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Application to obtain exemption for Novel Coronavirus (COVID-19) Antigen Test Kit (Colloidal Gold) nasal for use as self-test.

Applicant

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1. Product name: **Novel Coronavirus (COVID-19) Antigen Test Kit (Colloidal Gold) nasal**
Catalogue No. 303036
Referred to as: Lyher COVID-19 antigen test kit (nasal)

Manufacturer: Hangzhou Laihe Biotech Co. Ltd., Hangzhou, Zhejiang, China

2. Specific Conditions and criteria for the exemption procedure

The distributor has satisfied the following conditions and criteria:

The rapid antigen test in question already bears a CE-mark for professional use:

Declaration of Conformity (DOC): see attachment 1. The Lyher COVID-19 antigen test kit (Colloidal Gold) for professional use meets the requirements of in vitro diagnostic directive (98/79/EC) and the following harmonized standards EN ISO 14971-2012; EN ISO 18113-2-2011; EN ISO 234640-2015; EN ISO 18113-1-2011; EN 13612:2002+AC:2002; EN 13641-2002.

The manufacturer has already started a conformity assessment procedure with a notified body to obtain a CE-mark for the use of the rapid antigen test as a self-test.

The Lyher COVID-19 antigen test kit (nasal) for home use contains the exact same extraction buffer tube and test device for which this DOC applies for. The difference is the nasal swab device. The procedure for CE mark for the COVID-19 antigen test kit (nasal) for home use (self-testing) is in progress. Attachment 2.

The suitability of the rapid antigen test as a self-test has been demonstrated for a specifically defined target group.

The clinical report on Lyher COVID-19 Antigen test kit (nasal) dated 08-02-2021 produced by Hangzhou Laihe Biotech Co., Ltd. showed no statistically significant difference between Lyher COVID-19 antigen test kit results compared to PCR test results measured in nasal swab of patients and the clinical diagnosis results, which were highly consistent. That showed Lyher Kit was suitable for at home self-testing.

Summary Lyher clinical report on Lyher COVID-19 Antigen test kit (nasal) Attachment 3.:

3 Medical institutions in Liaoning, Heilongjiang and Hebei performed the clinical evaluation of Novel Coronavirus (COVID-19) Antigen Test Kit (nasal) developed by Hangzhou Laihe Biotech Co., Ltd. **The clinical trial was compared with PCR test results and clinical diagnosis results to investigate the consistency of the products of Hangzhou Laihe Biotech Co., Ltd. with the clinical diagnosis results.** A total of 411 patients' nasal swab were collected in this clinical trial, one by a specialist for PCR detection and one collected by patients themselves or their guardian for Lyher test. Samples for PCR test are blinded before testing, and unblinded after all test are finished. All the cases were diagnosed by Novel Coronavirus (2019-nCoV) Nucleic Acid Diagnostic Kit (PCR-Fluorescence Probing) of Sansure BioTech Inc. The analysis of **population of the subjects** are as follow:

Age distribution of the participants

Age group	Number	% of total
≤20	38	9.25%
21~40	92	22.38%
41~60	182	44.28%
61~80	89	21.65%
Above 80	10	2.43%

Sex of the participants

Gender	Number	% of total
Male	221	53.77%
Female	190	46.23%

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Educational background of the participants

Educational group	Number	% of total
Middle School	69	16.79%
High School	191	46.47%
Bachelor	106	25.79%
Others	45	10.95%

Occupational background of the participants

Profession	Number	% of total
Jobless	55	13.38%
Sales	128	31.14%
Clerk	166	40.39%
Others	62	15.09%

Whether used the COVID-19 testing products before?

	Number	% of total
Yes	0	0
No	411	100

The participants' ages range from 9 to 86, and most of them were from 21 to 80. They also showed different culture backgrounds. None of the participants had used a COVID-19 kit before. 68.13% reported that they were high-school graduates or lower and 53.77% participants were male.

The Lyher Kit tested was 152 positive out of 160 PCR positive, 250 negative out of 251 PCR negative. The **160 positive cases** were all **between 0 and 7 days of onset** and did not involve **asymptomatic patients**. Compared with the results of PCR and clinical diagnosis, the **clinical sensitivity** of Lyher Kit was **95.00%**, the **clinical specificity** of Lyher Kit was **99.60%**, the total coincidence rate was 97.81%, Kappa=0.972. There was no statistically significant difference between the test results of Lyher Kit and the clinical diagnosis results, the results of Lyher Kit were highly consistent with the results of clinical diagnosis and PCR test.

Lyher Results from Patients and PCR

Test Results of Lyher Kit	Clinical diagnosis (PCR results)		
	Positive (+)	Negative (-)	Total
Positive (+)	152	1	153
Negative (-)	8	250	258
Total	160	251	411

Conclusion: Novel Coronavirus (COVID-19) Antigen Test Kit (Colloidal Gold) produced by Hangzhou Laihe Biotech Co., Ltd. showed no statistical significant difference between Lyher Kit test results tested by patients and the clinical diagnosis results, which were highly consistent. That showed Lyher Kit was suitability for non-professional use (self-test).

Additional information on the Lyher COVID-19 antigen test kit (nasal):

- Stability study (Attachment 4), demonstrates that the test kit is stable for < 21 months under storage conditions between 2-30C. In addition, storage of nasal specimens (2-8C) and transportation has no adverse effect on product quality.
- LoD study (Attachment 5.1): detection limit is 1.35 x 10^2 $TCID_{50}$/mL.
- Cross reactivity (Attachment 5.2): the test kit shows no cross reactivity for common viruses, including other corona viruses, and respiratory bacteria.
- Blood, toothpaste and other mouth products do not affect the test results.
- A wide range of anti-viral and anti-inflammatory drugs do not affect the test results.
- The test kit does not show high virus dose hook effect (Attachment 5.3). Highest dose tested 1 x 10^7 $TCID_{50}$/mL.
- Nasal sample addition to the test kit should be completed within 40 min (Attachment 5.4, p1)
- The volume of specimen added to the test kit should be not less than 2 drops (Attachment 5.4, p2).
- The test provides a correct and valid result interpretation at a read time between 15 and 20 minutes (Attachment 5.4, p3).
- For accurate test results extracting the sample from the swab should be performed within 4 hours

(Attachment 5.4, p4).
- Appropriate treatment of nasal swab is to squeeze the swab at least 10 times in the buffer tube and let it stand for 2 minutes (Attachment 5.4, p5).
- Specimens and test kits should be used at room temperature (>16C) and humidity does not affect test results (Attachment 5.4, p6).
- The performance of test kits is not affected when they fall to the ground or their shells are damaged (Attachment 5.4, p7).
- Test results should be read under sufficient lighting conditions (Attachment 5.4, p8).
- The test kit should be put on a flat non-tilted surface (Attachment 5.4, p9).
- Vibration or noise does not affect the test results (Attachment 5.4, p10).

The rapid antigen test satisfies the requirements for devices for self-testing as set out in the Decree on *in vitro* diagnostic medical devices (IVDs) and existing standards for self-tests (with the exception of the design-examination certificate for self-tests, issued by a notified body).

Risk analysis report according to EN ISO 14971:2016,cl. 4.2 standards (Attachment 6): all the risk has been identified and the risks which are non accepted have been controlled by measure taken by the manufacturer.
Essential requirements report for Lyher CIVOD-19 antigen test kit (nasal) (Attachment 7).

3. General conditions and criteria for the exemption procedure

The Health Security Committee's 'A common list of COVID-19 rapid antigen tests',[1] published on 17 February 2021.

The Lyher COVID-19 antigen test kit (nasal) is not listed.

Another EU member state has already granted an exemption for use of the rapid antigen test as a self-test.

The Lyher COVID-19 antigen test kit (nasal) has been granted an exemption for use as self-test by BfArM in Germany.
The Lyher COVID-19 antigen test kit (nasal) is evaluated by Paul-Ehrlich-Institut, Federal Institute for Vaccines and Biomedicines, Langen (Hessen) Germany (Attachment 8). The LYHER COVID-19 antigen test kit (nasal) for home used was validated compared to PCR positive nasal samples (high viral load CT<25, CT25-30 & low viral load CT>30) and PCR negative samples.
Attached please find the approval letter for the Lyher COVID-19 antigen test kit (nasal) for home use from the Federal Institute for Drugs and Medical Devices (BfArM) Bonn, Germany. Attachment 9.1 and Attachment 9.2.

A post-market surveillance system is in place for recording and assessing experiences with using the rapid antigen test as a self-test, based on which appropriate measures can be taken if necessary

The distributor will outsource the post-market surveillance at BAAT Medical, Hengelo, the Netherlands.

Reporting of incidents and safety issues related to self-administering the test in question to the Health and Youth Care Inspectorate (IGJ).

We will report calamities and safety issues related to the self-sampling to the IGJ immediately.

The regular statutory vigilance procedures relating to general safety and performance requirements.

We comply with the regular statutory vigilance procedures relating to general safety and performance requirements.

CE-mark for use of the rapid antigen test as a self-test

When we will obtain a CE mark (Declaration of Conformity) for the Lyher COVID-19 antigen test (nasal) for self-test, we will inform IGJ and the Pharmaceuticals and Medical Technology Department (GMT) of the Ministry of Health, Welfare and Sport via 5.1.2e minvws.nl.

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4. Check list of required documentation

1. Evidence that the rapid antigen test bears a CE-mark for professional use, including the supporting documentation. Attachment 1.

2. Evidence that an application has been submitted to a notified body of one of the EU member states to obtain CE-certification for use of the rapid antigen test as a self-test. Alternatively, evidence that a contract has been signed for a conformity assessment procedure via a notified body of one of the EU member states for use of the rapid antigen test as a self-test, including a confirmed plan of action with a timetable for obtaining CE-certification (if available). Attachment 2.

3. Product information:
   - Product name/trade name and catalogue number. Attachment 11.
   - General description of the test and how it works. Attachment 11.
   - Intended use of the test, including type of sample/sampling method and description of the testing target group. Attachment 11.
   - Clear (digital) illustrations or photos of the various components of the test and photos of the packaging from all sides and of the labels.
     Attachment 11.
   - Validation studies: reports of analytical and clinical validation studies (describing methods and results) into the test's performance when self-administered without supervision (sensitivity and specificity).
     Nasal specimens were tested by lay persons and obtained results were compared with the clinical diagnosis results and PCR, to evaluate the sensitivity, specificity and other indicators of the product, and to verify the accuracy of the product in clinical determination, so as to determine whether it meets the requirements of safety and effectiveness.
     Attachment 3.
   - If the data used for validation is based on a study performed outside the Netherlands, explain how this data can be extrapolated to the Dutch situation. The tests have been validated by a German institution. The population of Germany is similar and comparable to the population of the Netherlands.
     Attachment 8, 9.1, and 9.2.
   - Validation studies: reports of analytical and clinical validation studies (describing method and results) into the test's performance when administered professionally (sensitivity and specificity).
     Attachment 3.
   - Study into user-friendliness of the rapid antigen test when self-administered, taking due account of the requirements set out in EN-IEC62366-1.
     Attachment 3, paragraph 4.3.2:
     All participants (n=412) understood how to interpret the results.
     The clarity of the package insert, feasibility of the test device was as follows:

     Clarity of the package insert

remarks	very clear	clear	ambiguous	very ambiguous
Instruction for use	289	122	0	0
Interpretation of results	313	89	0	0

     Clarity of test simplicity

remarks	very easy	easy	difficult	very difficult
Instruction for use	276	135	0	0

   - Instructions for use in Dutch. This is mandatory for all self-tests. If available: instruction videos in Dutch, and a link to or information about where these videos can be found.
     Attachment 11.
   - Description of the test kit components (device, reagents, accessories) needed for administering the self-test, as well as a description of differences compared to the original test for professional use; the names of suppliers of the individual components must also be provided.
     All test kit components: test device, prepacked extraction buffer and nasal swab device are provided by the manufacturer. The difference compared to the original test for professional use is the nasal swab device. Attachment 10.
   - The CE declaration of conformity for professional use of the rapid antigen test.
     Attachment 1.
   - The CE declaration of conformity for any components not included in the professional test,

if applicable. Not applicable.

- Checklist of essential requirements.
  Attachment 7.
- Risk management documentation, including an overview of risk estimation, risk control measures and residual risks, in accordance with EN ISO 14971. Clearly indicate any risks connected specifically to using the test as a self-test, for example by highlighting the relevant passages.
  According to the analysis of the risks, all the risks has been identified and the risks which are none accepted have been controlled by measure taken by the manufacturer.
  Attachment 6.

Evidence that another EU member state has already granted an exemption for use of the rapid antigen test as a self-test.
Attachment 9: granted exemption for the Lyher COVID-19 antigen test kit (nasal) for self-test by Federal Institute for Drugs and Medical Devices (BfArM) Bonn, Germany.

The instructions for use must contain the instructions laid down by the government, and explain the steps to be taken in response to a negative or positive test result, respectively
Attachment 12. For now, the 'instructions for use in Dutch' contain the following:
Positive results are indicative of the presence of SARS-CoV-2. Individuals who test positive should self-isolate and seek additional care from their health care provider.
Negative results do not preclude SARS-CoV-2 infection. Individuals who test negative and continue to experience COVID-like symptoms should seek follow up care from their healthcare professional.

A positive result indicates that you are likely to have COVID-19 disease.
You need to:

1. Consult your doctor as soon as possible. Please tell them that you tested positive for COVID-19.
2. If you have no symptoms, particularly if you live in low COVID-19 infection area and have had no exposure to anyone diagnosed with COVID-19, additional molecular testing to confirm may be required.
3. you should self-isolate at home as recommendation to stop spreading the virus to others.

A negative result indicates that you are unlikely to have COVID-19 disease currently.
You need to:

1. Please note that negative cannot rule out infection with SARS-CoV-2
2. If you have symptoms persist or become more severe, please consult your doctor.
3. you may need additional molecular testing to confirm your test results

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5. Table of attachments

Attachment n°	Name
1	Declaration of Conformity Lyher COVID-19 antigen test kit
2	
3	Lyher Antigen clinical report (nasal) 20210208
4	Stability study for nasal Lyher COVID-19 antigen test kit
5.1	LoD study for nasal Lyher COVID-19 antigen test kit
5.2	Cross reactivity for Lyher COVID-19 antigen test kit
5.3	High-dose hook effect Lyher COVID-19 antigen test kit
5.4	Flex studies for nasal Lyher COVID-19 antigen test kit
6	Lyher Risk Analysis Report 20210129 COVID-19 antigen kit (nasal)
7	Essential requirements report 20210129 COVID-19 antigen test kit
8	Germany PEI evaluierung-sensitivitate-sars-cov-2-antigentests 14-12-2020
9.1	BfArM approval letter for home test
9.2	BfArM Self-test listing
10	Product information
11	Instructions for use in Dutch