COVID-19 Antigen Rapid	3	1	Acceptable

Hazard	Risk Assessment before Mitigation					Risk Control Measure	Risk Assessment after Mitigation		
	Cause	Adverse Effect	Risk Estimation		Risk Evaluation		Risk Estimation		Risk Evaluation
			Severity	Probability of Occurrence			Severity	Probability of Occurrence	
		serious medical consequences				Test Cassette (Nasal Swab) (CE59-attachment 7.2) Validation studies - Interference Study Report (CE59PT0507)			
False-positive	Cross reaction with other interference substances	Can have extremely devastating psychological effects on the person tested ,or damage to the reputation, even lead to unemployment and serious medical consequences	3	3	Unacceptable	Interferences substances were tested during development and field trials The IFU indicates which samples to use. - Instruction for use of COVID-19 Antigen Rapid Test Cassette (Nasal Swab) (CE59-attachment 7.2) Validation studies - Analytical Specificity (Cross-reactivity) Study Report (CE59PT0503)	3	1	Acceptable
False-negative	Interferences due to the different types of samples	Physical harm caused to the person tested, and lead to some adverse effect on society	3	3	Unacceptable	The different samples to use are tested during development and field trials. The IFU indicates which samples to use. - Instruction for use of COVID-19 Antigen Rapid Test Cassette (Nasal Swab) (CE59-attachment 7.2) Validation studies	3	1	Acceptable
False Results	Storage and transport conditions are not correct	Users requires medical attention	3	3	Unacceptable	Labels and IFU provide the proper storage conditions. -Labels and Instruction for use of COVID-19 Antigen	3	1	Acceptable

Hazard	Risk Assessment before Mitigation					Risk Control Measure	Risk Assessment after Mitigation		
	Cause	Adverse Effect	Risk Estimation		Risk Evaluation		Risk Estimation		Risk Evaluation
			Severity	Probability of Occurrence			Severity	Probability of Occurrence	
						Rapid Test Cassette (Nasal Swab) (CE59-attachment 7.1、7.2) Validation studies - Stability Study Report (CE59PT0501)			
False Results	Deviate from the intended use	Users requires medical attention	3	3	Unacceptable	Labels and IFU provide the proper intended use. -Labels and Instruction for use of COVID-19 Antigen Rapid Test Cassette (Nasal Swab) (CE59-attachment 7.1、7.2)	3	1	Acceptable
False Results	Finger contact leads to contamination of the test	Users requires medical attention	3	3	Unacceptable	The operator is a trained professional. The IFU warns the operator not to touch the membrane. - Instruction for use of COVID-19 Antigen Rapid Test Cassette (Nasal Swab) (CE59-attachment 7.2)	3	1	Acceptable
False-negative	Insufficient sample applied	Physical harm caused to the person tested, and lead to some adverse effect on society	3	3	Unacceptable	Design control phase 3 & 4 reports require verification and validation and Information in IFU - Instruction for use of COVID-19 Antigen Rapid Test Cassette (Nasal Swab) (CE59-attachment 7.2)	3	1	Acceptable
False Results	Improper operation	Users requires medical attention	3	3	Unacceptable	The IFU describes the correct test procedure and stresses the critical procedure.	3	1	Acceptable

Hazard	Risk Assessment before Mitigation					Risk Control Measure	Risk Assessment after Mitigation		
	Cause	Adverse Effect	Risk Estimation		Risk Evaluation		Risk Estimation		Risk Evaluation
			Severity	Probability of Occurrence			Severity	Probability of Occurrence	
						- Instruction for use of COVID-19 Antigen Rapid Test Cassette (Nasal Swab) (CE59-attachment 7.2)			
Incorrect Reading	Improper operating environment (e.g. Ambient temperature too high or too low)	Users requires medical attention	3	3	Unacceptable	Appropriate operating environment are established during development and validation. And the IFU mentions the conditions. - Instruction for use of COVID-19 Antigen Rapid Test Cassette (Nasal Swab) (CE59-attachment 7.2)	3	1	Acceptable
Incorrect Reading	Instructions for use regarding Read Result Time not followed.	Users requires medical attention	3	3	Unacceptable	The read result times are established during development and validated during the validation studies. The IFU describes the correct reading time. - Instruction for use of COVID-19 Antigen Rapid Test Cassette (Nasal Swab) (CE59-attachment 7.2)	3	1	Acceptable
Incorrect Reading	Confusion between control line and test line results	Users requires medical attention	3	3	Unacceptable	Information presented in the IFU - Instruction for use of COVID-19 Antigen Rapid Test Cassette (Nasal Swab) (CE59-attachment 7.2)	3	1	Acceptable
Users contamination	Biological and/or chemical contamination	Health Risk	3	3	Unacceptable	The operator is a trained professional. The package insert warns the operator about	3	1	Acceptable

Hazard	Risk Assessment before Mitigation					Risk Control Measure	Risk Assessment after Mitigation		
	Cause	Adverse Effect	Risk Estimation		Risk Evaluation		Risk Estimation		Risk Evaluation
			Severity	Probability of Occurrence			Severity	Probability of Occurrence	
						any potentially hazardous material and the necessity to wear gloves. - Instruction for use of COVID-19 Antigen Rapid Test Cassette (Nasal Swab) (CE59-attachment 7.2)			
Users contamination	The operator is in contact with the sample during or after sample application	Health Risk	3	3	Unacceptable	The operator is a trained professional. The package insert warns the operator that the sample is potentially infectious. The package insert mentions the use of gloves -Labels and Instruction for use of COVID-19 Antigen Rapid Test Cassette (Nasal Swab) (CE59-attachment 7.1、7.2)	3	1	Acceptable
False Results	Unqualified samples are used	Users need more medical testing	3	4	Unacceptable	The requirements of sample collection and the storage conditions for sample are established during development and validation. This information will be mentioned in package insert. - Instruction for use of COVID-19 Antigen Rapid Test Cassette (Nasal Swab) (CE59-attachment 7.2)	3	1	Acceptable
Environmental contamination	Improper treatment the waste/appliance	Health Risk	3	4	Unacceptable	The IFU warns to handle all specimens and other castoff as potentially infectious.	3	1	Acceptable

Hazard	Risk Assessment before Mitigation					Risk Control Measure	Risk Assessment after Mitigation		
	Cause	Adverse Effect	Risk Estimation		Risk Evaluation		Risk Estimation		Risk Evaluation
			Severity	Probability of Occurrence			Severity	Probability of Occurrence	
						- Instruction for use of COVID-19 Antigen Rapid Test Cassette (Nasal Swab) (CE59-attachment 7.2)			

8. Conclusion

When we use some measurement to solve or reduce all the potential risks of the reagent, effect is obvious, as showing above. It can be seen that the residual risks are as low as reasonably practicable and is located in the area of comprehensive acceptable, so risk and advantage is proportional. The COVID-19 Antigen Rapid Test Cassette (Nasal Swab) has used for long time for all over the world, and that advantage is greater than risk is obvious.

As it is has been seen that the residual risk of the COVID-19 Antigen Rapid Test Cassette (Nasal Swab) is reasonably practicable, and the COVID-19 Antigen Rapid Test Cassette (Nasal Swab) is safe and effective in clinic.

9. Reference

MAUDE Database: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.CFM

The Risk Control Measure Effectiveness and Verification Methods Effectiveness have been reviewed and all hazards / risks are either acceptable or ALARP

Product Identification: COVID-19 Antigen Rapid Test Cassette (Nasal Swab)

Team Leader: Xingqiao Pang

Risk Analysis Team Membership **Date:** 2021-01-29

Attendees:

Printed Name	Signature	Department
Lulu Zhang		R & D
Qingqing chen		R & D
Jun Wu		Manufacturing
Xingqiao Pang		Quality
Guoqin Chen		Marketing

Design Review Committee Disposition

Department	Recommend Approval	Printed Name	Signature	Date
R & D	[√] Yes [ ] No [ ] Cond.	Qingqing chen		2021.01.29
Manufacturing	[√] Yes [ ] No [ ] Cond.	Jun Wu		2021.01.29
Quality	[√] Yes [ ] No [ ] Cond.	Xingqiao Pang		2021.01.29
Marketing	[√] Yes [ ] No [ ] Cond.	Guoqin Chen		2021.01.29

Risk Analysis Report Final Disposition (The final disposition is ruled by majority vote of the Design Review Committee. This portion is filled out by the Regulatory representative.)

☑ Approved

☐ Approved, but requires follow-up (see comments)

☐ Not approved, requires additional work (see comments)

Comments: _____

Approved By: _____ Date: 2021.01.29