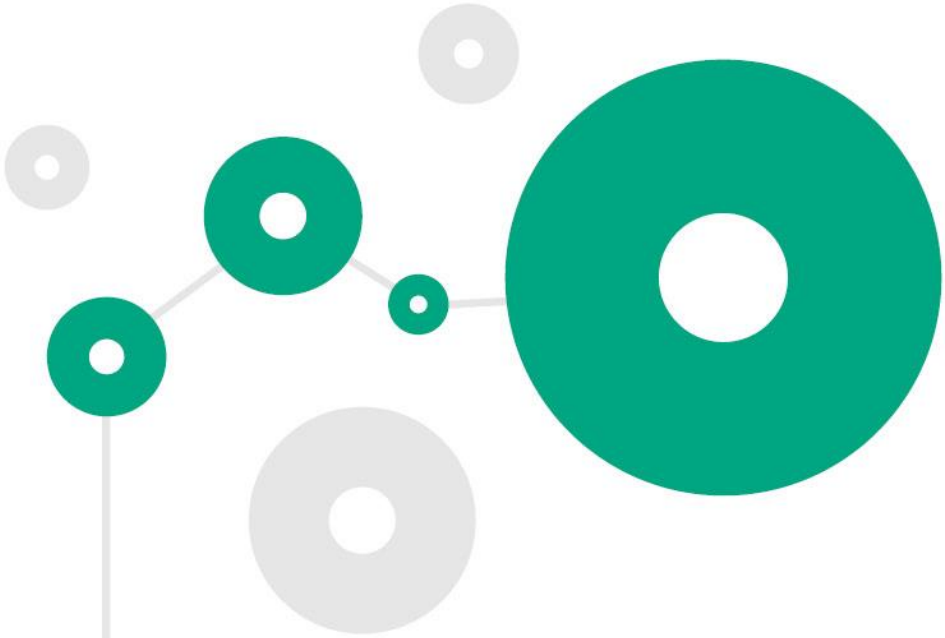

Guideline on the Review and Approval of In Vitro Diagnostic Devices for COVID-19 (For Industry)

November 2020

Ministry of Food and Drug Safety
Medical Device Evaluation Department

This Guideline provides a plain and accessible explanation of how to prepare the application preparation method and document requirements for the approval and review of medical devices for in vitro diagnosis of COVID-19 (respiratory syndrome caused by SARS-CoV-2 infection), a disease that spread in Korea in 2020, or describes the position of the Ministry of Food and Drug Safety regarding a specific issue.

This Guideline does not establish legally enforceable responsibilities. Please note that, despite some expressions contained herein (such as "should"), you are not required to comply with this Guideline. In addition, this Guideline has been prepared based on scientific and technical facts and statutes that are valid and effective as of May 22, 2020. The provisions in this Guideline are subject to change depending on the revision of the relevant statutes or specific factual developments.

※ Guideline for Industry refers to the description of legislation or administrative rules offered to industry to aid their understanding or the proclamation of the stance of regulatory authority in relation to certain civil affairs (Article 2 of the Regulations on the Management of Guidelines, etc. of the Ministry of Food and Drug Safety)

※ If you have any question or request regarding this Guideline, please contact the In Vitro Diagnostic Device Division, Medical Device Evaluation Department, National Institute of Food and Drug Safety Evaluation.

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Table of Contents

I Overview

1 Purpose, Background, and Scope

1. Purpose

The purpose of this Guideline document is to provide reference for the preparation of applications and submissions required for the review and approval of In-vitro Diagnostic Devices for COVID-19, a respiratory syndrome caused by SARS-CoV-2 infection, and help applicants understanding of review and approval relevant requirements.

2. Background

In December 2019, in Wuhan, Hubei, China, a mass outbreak of pneumonia caused by an unknown virus was reported. The cause of this respiratory infectious disease was initially unidentified. However, the World Health Organization (WHO) confirmed that it is caused by a new type of coronavirus. On January 20, 2020, the first case of COVID-19 was reported in Korea. The patient was a Korean who returned from another country. The government raised the disease alert level to “Blue.” Then, it was raised to “Yellow” on January 27, and “Red” on February 23 in the same year. As the disease spread in Europe, the United States, and other countries, WHO declared a pandemic, which is the third after the Hong Kong flu pandemic in 1968 and the H1N1 pandemic in 2009.

The pathogen causing the disease was structurally similar to the coronavirus that caused the Severe Acute Respiratory Syndrome (SARS) in 2002. For this reason, the International Committee on Taxonomy of Viruses named the new virus Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). On February 12, the Korean government named the disease “Coronavirus Disease-2019, COVID-19,” as recommended by WHO. Coronaviruses are RNA viruses that infect humans and animals, with a gene size of 30 kb. The Korea Centers for Disease Control and Prevention (KCDCP) analyzed the genes from six Korean patients on February 27, and found that the new coronavirus consists of 29,800 nucleic acids, which are 99.7% identical to those of the virus from patients outside of Korea. Only 0.03% (eight to nine sequences) were different.

The Coronaviridae family consists of four genuses (Alpha, Beta, Gamma, and Delta). The Alpha and Beta genuses are known to infect humans and animals. As the name suggests, coronaviruses are characterized by their crown-like shape surrounded by spike proteins.

Before the emergence of the new virus, six types of coronaviruses were known to infect humans. Four of them (229E, OC43, NL63, and HKU1) cause common cold, and the other two (SARS-CoV and MERS-CoV) cause severe pneumonia, which makes SARS-CoV-2 the third type of coronavirus causing severe pneumonia.

Genus	Human-Infecting Coronavirus	Coronavirus Infection Animals Other than Humans
Alpha coronavirus	229E and NL63	porcine epidemic diarrhea virus (PEDV), transmissible gastroenteritis virus (TGEV), canine coronavirus (CCoV), feline coronavirus (FCoV), Minopterus bat coronavirus 1, Miniopterus bat coronavirus HKU8, Rhinolophus bat coronavirus HKU2, and Scotophilus bat coronavirus 512
Beta coronavirus	OC43, KHU1, SARS-CoV, and MERS-CoV	porcine hemagglutinating encephalomyelitis virus (PHEV), bovine coronavirus (BCoV), equine coronavirus (EqCoV), murine coronavirus (MuCoV), Tylonycteris bat coronavirus HKU4, pipistrellus bat coronavirus HKU5, Rousettus bat, and coronavirus HKU9
Gamma coronavirus	None	Avian coronavirus, beluga whale coronavirus SW1
Delta coronavirus	None	Bulbul coronavirus KHU11, thrush coronavirus HKU12, and munia coronavirus KHU13

* Source: KCDCP

COVID-19 is an infectious disease caused by SARS-CoV-2. The virus is known to be transmitted through droplets generated when an infected person coughs or sneezes, or comes in contact with objects contaminated with the virus. The incubation period ranges from 1–14 days (4–7 days on average). Symptoms include fever, tiredness, cough, difficulty in breathing, or pneumonia, as well as phlegm, sore throat, headache, hemoptysis and nausea, and diarrhea. The virus's expression patterns in human bodies (recrudescence, etc.) have not been clearly verified.

As of May 2020, in Korea, COVID-19 is diagnosed by separating the virus from a sample or detecting genes unique to the virus, regardless of clinical manifestation. This method uses a genetic test called Real-time Reverse Transcription Polymerase Chain Reaction (Real-time RT-PCR). Several protocols have been proposed for this test, each detecting different parts of the genes. In Korea, products with two or more genes have been approved for use under the Emergency Use Authorization. Under the EUA, in the event that Korea has no or insufficient supply of approved diagnostic agents that are urgently required to respond to a new infectious disease or a foreign communicable disease, the Minister of Food and Drug Safety approves the products for temporary manufacturing, sale, and use at the request from a head of a central administrative body including the KCDCP. The system was created after the outbreak of the Middle East Respiratory Syndrome (MERS) and the Zika virus in Korea in 2016. As of May 22, 2020, six products are being used since the issuance of Emergency Use Authorization by MFDS

This Guideline document provides information on the technical documents and attachments required for an application for the manufacturing or import of in vitro diagnostic devices used for COVID-19. Moreover, the document incorporates the advice from the Medical Device Committee (Laboratory medicine Subcommittee) and expert on the use of Real-World Data.

3. Scope

The document has been prepared for the review and approval of all In Vitro Diagnostic Devices to support COVID-19 diagnosis by samples from patients suspected of respiratory diseases for SARS-CoV-2 using a genetic or a serological test. The examples in the main body of the documents are just for reference, so applicants should adapt the sentences to suit their own devices.

2 Definitions

1) Interference
Artificial increase or decrease in apparent concentration or intensity of an analyte due to the presence of a substance that reacts nonspecifically with either the detecting reagent or the signal itself. Interference may result from nonspecificity of the detection system, suppression of an indicator reaction, inhibition of analyte (enzymes), or any other cause of specimen-dependent bias.

2) Limit of Detection (LoD)
The minimum amount of detectable analyte (CLSI EP17-A, the minimum amount of analyte in a sample that can be detected with stated probability)

3) Limit of Blank (LoB)
The highest measurement that is likely to be observed for a blank sample (CLSI EP17-A, highest measurement result that is likely to be observed for a blank limit and sample)

4) Limit of Quantitation (LoQ)
The lowest measured concentration that satisfies pre-defined precision target (CLSI EP17-A, the minimum amount of analyte in a sample that can be quantifiably measured with precision and accuracy)

5) Cross-Reactivity
Specific reaction of an antibody with an antigen, as a result of shared, similar, or identical antigenic epitope

6) Control / Control Material
A device, solution, or lyophilized preparation intended for use in the quality control process

7) Specificity / Analytical Specificity
In quantitative testing, the ability of an analytical method to determine only the component it intends to measure; the extent to which the assay responds only to a specified analyte and not to other substances present in the sample

8) Non-specificity
Reactivity of an agent to materials except the analyte. Nonspecificity is usually caused by antibodies, enzymes, ionophores, with reagents

9) Calibration Material / Calibrator
A material of known or assigned qualitative/quantitative characteristics (e.g., concentration, activity, intensity, reactivity, responsiveness) used to adjust the output of a measurement procedure or to compare the response obtained with a test specimen or sample

A) The quantities of the analytes of interest in the calibration material are known within limits ascertained during its preparation and may be used to establish the relationship of an analytical method's response to the characteristic measured.
B) The calibration material must be traceable to a national or international reference preparation or reference material when these are available.
C) Calibration materials with different amounts of analytes may be used to establish a calibration or calibrator "curve" over a range of interest.
D) The terms "primary" and "secondary standard" are used by WHO and ISO to refer to calibration materials.

10) Confidence Interval
The computed interval that expects the true value of a variables such as a mean, proportion or rate, is contained within range of given probability.

11) Positive Predictive Value (PPV)
The proportion of patients with positive test results who have the target condition (as determined by the reference standard); the probability that, if the result of a quantitative testing is higher than the specified threshold, the patient is a member of a group for medical decisions (if the test is used to diagnose patients known to have diseases associated with quantitative testing) or the patient has a disease or a specific condition of a disease (if the testing is used for diagnosis).

[PPV = true positives (TP) / (TP + false positives (FP))]

PPV must be interpreted in context with the prevalence of the condition of interest (as determined by the reference standard). An estimate of PPV is calculated as 100 × TP / (TP + FP). If the specificity of a test is 100%, its PPV is 100% (all patients who test positive have the target condition).

12) Negative Predictive Value
The likelihood that a patient with a negative test results does not have the disease, or other characteristics, which the test is designed to detect; the probability that, if the result of a quantitative testing is lower than the specified threshold, the patient is a not member of a group for medical decisions (if the test is used to diagnose patients known to have diseases associated with quantitative testing) or the patient does not have a disease (if the test is used for diagnosis).

[NPV = true negatives (TN) / (TN + false negatives (FN))]

13) False-Positive Result / False Positive, FP
A positive test result that indicates the given condition is present when it is not.

14) False-Negative Result / False Negative, FN
A negative test result that indicates the given condition is present when it is not.

15) Human-Derived Material
Tissues, cells, blood, bodily fluid, and other human body components collected or sampled from human bodies, or serum, plasma, chromosome, DNA, RNA, and protein separated from them

16) Clinical Sensitivity
The proportion of people with a specific condition that tested positive

A) It is the ratio of clinically true positives divided by the sum of clinically true positives and clinically false positives.
B) The condition should be defined based on a criteria independent from the test.
C) Clinical sensitivity (US) is a synonym to diagnostic sensitivity (EU). The ratio of patients with positive test results who suffer from specific conditions

17) Clinical Specificity
The proportion of subjects who do not have a specified clinical disorder whose test results are negative; the ability of a test to report a negative result for patients who do not have the disease or condition for which they are being tested

A) It is the ratio of clinically true negatives divided by the sum of clinically true negatives and clinically false positives.
B) Clinical specificity (US) is a synonym to diagnostic specificity (EU).

18) Remaining Specimens
A specimen originating from a human body that remains after being collected and used for diagnosis or treatment at a medical institution or used for a specific research, for which a comprehensive consent has been obtained from the provider of the specimen for its secondary use for other purposes

19) Reproducibility
Closeness of agreement between measurement results from the same sample obtained under different conditions

20) Precision
Closeness of agreement between independent test results obtained under stipulated conditions. Precision is not typically represented as a numerical value but is expressed quantitatively in terms of imprecision (the standard deviation or the coefficient of variation of the results in a set of replicate measurements). Agreement between independent test results obtained under stipulated conditions. Precision depends only on the distribution of random errors and does not relate to the true value or the specified value.

21) Accuracy
Evaluation of agreement between the result of a measurement and a true value. It can be quantified in terms of inaccuracy, expressed as systematic error or bias.

22) Linearity
The ability to provide results that are directly proportional to the concentration (amount) of the analyte in the test sample

23) Combined Medical Device
A single medical device composed of two or more medical devices, which provide a combination of functions

24) Medical Device Package
Two or more medical devices packaged in a single unit

25) Reference Material (RM) / Reference Preparation

A) Material or substance, one or more of whose property values are sufficiently homogeneous and well established to be used for the calibration of a measuring system, the evaluation of a measurement procedure, or for assigning values to materials

B) Certified Reference Material (CRM): A reference material that has one or more values that is traceable or certified by a technically valid procedure and is accompanied by a certificate or other document that is issued by a certificate institution
   a) CRM is defined as “reference material, accompanied by a certificate, one or more of whose property values are certified by a procedure which establishes traceability to an accurate realization of the unit in which the property values are expressed, and for which each certified value is accompanied by an uncertainty at a stated level of confidence.”
   b) The term “Standard Reference Material (SRM)” is the name of a Certified Reference Material (CRM), which is the trademark name of a certified reference material that has been certified and distributed by the National Institute of Standards and Technology, a US government agency formerly known as the National Bureau of Standards.

26) Reference Standard
The most available method for establishing the presence or absence of the condition or characteristic of interest

A) The reference standard can be a single test or method, or a combination of methods and techniques, including clinical follow-up study

B) The reference standard will evolve with the advancement of analytical systems and may, in a given situation, be different from a reference standard determined by a regulatory authority.

27) Analytical Measurement Range (AMR)
The range of analyte values that a method can directly measure in the sample without any dilution, concentration, or pretreatment that is not part of the typical assay process

28) Cutoff Value
The quantitative value of a measurand that is used to decide whether the result is considered above or below a clinical or analytical decision point

3 Applicable Regulations

- Article 4, Act on In Vitro Diagnostic Medical Devices (Relationship with Other Laws)
- Article 5, Act on In Vitro Diagnostic Medical Devices (Approval for Manufacturing Business)
- Article 11, Act on In Vitro Diagnostic Medical Devices (Approval for Import Business)
- Article 6, Enforcement Rule of the Act on In Vitro Diagnostic Medical Devices (Procedure and Method, etc. for Manufacturing Approval)
- Article 8, Enforcement Rule of the Act on In Vitro Diagnostic Medical Devices (Procedure and Method, etc. for Manufacturing Certification)
- Article 9, Enforcement Rule of the Act on In Vitro Diagnostic Medical Devices (Procedure and Method, etc. for Manufacturing Notification)
- Article 26, Enforcement Rule of the Act on In Vitro Diagnostic Medical Devices (Procedure and Method, Etc. for Import Approval, etc.)
- Regulations on the Approval, Notification, and Review of In Vitro Diagnostic Medical Devices
- Regulations on the Products and Classification of In Vitro Diagnostic Medical Devices
- Test Standards for Medical Device Stability

Ⅱ Application and Submissions on Technical Document

1 List of Application form for Manufacturing/Import Approval

- ❍ Name (product name, description, and model number)
- ❍ Classification number (class)
- ❍ Shape and structure
- ❍ Raw materials
- ❍ Manufacturing method
- ❍ Intended use
- ❍ Performance
- ❍ Method of use
- ❍ Precautions
- ❍ Packaging unit
- ❍ Storage method and period of use (Shelf-Life)
- ❍ Test standard
- ❍ Manufacturer (for imported items or OEM items)

2 Submissions on Technical Document

- ❍ Data regarding origin and development history, detection or measurement principles and methods, and product use in and outside Korea
- ❍ Data regarding status of use in and outside of Korea
- ❍ Data regarding raw materials and manufacturing methods
- ❍ Data regarding the intended use
- ❍ Data regarding storage methods and period of use or shelf-life
- ❍ Data for verifying the product's performance
- ❍ Data regarding safety for personnel handling in vitro diagnostic reagents
- ❍ Data that compare the product with previously approved/certified products

Ⅲ Item List of Application Form for Manufacturing/Import Approval

1 Name (Product Name, Device Description, and Model Number)

1. The name of the in vitro diagnostic medical device should be provided in accordance with one of the following subparagraphs.

   A. In case of providing the product name, the following order should be observed: “manufacturing (importing) entity name / product name,” “item name,” followed by “model name.” However, the manufacturing (importing) entity name may be omitted, and two or more product names may be provided; or

   B. In case of not providing the product name, “manufacturing (importing) entity name / item name,” and “model name” should be provided.

2. The product name may not be identical to the product name of a previously approved, certified, or declared medical device unless:

   A. The in vitro diagnostic medical device has the same intended use, operational principle, and raw materials as a medical device of which approval, certification, or notification has been revoked, and a year has passed since the date of the revocation;

   B. The approval, certification, or notification is for the same product for which the same manufacturer (importer) withdraw a notification or an approval/certification approval; or

   C. Different importers import the same product from the same manufacturer, and distinguish products imported by different importers by providing the name of the importer along with the product name.

3. In the event that the product name falls under any of the item classifications under the Regulation on Items and Classes of In Vitro Diagnostic Medical Devices announced by the Minister of Food and Drug Safety, the classification number and the class of the product should be provided along with the item name.

4. In the event that the product is a combined in vitro diagnostic medical device or an in vitro diagnostic medical device package, the names should be provided for each in vitro diagnostic medical device based on their primary intended use and classes.

5. In case of an item of which the intended use is similar to that of a previously approved or declared product, the name of the new item may be named by adding or replacing certain characters, words, or numbers to or in the previously approved/certified product (e.g., □□-ADS, □□-2, etc.).

6. In the event that a separate name needs to be provided for export purposes, an export name should be provided in parentheses as follows: “Export name: ○○○○”.

□ Example: manufacturer (importer) name, item name, and model name

Osong Diagnostics, Co., Ltd.	High-Risk Immunological Test Reagent	Pathogen 2019-nCoV IgG/IgM
↓	↓	↓
Manufacturer (importer) name	Item name	Model name

※ Example 1 in the attachment.

<Product Name>
1. Item name: High-Risk Pathogen Immunological Test Reagent
2. Model name: 2019-nCoV IgG/IgM
3. Classification no.: K05030.01
4. Class: 3

※ Example 2 in the attachment.

<Product Name>
1. Item name: High-Risk Pathogen Genetic Test Reagent
2. Model name: 2019-nCoV RT-PCR
3. Classification no.: N05030.01
4. Class: 3

2 Classification Number (Class)

1. The classification number and class specified in the Regulations on Medical Device Items and Classes should be provided.

※ Example

- High-Risk Pathogen Genetic Test Reagent [N05030.01, Class 3]

- High-Risk Pathogen Immunological Test Reagent [K05030.01, Class 3]

3 Shape and Structure

1. Shape and Structure – Operational Principles

The operational principles, scientific evidence, and composition of the product should be provided, along with an overview of the product. Moreover, the description should include equipment used exclusively for the product, if any.

A. Background (Clinical Significance, etc.): The description may include the clinical significance of the test, if necessary.

※ Example

1) Immunological Test Product

The Coronaviridae family consists of four genuses (Alpha, Beta, Gamma, and Delta). The Alpha and Beta genuses are known to infect humans and animals. As the name suggests, coronaviruses are characterized by their crown-like shape surrounded by spike proteins. Before the emergence of the new virus, six types of coronaviruses were known to infect humans. Four of them (229E, OC43, NL63, and HKU1) cause common cold, and the other two (SARS-CoV and MERS-CoV) cause severe pneumonia, which makes SARS-CoV-2 the third type of coronavirus causing severe pneumonia.

This product is designed to use immunochromatography to verify whether a blood sample from a person showing symptoms of coronavirus infection has any coronavirus antigen.

2) Genetic Test Product

The Coronaviridae family consists of four genuses (Alpha, Beta, Gamma, and Delta). The Alpha and Beta genuses are known to infect humans and animals. As the name suggests, coronaviruses are characterized by their crown-like shape surrounded by spike proteins. Before the emergence of the new virus, six types of coronaviruses were known to infect humans. Four of them (229E, OC43, NL63, and HKU1) cause common cold, and the other two (SARS-CoV and MERS-CoV) cause severe pneumonia, which makes SARS-CoV-2 the third type of coronavirus causing severe pneumonia.

This product is designed to amplify certain genes in coronavirus (RdRp, N, E gene, etc.) using RT-PCR, and verify whether the subject is infected.

B. Measurement Principles: A description of the measurement principles of the diagnosis should be provided as follows.

※ Example

1) Immunological Test Product

A control line and a test line for COVID-19 antigen are placed on the surface of the nitrocellulose membrane. They are not visible on the result window until a sample is introduced. Mouse monoclonal anti-COVID-19 IgG is coated at the test line area, and mouse monoclonal anti-Chicken IgY is coated at the control line area. The gold nanoparticles bonded with the mouse monoclonal anti-COVID-19 IgG are used to detect COVID-19 antigens. During a test, the COVID-19 antigens in the sample react to the monoclonal anti-COVID-19 IgG bonded with the gold nanoparticles to create an antigen-antibody complex. The complex is transferred to the test line by the capillary action of the membrane, to be captured by the mouse monoclonal anti-COVID-IgG at the test line. A purple line emerges on the result window if the sample contains any COVID-19 antigen. If not, no colored line emerges on the test line.

2) Genetic Test Product

The Real-time Reverse Transcription Polymerase Chain Reaction (Real-time RT-PCR) method verifies an increase in amplification product by measuring the amount of fluorescence emitting from a probe combined with the amplification product. It consists of an oliogomer in which fluorescence is attached at the end of 5′, and a quencher to suppress the coloration of the fluorescent pigment at the end of 5′ is attached at the end of 3′. During the annealing process stage of the PCR, the probes specifically bond with the DNA target. During the extension stage, the probe is hydrolyzed by the 5′ to 3′ exonuclease activity of the Taq DNA polymerase. As a result, the fluorescent reporter is separated from the quencher, and the fluorescence from the reporter is detected by the fluorescence meter attached to the real-time PCR. The Real-time PCR method is capable of quantifying an increase in the PCR product by converting it to the amount of fluorescence. It offers rapid and simplified analysis because it does not require electrophoresis. cDNA is massively amplified by the polymerase chain reaction with the COVID-19-specific primers after synthesizing complementary DNA from the COVID-19 RNA using reverse transcriptase. The fluorescence probe produces signals in the promotion to the amplification, which allows for the detection of COVID-19 viruses.

C. Equipment and Software

In the event that the product uses specific equipment or software, the name, characteristics, and principles of the equipment/software products should be described. In case of a previously approved product, information about the approval (approval no., item name, etc.) should be provided as well.

2. Shape and Structure – Appearances

A. A detailed description should be provided in keeping with the nature of in vitro diagnostic devices. The description should include the external characteristics of each component, including its weight, material, color, property, and liquidity.

B. In case of a liquid product, its property (color, transparency) and shape should be described.

C. In case of a product using immunochromatography (strip or cassette), a description about the material used in the test strip, its lamination structure and sample well, and the result window should be provided.

D. Color photographs or figures should be attached.

 If there exists any component (sold separately) that should be used along with the device (reagent), additional photographs and a composition sheet should be provided for the separately sold components.

※ Example 1.

1. Composition

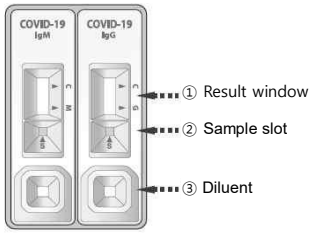
000 consists of a test strip and chromatography solvent.

Serial No.	Name	Composition	External Characteristics
1	Test strip	Single component	A white rectangular plastic cassette. Round sample wells are placed on either side at the bottom, and the display window indicates the position of the control line (C) and the test line (T).
2	Chromatography solvent	Single component	Colorless, transparent liquid in a colorless, transparent tube.

2. Photographs

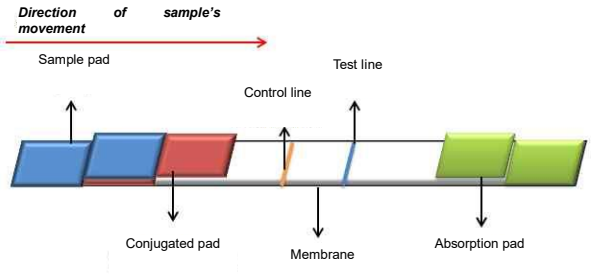
A. Test strip

1) External Shapes



<Testing Device>

2) Test strip structure



B Chromatography solvent

□ Example 2.

1. Composition

The in vitro diagnostic device consists of primer/probe mix, RT-PCR mix, positive control, internal control, and nuclease-free water.

Serial No.	Name	Composition	External Characteristics
1	000 Primer/Probe Mix	Single component	Transparent, light blue liquid in a brown opaque tube
2	000 RT-PCR Mix	Single component	Colorless, transparent liquid in a colorless, transparent tube.
3	000 Positive control (E, RdRp)	Single component	Colorless, transparent liquid in a colorless, transparent tube.
4	Internal control	Single component	Colorless, transparent liquid in a colorless, transparent tube.
5	Nuclease free water	Single component	Colorless, transparent liquid in a colorless, transparent tube.

2. Photographs

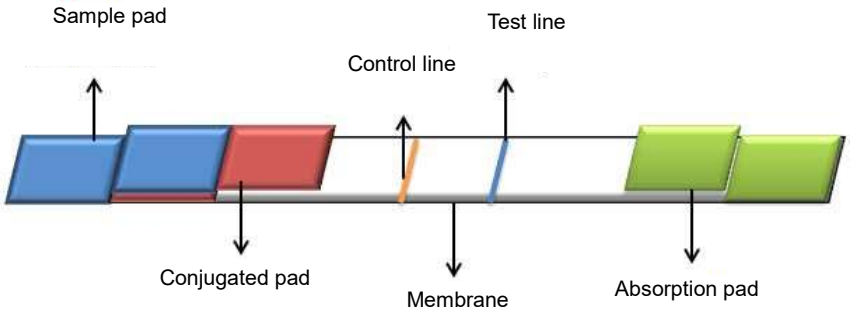
Serial No.	Name
1	000 Primer/Probe Mix
2	000 RT-PCR Mix
3	Nuclease free water
4	000 Positive control (E, RdRp)
5	Internal control

3. Shape and Structure – Dimensions

A. For products using immunochromatography, the strip's dimensions should be provided.

B. The length, width, and thickness of the strip should be provided, along with the distance between the sample well and the control line, and the distance between the sample well and the test line.

※ Example



1. Strip dimensions (width × length × thickness): 5.0 mm × 50.0 mm × 0.1 mm
2. Distance from the sample well to the control/test line
   - Distance from the sample well to the control line: 20.0 mm
   - Distance from the sample well to the test line: 30.0 mm

4 Raw Materials

1. Information regarding raw materials should be provided in accordance with the following table.

Serial No.	Name	Purpose of Mix	Material/Component Name	Amount	standard	Note

2. Name: The generic names of the components should be provided.

A. The names of in vitro diagnostic reagents comprising each product should be provided.

B. For strip or cassette products, the information should be provided for each part.

3. Purpose of mix and material (component) name

A. In keeping with the nature of in vitro diagnostic devices, the purpose of mix (e.g., main component, stabilizer, and preserver, etc.) and the generic name and chemical name of each raw material should be provided.

B. The origin (human or an animal species) should be provided if the main component is an antibody. For a monoclonal antibody, the clone number should be provided.

C. For recombinant antigens, the name of the expression system should be provided.

4. Amount

A. The amount of each component (potency, required amount, etc.) and the unit (mL, mg, v/v, w/v, w/w) should be provided.

B. The amount of components (auxiliary reagent, preserver, reaction stabilizer, stopper, diluent, etc.) other than the main components (antibodies, antigens, polymerase, reverse transcriptase, primer, and probe, etc.) may be indicated as “suitable amount.”

C. For polymerase, the activity of the enzyme (μ/λ, etc.) should be provided, along with the definitions of the units.

5. Standards

A. The standards of the raw materials should be provided (KP and USP, etc.), if any. If there is none, the standards used by the company should be provided.

B. The company's standards for recombinant antigen, primer, and probe should be provided in detail. For recombinant antigens, the expression system, molecular weight, and purity should be provided. For primers and probe, the molecular weights and the number of mer should be provided.

6. Note: The amount of each in vitro diagnostic reagent should be provided.

※ Example 1.

Serial No.	Name			Purpose of Mix	Material/Component Name	Amount (for 1 Test)	Standards	Note
1	Test strip	Sample pad		Support	Glass fiber	5.0 × 10.0 × 0.1 mm	Company's standards	20 strips / 1 box
		Conjugated pad		Main component	Gold nanoparticle Conjugated mouse monoclonal anti-human SARS CoV-2 IgG (Clone: ABC1A)	1.0 ± 0.1 mg	Company's standards	
				Main component	Gold nanoparticle conjugated Goat anti-Chicken IgY	1.0 ± 0.1 mg	Company's standards	
				Support	Glass fiber	5.0 × 10.0 × 0.1 mm	Company's standards	
		Membrane	Control line	Main component	Chicken IgY	1.0 ± 0.1 mg	Company's standards	
			Test line	Main component	Mouse monoclonal anti-human SARS-CoV-2 IgG (Clone: BCD2D)	1.0 ± 0.1 mg	Company's standards	
				Support	Nitrocellulose membrane	5.0 × 50.0 × 0.1 mm	Company's standards	
		Absorption pad		Support	Cotton membrane	1.0 ± 0.1 mg	Company's standards	
		External plastic		Support	PVC	6.0 × 55.0 × 0.2 mm	Company's standards	
2	Chromatography solvent			Surfactant	Triton-X 100	20%	Company's standards	5 mL/bottle ×1
				Preservative	Sodium citrate	10%	Company's standards	
				Buffer	PBS	70%	Company's standards	

※ Example 2.

Serial No.	Name	Purpose of Mix	Material/Component Name	Amount	Standards	Note (Volume and Quantity)
1	Internal control	Control material	Internal control DNA	5 pmol/μL	Company's standards	0.53 mL /bottle
		Preservative	Sodium azide	Suitable amount	Company's standards	
		Buffer	Tris Buffer	Suitable amount	Company's standards	
2	Real-time RT-PCR Premix	Main component	DNA Polymerase (6–7 Units/μL)	50 μL	Company's standards	120 μL/bottle
		Main component	Reverse transcriptase (50 Units/μL)	50 μL	Company's standards	
		Buffer	Tris Buffer	Suitable amount	Company's standards	
		Surfactant	Surfactant	Suitable amount	Company's standards	
3	Primer/Probe Mix (E/RdRp)	Main component	Internal control primer(F)	2 pmol/μL	Company's standards *	0.6 mL/bottle
		Main component	Internal control primer(R)	2 pmol/μL	Company's standards *	
		Main component	2019-nCoV-E primer(F1)	2 pmol/μL	Company's standards *	
		Main component	2019-nCoV-E primer(R1)	2 pmol/μL	Company's standards *	
		Main component	2019-nCoV-RdRp primer(F1)	2 pmol/μL	Company's standards *	
		Main component	2019-nCoV-RdRp primer(R1)	2 pmol/μL	Company's standards *	
		Main component	dNTPs	5.8 mM	Company's standards *	
		Main component	2019-nCoV-E Probe	0.196%	Company's standards *	
		Main component	2019-nCoV-RdRp Probe	0.109%	Company's standards *	
		Main component	IC Probe	0.01%	Company's standards	

					*	
		Buffer	Tris Buffer	Suitable amount	Company's standards	
		Preservative	Sodium azide	Suitable amount	Company's standards	
4	Control (E/RdRp)	Main component	2019-nCoV-E, RdRp in vitro transcript RNA	Suitable amount	Company's standards	0.7 mL/bottle
		Buffer	Distilled water	Suitable amount	Company's standards	
		Preservative	Proclin 950	Suitable amount	Company's standards	

<Company's Standards*>

Raw Material/Component Name	Molecular Weight (Dalton)	The number of Nucleic Acid Sequence (Oligonucleoide Length (bp))
Primer ㅇㅇㅇ Foward	ㅇㅇㅇ	ㅇㅇ
Primer ㅇㅇㅇ Reverse	ㅇㅇㅇ	ㅇㅇ
Probe ㅇㅇㅇ	ㅇㅇㅇ	ㅇㅇ

5 Manufacturing Method

1. The following phrase should be included: “Follow the manufacturing method of the manufacturer.” In case of sterilized in vitro diagnostic medical devices and in vitro diagnostic medical device packages, the following should be described.

   A. For the sterilization method used for sterilized in vitro diagnostic medical device, the sterilization method under the Regulations on the Approval, Notification, and Review of In Vitro Diagnostic Medical Devices (MFDS Public Announcement) [Attached Table 2] or its equivalent or higher should be described.
   B. For IVDDs except Medical Devices Packages, the manufacturing methods for the medical devices should be added in accordance with Article 11 of the Regulations on the Approval of Medical Devices.
   C. In case of a product containing or using an animal-derived component for manufacturing, the name of the animal, the country of origin, the animal’s age, the part used, the handling process, and the name of the substance should be appropriately provided based on the standards (KS, ASTM, or ISO, etc.)

6 Intended Use

1. The intended use should be provided in detail including subjects, sample type, analytes (test items), diagnosed diseases, operational principles, and (quantitative or qualitative) result determination methods, in accordance with the supporting data.

   A. Subjects: The population (subjects) of the test's indications should be specified.

   B. Sample Type: The type of sample applicable to the product should be described. For blood plasma, the type of anticoagulant applicable to the product should be provided as well.

   C. Analytes (test Items)

      1) The antigens, antibodies and genes to be detected should be clearly provided.

         - Two or more genes should be used, and

         - IgM or IgG should be clearly distinguished for antibodies.

      2) For products using IgM or IgG from antibodies or antigens, it should be clearly indicated that the product is intends to assist with COVID-19 diagnosis.

※ Example 1.

In vitro diagnostic devices that uses the SARS-CoV-2 genes (E gene and RdRp gene~~)~~ in ~~a~~ upper and lower samples from a patient suspected of respiratory infectious disease (a sample taken from phlegm, oropharynx, and nasopharynx) with the Real-time RT-PCR method to diagnose (confirm). SARS-CoV-2 infection.

※ Example 2.

In vitro diagnostic devices that uses the SARS-CoV-2 antigen (N protein) in ~~a~~ upper and lower samples from a patient suspected of respiratory infectious disease using the immunochromatographic assay (ICA) method to diagnose (select). SARS-CoV-2 infection.

※ Example 3.

In vitro diagnostic devices that detect the SARS-CoV-2 IgM and IgG antibodies in the ~~blood~~ serum and plasma (treated with lithium herapin) of a person using the immunochromatographic assay (ICA) method to assist to identify whether the antibodies are generated or not.

7 Performance

1. Performance should be numerically presented based on the supporting materials (technical documents). It should be stated in a way suitable for the characteristics of the product, and should not include abstract and unclear descriptions. The supporting data should be those backed by valid evidence.

Examples of Immunological Test

The performance information is for reference only. Some items are subject to change depending on the product's characteristics.

1. Analytical Sensitivity (LoD): 1.0 pfu/mL

Type-B COVID-19 viruses were added to negative samples from humans' upper and lower airways to create samples with concentration levels of 10.0 pfu/mL, 5.0 pfu/mL, 2.5 pfu/mL, 1.0 pfu/mL, 0.5 pfu/mL, and 0 pfu/mL. Each sample was tested 20 times for 5 days using 3 lots of the product. The minimum concentration that tested positive for 95% of the tests was as follows. The LoD was confirmed at 1.0 pfu/mL.

Serial No.	Concentration of Sample (pfu/mL)	Test Cycle	No. of Positives	Percentage of Positives (%)
1	10.0	20	20	100
2	5.0	20	20	100
3	2.5	20	20	100
4	1.0	20	20	100
5	0.5	20	10	50
6	0	20	0	0

2. Reactivity

Type A, B, and C COVID-19 viruses were added to negative samples from humans' upper and lower airways to create samples at the LoD (1.0 pfu/mL). The samples were tested 20 times for 5 days using 3 lots of the product. Then, 100% of the tests produced positive results at 1.0 pfu/mL.

3. High-Concentration Hook Effect

Type B COVID-19 viruses were added to negative samples from humans' upper and lower airways to create samples at 100 times the LoD (100 pfu/mL. The negative upper/lower airway samples were diluted at 1:10 with negative upper/lower airway samples to create samples at five concentration levels. Each sample was tested 20 times for a high-concentration hook effect. This effect was not observed at concentration levels not exceeding 100 pfu/mL.

4. Analytical Specificity (Interference)

Type B COVID-19 viruses were added to negative samples from humans' upper and lower airways to create low/medium/high-concentration samples. Interfering substances were added to the negative samples as follows to test for interference. No interference was observed.

Serial No.	Interfering Substance	Concentration (mg/mL)
1	Conjugated Bilirubin	20
2	Cholesterol	15
3	Lipids	20
4	Sodium heparin	30
5	Sodium citrate	10
6	K3-EDTA	20
7	Albumin	30
8	Hemoglobin	40

5. Analytical Specificity (Cross-Reactivity)

B-type COVID-19 viruses were added to negative upper/lower airway samples to create samples. The samples were added with the following cross-reactive materials to evaluate cross-reactivity. No cross-reactivity was observed.

Serial No.	Cross-Reactive Materials	Concentration
1	Legionella pneumoniae	10^5 cfu/mL
2	Mycoplasma pneumoniae	10^5 cfu/mL
3	Human coronavirus NL63	10^5 pfu/mL
4	Human coronavirus 229E	10^5 pfu/mL
5	Betacoronavirus(strain HCoV-OC43)	10^5 pfu/mL
6	Human coronavirus HKU1(HCOV-HKU1)	10^5 pfu/mL
7	Middle East respiratory syndrom-related coronavirus (MERS-CoV)	10^5 pfu/mL
8	SARS	10^5 pfu/mL
9	Influenza A	10^5 pfu/mL
10	Influenza B	10^5 pfu/mL
11	Rhinovirus/Enterovirus	10^5 pfu/mL
12	Respiratory syncytial virus A/B	10^5 pfu/mL
13	Parainfluenza 1, 2, 3 virus	10^5 pfu/mL
14	Parainfluenza A, B virus	10^5 pfu/mL
15	Human metapneumovirus	10^5 pfu/mL
16	Adenovirus	10^5 pfu/mL

6. Precision

1) Repeatability

B-type COVID-19 viruses were added to negative samples from humans to create low/medium/high-concentration positive samples and negative samples. A single tester tested the samples twice per day for 20 days, conducting 2 runs at each test. All of the tests produced the same results.

2) Replicability

B-type COVID-19 viruses were added to negative samples from humans to create low/medium/high-concentration positive samples and negative samples. Three testers tested the samples using three lots of the product at three different places twice per day for five days, conducting two runs at each test. All of the tests produced the same results.

7. Clinical Performance

1) Clinical sensitivity and specificity

The existence of COVID-19 virus antigen was evaluated with an EUA RT-PCR product using phlegm from patients suspected of COVID-19 infection. Then, the product's clinical performance was evaluated using 470 serums (270 positive, 200 negative).

		Standard Testing method		Total
		Positive	Negative	
Target Product	Positive	265	0	265
	Negative	5	200	205
Total		270	200	470

① Clinical sensitivity: 98.1%(265/270) (95% CI: 00%–00%)
② Clinical specificity: 100.0%(200/200) (95% CI: 00%–00%)
③ Positive prediction ratio: 100.0%(265/265) (95% CI: 00%–00%)
④ Negative prediction ratio: 97.6%(200/205) (95% CI: 00%–00%)

8. Correlation with a Previously Approved Product

The correlation between a previously approved comparator (Product A) and the target product was verified using 470 phlegm samples (270 positive, 200 negative) tested for COVID-19 virus antigens using RT-PCR products.

		Control Medical Device		Total
		Positive	Negative	
Target Product	Positive	250	20	270
	Negative	20	180	200
Total		270	200	470

① Positive Percent Agreement: 92.6%(250/270) (95% CI: 00%–00%)
② Negative Percent Agreement: 90.0%(180/200) (95% CI: 00%–00%)
③ Overall Percent Agreement: 91.5%(430/470) (95% CI: 00%–00%)
④ Cohen's kappa: 0.8

Examples of Genetic Test

The performance information is for illustrative purposes only. Some items are subject to change depending on the product's characteristics.

1. Analytical Sensitivity (LoD): 1.0 pfu/mL
   RNAs produced using in vitro transcription were diluted to 100–106 copies/ to measure analytical sensitivity and verify the detectable range. Tests were repeated 24 times at concentration levels between 101 and 100 copies/μL to determine the lower limit of detection. (Bio-rad CFX96)

1) E gene LoD

   LoD: 5 copies/μL

2) RdRp gene LoD

   LoD: 3 copies/μL

2. Analytical Specificity (Interference)
   The effects of interfering substances were verified using E gene and RdRp reference materials at the LoD. Tests were repeated three times using a single piece of equipment and a single lot. The substances were found to have no effect on the test results.

Interfering Substance	Concentration
Human blood	5% v/v
Mucin (bovine submaxillary gland, type 1-S)	60 μg/mL
Nasal spray	0.1%

3. Analytical specificity (Cross-Reactivity)
   Cross-reaction tests were performed for pathogens and virus-positive substances that may cause similar symptoms or reside in samples. The tests showed that the substances are not detected in samples other than the positive control group. IC was detected from all reaction solutions, which confirmed the validity of the result. Tests were repeated three times using a single piece of equipment and a single lot. The tests showed that the target nucleic acid was not amplified or detected from the other bacteria or viruses.

<Examples of Virus Strains Used>

No.	Organism	Source	Concentration
1	HCoV OC43	Self-produced	10^6 PFU/mL
2	HCoV 229E	Self-produced	10^6 PFU/mL
3	HCoV NL63	Self-produced	10^6 PFU/mL
4	HCoV HKU1	Self-produced	10^6 PFU/mL
5	MERS-CoV	Self-produced	10^6 PFU/mL
6	Influenza A(H1N1)	Vircell	10^6 PFU/mL
7	Influenza A(H3)	Vircell	10^6 PFU/mL
8	Influenza A(H5)	Vircell	10^6 PFU/mL

9	Influenza B	Vircell	10^6 PFU/mL
10	Adenovirus	Vircell	10^6 PFU/mL
11	Parainfluenza virus 1	Vircell	10^6 PFU/mL
12	Parainfluenza virus 2	Vircell	10^6 PFU/mL
13	Parainfluenza virus 3	Vircell	10^6 PFU/mL
14	RSV subtype A	Vircell	10^6 PFU/mL
15	RSV subtype B	Vircell	10^6 PFU/mL
16	Enterovirus D68	Vircell	10^6 PFU/mL
17	Human Rhinovirus	Vircell	10^6 PFU/mL
18	Coxsackie A6	Vircell	10^6 PFU/mL
19	Echovirus 5	Vircell	10^6 PFU/mL
20	Enterovirus 71	Vircell	10^6 PFU/mL
21	Streptococcus pneumonia	Vircell	10^6 CFU/mL
22	Haemophilus Influenzae	Vircell	10^6 CFU/mL
23	Mycoplasma pneumoniae	Vircell	10^6 CFU/mL
24	Legionella penumophila	Vircell	10^6 CFU/mL

4. Precision

1) Repeatability

A total of 21 samples (3 per target) consisting 18 positive samples including low-positive samples near the LoD and 3 negative samples were tested. The concentration levels of each sample were set at 0.5 × LoD, 1 × LoD, 3 × LoD. Two testers repeated tests twice per day (before/after noon) for 20 days using 1 lot. Detection was confirmed for 100% samples at the moderate positive (3 × LoD), as well as at the low positive (1 × LoD). The CV (%) of within-run, run-to-run, and day-to-day results were analyzed using the following method. CV (%) = [(Standard Deviation/Mean) × 100]

The within-run CV (%) was found to range from 0.91% to 2.98%. The run-to-run CV (%) ranged from 0.8% to 3.1%, and the day-to-day CV (%) ranged from 0.51% to 2.7%.

In conclusion, the results satisfied the repeatability criteria of 100% at moderate positive (3 × LoD) and 96.67% at low positive (1 × LoD). Therefore, repeatability was verified.

2) Reproducibiltiy

A total of 21 samples (3 per target) consisting 18 positive samples including low-positive samples near the LoD and 3 negative samples were tested. The concentration levels of each sample were set at 0.5 × LoD, 1 × LoD, 3 × LoD. Tests were repeated three times using three pieces of equipment and three lots at three different locations (at least one tester at each location) for five days, to evaluate replicability. Then, 100% detection was confirmed for all samples at the moderate positive (3 × LoD), and 96.67% or higher detection was confirmed at the low positive (1 × LoD). 23.3% positive ratio was confirmed at the concentration level under the LoD (0.5 × LoD). The results satisfied the reproducibility criteria of 100% detection at moderate positive (3 × LoD) and 96.67% detection at low positive (1 × LoD). Therefore, repeatability was found to be maintained regardless of the place, equipment, tester, date, or lot.

5. Clinical performance

1) Clinical sensitivity and specificity

A single medical device clinical trial body conducted the tests, using the remaining samples from in-patients suspected of COVID-19 that were sent for testing. Then, the test results using the evaluated product and the definite diagnosis results at the institutes were compared for the remaining positive/negative samples that had been confirmed and depersonalized. The tests used 100 positive samples and 600 negative samples, with no excluded samples.

2) COVID-19 Real-time PCR Kit Results

		Sample Results	
		Positive	Negative
COVID-19 Real-time PCR Kit	Positive	98 (True Positive)	1 (False Positive)
	Negative	2 (False Negative)	599 (True Negative)

COVID-19 sensitivity = 98% (98/100) (95% CI: 93%–99%)

COVID-19 specificity = 99.8% (599/600) (95% CI: 99%–100%)

8 Test Procedure

1. Information on the sample preparation and storage method, pretest preparations, test process, result determination and quality control, and equipment used (manufacturer, model number, approval no., etc.) should be provided as follows. The amount (scope) of reagents used should be specific enough to verify performance.

A. Sample Preparation and Storage

1) Sampling targets and methods (for blood samples, indicate the applicable anticoagulant types)

2) Required amount of samples by type

3) Sample storage conditions, method, and period, etc.

4) Applicability of frozen and unfrozen samples and limitations, etc.

5) Pre-treatment process of samples (centrifugation conditions, RNA extraction kit, etc.)

B. Pretest Preparations

1) Conditions of use of the test kit and reagents (temperature, humidity, etc.)

2) Reagent preparation method and conditions, if pretest reagent preparation is required

3) Storage method and period of use of prepared reagents

4) Instruments and equipment required for the test, and conditions

5) Equipment that may affect the performance determination of the reagents (extraction, amplification, and measurement equipment, etc.)

6) Description of calibration materials and calibration methods

C. Test Process

1) Detailed description of each test method

2) Description of the amounts of samples used

3) Description of pre-treatment process of samples (including diluent amount and dilution method, if the samples are diluted), and suspension preparation, and other pretreatment methods

4) Description of reaction time, temperature, and conditions

5) Indication of result determination time

6) Description of matters requiring cautions during the test

D. Result Determination

1) Description of the result determination process

2) Description of expected test results including positive, negative, invalid, and retest, and the interpretation criteria for each

 Given that the COVID-19 outbreak is an ongoing issue in Korea, the determination criteria should be based on the 'Guideline for the Laboratory Diagnosis of COVID019 in Korea' issued by the KCDCP.

3) Description of handling of invalid findings

E. Quality Control

1) Proposal for quality control by user

2) If quality control materials are provided and the target values for the materials exist, a process for verifying that the materials satisfy the proposed values

3) Alternative techniques for use in cases where the quality control results are not valid

Examples of Immunological Test

1. Sample Preparation and Storage

A. Use upper airway samples (oropharynx and nasopharynx swab) and lower airway samples (phlegm).

B. Store the collected samples under refrigerated condition at 2°C–8°C, and make sure that the test is carried out within 72 hr. Freeze the samples at -20°C or a lower temperature if the test is carried out after 72 hr.

2. Pretest Preparations

A. Place all samples and reagents at the room temperature of the test lab (15°C–30°C).

B. Refrain from repeatedly freezing/unfreezing the samples.

3. Testing Process

A. Before the test, place the foil pouch (packaged testing device) and the diluted samples at room temperature.

B. Immediately before the test, and place it on a level surface.

C. Use a disposable dropper to suck up the sample up to the marked line, and drop 4 drops (approximately 100 μL) at the sample well (S) of the device.

D. Interpret the result at 15 min after the test start. Results taken after 15 min should not be included in the interpretation.

4. Result Determination

A. Negative: A band appears only at the control line (C) position.
B. Positive: Bands appear both at the control line (C) and test line (T) positions.
C. Invalid: No band appears, or a band appears only at the test line (T) position.
   - The test may be wrong, or the quality of the reagents may be defective if no band appears at the control line (C) or a band appears only at the test line (T) position. Therefore, the `test should be invalidated, and a retest should be carried out with new reagents.

Examples of Genetic Test

1. Sample Preparation and Storage

A. Upper airway samples (oropharynx and nasopharynx swab) and lower airway samples (phlegm) can be used for the test.
B. Samples stored in a sample container under refrigerated conditions at 2°C–8°C should be tested within 48 hr. The samples should be stored below -70°C in case of long-term storage. Samples stored in a transfer container should be kept under refrigerated condition at 2°C–8°C until the test. The samples may be stored below -70°C in case of storage exceeding two or three days.
C. Refrain from repeated freezing/unfreezing the samples, because it disintegrates the nucleic acids and reduces the samples' test sensitivity.

2. Pretest Preparation Process

A. Store samples at -20°C, and refrain from repeated freezing/unfreezing.
B. Use reagents after completely thawing them from the frozen state.
C. Equipment required for testing
   1) Nucleic acid extraction instrument
   2) Gene amplification device

3. Testing Process

A. Pretest Preparations
   Follow the manual of the equipment.

B. Pretreatment of Samples
   1) Samples
   A) Take 3 mL or more of lower airway samples (phlegm) from a 50 mL sterilized tube, and take oropharynx and nasopharynx swab simultaneously using a single VTM. Store the samples at 4°C or, if the samples cannot be transported within 72 hr, store at –80°C.

C. Nucleic Acid Extraction

1) Use the DNA/RNA Extraction Kit (No. 00-00, MFDS) indicated in the manual to extract nucleic acids.

 Extract the samples in accordance with the user manual from the manufacturer.

D. Reagent Preparation

1) Open the box and take out the kit components, and then thaw the components. Lightly centrifugate the completely thawed reagents until they are collected at the bottom of the tube.

E. Reagent Mixing

1) Mix Real-time RT-PCR Master Mix, Primer/Probe Mix (E/RdRp), Internal control, and Template RNA as follows.

Composition	Volume / 1 Time
Real-time RT-PCR Master Mix	8 μL
Primer/Probe Mix (E/RdRp)	5 μL
Internal Control	2 μL
Template RNA	5 μL
Total	20 μL

2) The positive control (PC) with the positive control DNA provided with the product and the no template control (NC) with D.W. should be reacted together.

F. Equipment Setting

Set 2 targets used for COVID-19 Real-time PCR Kit, in accordance with the following conditions.

Target	Fluorophore
E	FAM
RdRp	VIC
IC	Cy5

G. Reaction Conditions

The reaction conditions of COVID-19 Real-time PCR Kit are as follows.

Temperature	Time	Cycle
50°C	30 min	1
95°C	10 min	1
95°C	15 s	40
60°C	1 min	

4. Result Determination and Interpretation

A. Set the thresholds and baselines for the targets as follows.

Target	Threshold	Baseline Start	Baseline End
E	0.40	5	15
RdRp	0.40	5	15
IC	1.50	5	15

B. Check each sample's Ct value for each target. Write "+" if Ct value ≦ 35, or "-" if Ct value > 35.

Sample Type	Positive Control	Negative Control	Target			Interpretation
			E	RdRp	IC	
Case 1	+	-	+	+	+	2019-nCoV positive
Case 2	+	-	-	-	+	Negative
Case 3	+	-	-	-	-	Invalid result / Retest
Case 4	+	+	+/-	+/-	+/-	Invalid result / Retest
Case 5	-	+	+/-	+/-	+/-	Invalid result / Retest
Case 6	-	-	+/-	+/-	+/-	Invalid result / Retest

9 Precautions

1. Precautions should be included that the device is for in vitro diagnosis only.

2. Precautions should be included that the device should be used by professionals (including healthcare professionals).

3. The following should be specified for antibody test products, depending on their intended use.

   A. SARS-CoV-2 cannot be diagnosed based only on the results of the antibody test products. Infection must be verified by RT-PCR product which is approved or issued as an EUA along with the final decision of physicians based on the clinical symptoms.
   B. The antibody test products are intended to check the existence of certain antibody against SARS-CoV-2, so it shall not be used for diagnosing the infection of SARS-CoV-2 solely.
   C. In case where antibody concentration is below limit of detection or derived or transported in an inappropriate way, tends to be shown a false negative result, so the infection of SARS-CoV-2 may not be excluded even in the negative results.
   D. Positive test results do not rule out co-infections with other pathogens.
   E. the antibody test products only detect whether the specific antibodies to SARS-CoV-2 exist. There is no correlation between the strength of the test line (or measurements) and the titer of SARS-CoV-2-specific antibodies.
   F. False positive results can be shown due to the cross-reaction with the other factors and antibodies existing in the sample.
   G. Negative result can be shown in case where the variation exists in the part, included in the antibody test products, to connect with the antigen.
   H. The results of the antibody test products may not be used to check the conditions of infection (beginning, recovery and etc.,) of SARS-CoV-2.
   I. The sensitivity may be low in the sample derived before 00 days after the symptoms.

4. For antigen test products, the following should be provided depending on its intended use.

   A SARS-CoV-2 cannot be diagnosed based only on the results of the antigen test products. Infection must be verified by RT-PCR product which is approved or issued as an EUA along with the final decision of physicians based on the clinical symptoms.
   B Positive test results do not rule out co-infections with other pathogens.
   C. In case where antibody concentration is below limit of detection or derived or transported in an inappropriate way, tends to be shown a false negative result, so the infection of SARS-CoV-2 may not be excluded even in the negative results.
   D. Antigen test products only detect whether specific antibodies to SARS-CoV-2 exists. There is no correlation between the strength of the test line (or measurements) and concentration of antigen in SARS-CoV-2.
   E. If the variation exists in the part which connects to monoclonal antibodies included in the antigen test products, the sensitivity may be lower.
   F. Positive test results do not differentiate between SARS-CoV and SARS-CoV2. (This item can be waived if you submit the documents to verify the differentiation of SARS-CoV and SARS-CoV2.)
   G. The samples derived after 00 days after the symptoms are most likely to be shown negative results as the amount of antigen may be decreased according to the outbreak of the symptoms.
   H. Compared to RT-PCR results, the sensitivity may be lower in case where the samples derived after 00 days after the symptoms.

5. General lab safety information and safety cautions for biological hazards (samples, potential infectious materials, wastes, etc.) should be included.

6. Warnings and cautions regarding product handling, storage, application, result determination, and disposal should be included.

   A. Cautions regarding hazardous materials in the component reagents, if any

   B. Method and caution for handling and disposal of used samples and products

C. Caution for sample and product handling and storage (effect of temperature and humidity, etc.)

D. Indication of the possibility of false positive or negative

E. Caution for possible interfering materials or cross-reactive materials

F. Description of the limitations of the test, etc.

7. Information regarding appropriate mix in case that the device combine with other in vitro diagnostic devices

8. In case of a disposable product, a caution against reusing the product

9. In case of acquiring new safety information regarding the product in and outside of Korea (the information recommended to be included in the cautions by a domestic or foreign government body), it should be added to the cautions.

10 Packaging Unit

The packaging unit for an in vitro diagnostic device should be the smallest unit that offers convenient handling. The unit may be indicated as “the company’s packaging unit” for a manufactured in vitro diagnostic device, or “the manufacturer’s packaging unit” for an imported in vitro diagnostic device.

11 Storage and Stability

1. The storage method and period of use or shelf-life should be set in accordance with the Medical Device Stability Test Standards (MFDS Public Announcement).

   A. In case of a kit or a set, the storage temperature of each component should be provided. If the period of use (shelf-life) differs from component to component, the shortest period should be described.

   B. The storage method of the reagents after opening the package should be provided, along with the period of use or the shelf-life. In this case, disposable in vitro diagnostic medical devices are excluded.

   C. For products requiring reconstitution of the reagents, the storage conditions after reconstitution and the period of use (shelf-life) should be provided.

Examples of Immunological Test

Medical Devices for In Vitro Diagnosis: 24 months from the manufacturing date

Serial No.	Name	Open / Not Open	Storage Conditions	Shelf-Life (From the Manufacturing Date)	Note
1	Test strip	Not open	1°C–30°C	24 months	Finished product (disposable)
2	Sample diluent	Not open	1°C–30°C	24 months	Finished product
		Open	1°C–30°C	24 months	

Examples of Genetic Test

Serial No.	Name	Open / Not Open	Storage Conditions	Shelf-Life (From the Manufacturing Date)	Note
1	Internal control	Not open	-20°C (freezing)	24 months	Finished product
		Open	-20°C (freezing)	1 month	
2	Real-time RT-PCR Premix	Not open	-20°C (freezing)	24 months	Finished product
		Open	-20°C (freezing)	1 week	
3	Primer/Probe Mix (E/RdRp)	Not open	-20°C (freezing)	30 months	Finished product
		Open	-20°C (freezing)	1 month	
4	Control (E/RdRp)	Not open	-20°C (freezing)	24 months	Finished product
		Open	-20°C (freezing)	1 week	

12 Test Standard

1. Test standard that are applicable to the verification of safety and performance for each manufacturing unit and stage according to the evidence determined by the manufacturer should be provided, considering product characteristics and performance, etc., to ensure adequate quality control and safety of the in vitro diagnostic medical devices.

2. For the test standard, the test items, criteria, and methods specified by the company should be provided in accordance with the quality control test documents of the manufacturer.

   A. Test Items

      1) Test items should include a performance test for the final quality control of the finished products.

      2) It is recommended to include analytical performance tests (sensitivity, specificity, and replicability, etc.). The company may also specify and add other items.

   B. Test Criteria: The tolerance range of reference values should be clearly indicated to serve as the pass/fail criteria. Moreover, the relevant conditions should be specified if the test results are affected by ambient conditions including temperature and humidity.

   C. Test Methods: Test methods should be provided in detail using bullet points. If the reference materials are used, the name of the materials (management no. or product name) should be described.

Examples of Immunological Test

Serial No.	Test Items	Test Criteria		Test Methods
1	Visual inspection	Testing device	Check for label printing, foreign matters, product damage, pouch sealing, and missing components.	Comply with the manufacturer's quality control test procedure document for finished products (document no.: MFDS-1234)
		Sample diluent		
		Disposable dropper		
2	Performance test	Positive reference material	Should be low-concentration reference materials (COVID-19 virus 10 pfu/mL) that test positive at all of the 10 tests	
		Negative reference material	Should be negative reference materials that test positive at all of the 10 tests	

Examples of Genetic Test

In case of conducting self-quality control for this product, the test should be performed as follows.
- Sample: Use the positive control (PC) and the negative control (NC) included in the product.

No.	Test Items	Test Criteria	Test Methods
1	Visual inspection	Check for foreign matters in the tube, label printing, component arrangement and missing component, product box type, Cat. no., Lot no., and other possible abnormalities.	Comply with the quality control procedure document (document no: MFDS-123)
2	Performance test	- Negative control: Should not be amplified except for IC - Positive control: Should be verified to see whether the Ct value comes within the 25±2 range. - Open the product, mix as instructed, and perform the test using the control DNA (10^5 copies/μL) and the negative control included in the kit. Negative control: Repeat five times. Positive control: Repeat three times.	Comply with the quality control test procedure document (document no.: MFDS-212).

13 Manufacturer

1. For an imported in vitro diagnostic medical devices, the manufacturer's nationality, the manufacturer's name, and its address should be provided.

2. In case of an original equipment manufacturing (OEM) product, the names and addresses of both the manufacturer and the legal manufacturer should be provided. If the manufacturer is a foreign company, the company's nationality should be provided as well.

3. If the manufacturer and the legal manufacturer are different, the information regarding the two should be provided separately.

※ Example

1. Legal manufacturer

   A. Trade name: Osong Diagnosis Reagent Co.,Ltd.,

   B. Address: 187 Osongsaengmyeong2-ro, Osong-eup, Heungdeok-gu, Cheongju-si, Chungcheongbuk-do

2. Manufacturer:

   A. Trade name: ABCD

   B. Manufacturing country: United States

   C. Address: 0000 U.S Highway 000, CA 0000, USA

IV Submissions on Technical Document and Others for Review

1. Attachments for approval should consist of the technical documents and data regarding clinical performance testing under Article 6 (1) of the Enforcement Rule of the Act on In Vitro Diagnostic Medical Devices. The attachments should conform to the types and scope under Article 25 (1) of the Regulations on the Approval, Notification, and Review of In Vitro Diagnostic Medical Devices, and the requirements and supporting data under Article 27 of the same Regulations.

2. The attachments should be prepared using the program designated by the Minister of Food and Drug Safety, or submitted along with electronic medium (CD-ROM, USB memory, etc.)

3. If attachments are unnecessary due to the characteristic of the product, the reason should be provided.

4. Data from other countries should be submitted along with a summary of its key points prepared in Korean, as well as the original copies of the documents. Translated versions of the documents may be requested only if necessary. For documents in foreign languages other than English, notarized full translations should be attached.

1 Development History, and Domestic and International Status

1. For the development history, a description of the measurement targets or a description of the disease or syndrome should be provided along with paper or literature describing the background for the development.

2. For measurement principles and methods, data regarding the principles applied to achieve the measurement and diagnosis targets of the product should be submitted.

   A. Information regarding the reason for inclusion of the targets (genes, antibodies, and antigens)

   B. For immunological test products, data to verify their reaction stages

   C. For genetic test products, data to verify the primer used for amplification, probe, positive control liquid, internal control material, and nucleic acid sequence design method, and the supporting documents

      1) Method for minimizing self-conjugation (self-dimer, etc.) in the primer or the probe, and the rationale for the method

      2) Method for minimizing competition between probe and primer used for gene amplification, and the rationale for the method

      3) In silico analysis data for primer/probe specificity* (inclusivity/exclusivity) (should indicate analysis parameters including NCBI blast and GASAID, etc.)
         * Specificity: Whether the specific primer and probe detect only the targeted genes, or, if not, whether how the other genes are similar with the targeted genes (homology)

2 Domestic and International Status

1. The following data should be submitted regarding the use of the product in and outside of Korea.

   A. Data regarding the status in Korea, sales or approval, and the progress of manufacturing approval (certification)

   B. Measurement errors reported by users

   C. If the product is not used in the manufacturing country, reason for not using the product

※ Example

A. Approval in other countries: Supporting documents on the United States (510 K (K000000) October 5, 1999)

B. Measurement error reported by users: Measurement errors reported over the years (by the management system of the manufacturing country's government, the company's own investigation, etc.)

C. Data regarding the progress of manufacturing approval and other matters: Approval process for the product in multiple countries

D. Reason for not using the product in the manufacturing country: Cases such as those where the product is approved in a country before it is approved in the manufacturing country, on account of the manufacturer's circumstances

3 Raw Materials and Manufacturing Methods

1. Supporting data to verify the components of the raw materials or their quantities

   A. Data to verify the components of the product, purpose of mix, and their quantities

   B. Data to verify the origins and characteristics of the main components

   C. In cases where the supplier cannot provide information regarding the quantities and characteristics of the raw material (master mix, etc.) directly to the applicant, the supplier may submit the information to the MFDS (reviewer).

※ Example

1) Data to verify the individual components included in the reaction enzyme (amplification enzyme), DNTP, and master mix, etc.

2) Gene selection locations, nucleic acid sequence, molecular weights, and purity of primers, probes, positive control materials, and internal control materials

3) Clone numbers, immunogens, origins, titers, molecular weights, and purity of antibodies

4) Nucleic acid or amino acid sequences, expression systems (vector, etc.), molecular weights, and purity of recombinant antigens

2. Data regarding manufacturing processes, including process flow charts

   A. Data to identify the flow of the manufacturing processes (documents that indicate the tests performed at each manufacturing phase and the quality control testing stages for finished products) should be submitted.

   B. Data that briefly describe the manufacturing methods of the raw materials (antibodies, antigens, primers, probes, and enzymes, etc.) should be submitted, along with data supporting the purchase of the materials, if any of the materials were purchased.

   C. If a part of the components are OEM products, data should be submitted to identify the manufacturer of the components (the manufacturer’s name and address).

4 Intended Use

1. Supporting data should be provided for the detailed intended use of the product indicated in the application (test targets, sample types, analytes (test items), diseases, operational principles, and methods to determine the results).

2. In case of a manufactured product, the test targets, sample types, and analytes (test items) of the product should be provided based on supporting data, and manuals and other supporting data should be submitted as well.

3. In case of an imported item, the manufacturer’s user manual (in English or Korean) should be submitted. The manual should indicate the test targets, sample types, and analytes (test items) of the product.

5 Storage Methods, Period of Use, and Shelf-Life

1. A test report from a test performed in accordance with the Medical Device Stability Test Standards (MFDS Public Announcement) should be submitted as a document indicating the storage conditions and the period of use (shelf-life).

2. The submissions on stability test should be provided along with the test results and the test protocols regarding the evaluation plan, evaluation method, tolerance, and testing intervals (first two tests including the beginning of the first test and the last test).

   A. As for the genetic diagnostic reagents, in vitro transcript RNAs or national (international) standard products manufactured based on SARS-CoV-2 genes may be evaluated at various concentration levels.

      * The concentration levels may contain various levels (low, medium, and high) including the cutoff level.

   B. For tests on storage methods and period of use (shelf-life), pre-opening test reports on three lots and post-opening test reports on one or more lots should be submitted (see ISO 23640).

   C. If relevant to the method of use of the product, the submissions on the shelf-life after opening the package should be included.

      1) “On-board” for products used by attaching it to equipment

      2) “Reconstitution” for products that require reconstitution such as dissolving it in a solvent

      3) “Open vial/bottle” for products used multiple times after opening the vial and bottle.

         The documents are not required for individually packaged disposable in vitro diagnostic medical devices

3. With regard to the determination of the shelf-life, Stability Test Standards of the Medical Device (MFDS Notification) should be observed even when verifying the validity in a short period through accelerated aging. In such cases, the supporting data for the calculation of the accelerated aging time should be submitted as well.

4. Stability tests for post opening should be performed under the conditions indicated in the user’s instructions, considering the actual environment in which the product is used.

6 Verification for the Performance of the Product

1. Submissions to verify the performance of the product should include the following documents.

   A. Submissions on analytical performance testing

      1) Analytical sensitivity (cutoff value, LoD, and measurement scope, etc.)

      2) Analytical specificity (cross-reactivity, etc.)

      3) Precision (repeatability and replicability, etc.)

      4) Accuracy

   B. Submissions on clinical performance test

      It refers to submissions on tests performed on human-derived samples to verify the performance and effectiveness of the in vitro diagnostic medical devices, and includes the following evaluation items.

      1) Clinical sensitivity

      2) Clinical specificity

   C. Submissions on quality management test

      1) Test reports on quality management for finished products or data regarding quality control tests (one or more test of three batches; or three or more tests of one batch)

   D. Submissions on standard materials and storage of samples

      1) Submissions on the reference materials used for the quality control testing of finished products

      2) Supporting documents for sample storage and handling conditions (temperature and humidity, etc.)

2. The submissions on analytical performance tests or clinical performance tests should include comparative test reports to verify the correlation with other approved in vitro diagnostic devices in and outside of Korea. However, the product may be compared against a product with same intended use, if the product's measurement principles and items are unprecedented. In case of an in vitro diagnostic medical device for which clinical performance testing submissions are required, should submit clinical performance data and a comparative test report.

3. Applicable submissions on analytical performance test are as follows.

   A. Test reports issued by test labs designated by the Minister of Food and Drug Safety.

   B. Test data for the medical device submitted to an OECD member state for evaluation at the time of the approval, which verify or certify that the device was submitted to and approved by the regulatory authority or a devolved registration body.

   C. Test reports from the tests performed under the manufacturer's quality control system satisfying the standards equivalent to, or higher, than those under the Good Manufacturing and Quality Control Practices of In Vitro Diagnostic Medical Devices (MFDS Notification)

   D. Test reports from the tests performed by a professional body in and outside of Korea, such as a university or research lab, which were issued by the head of the body, and the content of which (overview of its testing facilities, key equipment, research workforce, and research experiences of the testers) can be accepted as valid

4. Submissions on clinical performance should fall under one of the following.

    1) Data regarding tests performed by a clinical trial institute designated by the Minister of Food and Drug Safety

    2) Data from other countries where the testing body's reliability can be accepted after reviewing the content, and the data themselves can be accepted as equivalent to data on tests performed in accordance with the clinical performance testing implementation and management standards under Article 17 (1) of the Enforcement Rule of the Act on In Vitro Diagnostic Medical Devices

    3) Clinical test data for the medical device submitted to an OECD member state for evaluation at the time of the approval, which verify or certify that the device was submitted to and approved by the country's government or a registration body authorized by the government to approve the device

    4) Data published in an academic journal listed in the Science Citation Index or the Science Citation Index Expanded

5. Submissions on clinical performance test should include the following.

    1) Test methods of clinical performance

        A) Inclusion and exclusion criteria for subjects and the target number of subjects
        In principle, for each disease being tested, it should include the data to prove that the number of subjects for the clinical performance test was determined in a statistically valid manner, considering the characteristics of the in vitro diagnostic reagent, the testing methods of clinical performance, and other factors. In cases where it is difficult to secure a sufficient number of subjects due to the low occurrence of the indication, the data to prove such difficulty should be attached as well.

        B) Methods of operation or use, and the rationale for the methods

        C) In case of using an in vitro diagnostic reagent for comparative test, the reason for using the reagent

        D) Whether the combined use will be used or not.

        E) Observation items, measurement items, clinical test items, measurement criteria, and test methods

        F) Efficacy evaluation criteria, evaluation methods, and interpretation methods

        G) Safety evaluation criteria and test methods, including side effects

    2) Data regarding clinical performance results should include the following.

        A) Clinical performance test results (including the planned number of subjects, the actual number of subjects, the number of subjects that completed the test, the number of dropouts, and the reason for the dropouts, along with the side effects observed with each subject, etc.)

        B) Summary of case reports

        C) Other data required for the verification of the clinical performance test results

7 Safety for Handlers of In vitro diagnostic reagents

1. If any of the component reagents include materials derived from human blood, data should be submitted to prove that the reagents have tested negative for human immunodeficiency virus (HIV), hepatitis C virus (HCV), and hepatitis B virus (HBV), or the viruses are inactive and incapable of infecting humans.

2. Data should be provided to verify the safety and conformity for handlers of hazardous materials (toxicity, inflammability) .
(e.g., MSDS).

8 Comparison with Pre-Approved or Certified Products

A comparison sheet should be submitted using Attached Form No. 2 of the Regulations on the Approval, Notification, and Review of In Vitro Diagnostic Medical Devices (MFDS Notification) that compare the name (product name, item name, and model name), manufacturer (importer) name, manufacturer and its location, approval (certification) number, intended use, operational principles, raw materials, performance, etc. of the product with those of previously approved/certified products. For now, there is no product approved for COVID-19, data should be submitted to compare the diagnosis kits for known coronaviruses (OC43, Hku1, etc.).

Attached Form No. 2

Substantial Equivalence Comparison Sheet for In Vitro Diagnostic Reagents

No.	Items for Comparison[1)]	Previously Approved (Certified) Product	Applied Product	Equivalence[2)]	
1	Name (product name, item name, and model name)				
2	Classification number and class				
3	Manufacturer (importer) name				
4	Manufacturer and its location				
5	Approval (certification) number				
6	Intended use			Yes	[ ]
				No	[ ]
7	Operational principles			Yes	[ ]
				No	[ ]
8	Raw materials			Yes	[ ]
				No	[ ]
9	Performance			Yes	[ ]
				No	[ ]
Equivalence is certified as above. Date: Applicant (Signature or seal)					

V Detailed Information Regarding Performance Test

□ Despite the paragraphs below, given the nature of the product, if any of the items are not available for testing or can be replaced with other data, the reason for the non-testing or replacement should be provided.

1. For data regarding performance test, the following should be submitted: analytical performance test data, clinical performance test data, quality control test report for finished products, data regarding reference materials used for analytical performance test, and supporting data for sample storage and handling conditions (temperature, humidity, etc.).

2. Analytical performance tests may be performed in accordance with the testing methods under the Guideline of MFDS or other countries (including the CLSI Guidelines). The test criteria for analytical performance tests should be appropriately determined based on these Guidelines.

3. A test report for a product performance test under the manufacturer's quality control system should include the following items.

   A. Name and address of Manufacturer

   B. Serial number of the test report, number of each page and number of total pages

   C. Name and information regarding test targets
      1) Item name, model name, product name, and storage conditions, etc.

      2) Information regarding reference materials used for the test and sample, and storage conditions, etc.

   D. Test date (period)

   E. Issuance date of test report

   F. Signature or official seal of the person responsible for the test report

   G. Test methods and criteria

   H. Test results and conclusions

I.) Environmental factors (only those affecting the test results)

4. In case of submitting a test report issued by a professional body in or outside of Korea such as a university or a research lab as performance data, the following data should be submitted to ensure the reliability of the test report.

   A. Name and address of testing body

   B. Name, representative, and address of the company that requested the test

   C. Serial number of the test report, number of each page and number of total pages

   D. Name and information regarding test targets

      1) Item name, model name, product name, and storage conditions, etc.

      2) Information regarding reference materials used for the test and sample, and storage conditions, etc.

   E. Date of receipt of the test or test date (period)

   F. Issuance date of test report

   G. Signature or official seal of the person responsible for the test report

   H. Test method and criteria; if there is no standard, the grounds for determining the method and criteria

   I. Test results and conclusions

   J. Environmental factors (only those affecting the test results)

5. Additional submissions (for data on tests performed by a professional body in or outside of Korea such as a university or a research lab)

   A. Overview of test facility: The name, address, certification status, test areas, research workforce, and list if key equipment of the professional body should be provided.

   B. Key equipment: The name and specification of the equipment used in the test, inspection/calibration records should be provided, along with the supporting data.

   C. Research workforce: The information regarding the research workforce affiliated with the dedicated department of the testing body should be provided.

   D. Testers' research experience: Information should be provided to verify whether the testers are educated or experienced enough to conduct the test, or whether the test was performed by testers satisfying the requirements specified by the professional body.

1 Submissions on Analytical Performance Test

□ The following should be considered when preparing submissions on the analytical performance test.

1. Analytical Sensitivity

In case of a quantitative product, its LoB, LoD, LoQ, and measurement range should be evaluated, and the background for determination should be provided. In case of a qualitative product with a cut-off value for positive/negative determination, the evidence for selecting the cut-off value should be provided. In case of a qualitative product, testing may be waived for some of the items, given the nature of the product.

A. LoB, LoD, and LoQ

1) General Information

A) The samples indicated in the intended use for the applied product (serum, plasma, blood, nasopharynx swab, oropharynx swab, phlegm, etc.) should be used for measurement.

B) Samples diluted with a compatible matrix or added with the analyte can be used as low-concentration samples.

C) In case of a genetic product, information regarding the reagent used for extracting nucleic acid from the samples and the measurement equipment (PCR equipment) should be provided.

- For the nucleic acid extraction reagents, only pre-approved reagents should be included. In addition, the testing data for each extraction reagent should be submitted.

- In case of using multiple genetic amplification devices, the testing data for each device should be submitted.

D) In case of antibody extraction products, it is recommended to use samples that allow for accurate verification of the titers of the antibodies.

E) For products for detecting nucleic acids and those for testing antigens, it is recommended to measure the LoD of 2019-nCoV using samples culturing the entire viruses or the stocks with accurately known amounts of viruses (pfu/mL, copies/mL, and μg/mL). In case of a genetic test product, it is recommended to evaluate the product using in vitro transcription RNA or virus isolates (or standard product).

F) In case of storing samples in transport media, the analytical performance testing data for each transport media should be submitted.

2) Test Materials

A) The test results for each type of measurable sample should be provided.

※ Example - Phlegm: 10 pfu/mL, oropharyhngeal swab: 20 pfu/mL

B) For antibodies, the method used for titer verification should be indicated. For antigens, the cell lines (ex: 2019-nCov/USA-WA1/2020 and etc.,) used shall be described.

C) The samples created by adding the analyte to matrix commutable with the samples proposed by the manufacturer, or samples created by diluting reference materials or positive samples should be used.

D) It is recommended to use at least five levels of samples including the concentration values before and after the estimation of LoD.

3) Test Methods

A) The sample types and the sample preparation processes (sample types, matrix, number of samples, number of measurements, concentration of analytes, and method used to verify concentration) should be provided.

B) For the part of the test methods based on other literature, a summary of test methods citing literature symbols may by submitted.

C) It is recommended to perform tests for 3–5 days or longer, and repeat measurements 20 times or more to consider different variables affecting the LoD.

D) It is recommended to evaluate the product in accordance with the Guideline under CLSI EP17.

4) Results

A) The statistically valid LoD should be provided, along with the sample types, number of samples, number of repetitions, and calculation used for the determination.

B) For a gene detective product, the results should be provided in terms of pfu/mL or RNA copy number.

C) For an antigen detective product, the results should be provided in terms of pfu/mL.

D) For an antibody detective product, the results should be provided in terms of titers, along with the method used for verifying titers.

E) Results should be provided for each matrix if different samples have different matrixes.

B. Cut-off Values

1) General Information

A) Clinical performance test (other test results, reaction to treatment, and clinical diagnosis) can be used to evaluate the conformity of the cutoff values.

B) It is recommended to use the samples indicated in the intended use for the applied product (serum, plasma, blood, nasopharynx swab, oropharynx swab, phlegm, etc.).

C) Supporting data should be provided for the determination of the cutoff values.

D) It is recommended to consult with experts group as the setting methods of cut-off value can be different depending on the measurement items, principles, and interpretation methods.

2) Test Methods

A) The method for calculating cut-off values during the test should be specified.

B) It is recommended to determine the cutoff values by drawing the Receiver Operating Curve (ROC) with the clinical sample test results.

C) If there is any equivocal section other than the positive and negative results, the support data for determining the section should be provided.

3) Results

A) Cut-off values (concentration)

B) Clinical sensitivity and specificity at the cutoff values

C) The cutoff values for a molecular genetic product should be determined based on the Ct value or copy number during real-time polymerase chain reaction.

C. Measurement Range

1) General Information

A) Qualitative tests may be omitted in typical cases.

B) Measurement range refers to the range of previously known concentration values that the test can accurately replicate. The LoD and the LoQ represent the lowest concentration level of the measurement range.

B) It is recommended to consult with experts group as the substances used for measurement range evaluation, the dilution methods, and the result evaluation methods may vary depending on the measurement items, measurement principles, and interpretation methods.

D) Information should be provided regarding whether a value can be diluted beyond the measurement range and be reported, along with the supporting data.

2) Test Materials

A) The test materials should have a suitable matrix for the measurement method used.

B) It is recommended to use reference materials compared with reference standards with suitable matrix and target values.

C) In cases where reference materials are not available, high-concentration clinical samples with known concentration levels of the materials to be measured should be used.

D) In case of a product capable of detecting two or more SARS-CoV-2 sub-type infections, positive samples for each sub-type should be prepared, and the LoD and the measurement range should be determined for the test for each SARS-CoV-2 sub-type.

E) If clinical samples are not available, samples not including the materials (antibodies or antigens) to be measured should be used after spiking the concentration of the corresponding material to a certain level. It should has well-known matrix and concentration.

F) For negative samples to be spiked or used for dilution, negative samples from persons in the target group for the product (nasopharyngeal swab, oropharyngeal swab, phlegm, plasma, serum, and blood, etc.) should be used in consideration of the matrix effect.

3) Test Methods

A) Test materials should be provided by mixing high-concentration samples with negative samples, or diluting high-concentration samples by using serial dilution (at least five concentration levels should be used).

B) The concentration levels should include both the upper limit and the lower limit of the expected measurement range, and other clinically important concentration levels.

C) The LoD measurement may be omitted if the analyte is produced in human bodies (e.g.,

antibodies) or it is extremely difficult to acquire objectively quantifiable pure materials. However, even in such cases, the quantitative test should measure and propose an LoB and a scope of linearity, and the qualitative test should propose an LoB.

D) LoB can be calculated by adding a value 1.65 times the standard deviation and 20 or more repeated measurements of samples not containing the analyte to the mean value of the measurements.

E) Three measurements should be taken at each concentration level, using the reagents from the same lot.

F) Linearity range: Series samples with at least five known concentration levels including the proposed linearity range (recommended to cover a range 20%–30% wider than the expected measurement range), or samples with concentration levels established through dilution should be used. It is recommended to create medium-concentration samples by mixing high-concentration and low-concentration samples at a specific ratio. However, the intervals between concentration levels may be uneven. Two to four measurements should be taken at each concentration level.

4) Results

A) As for results, the section where linearity is maintained should be proposed after analyzing the samples using the linear or best fit model.

B) The difference between the estimates and the measurements should be proposed along with the reproducibility at each concentration level.

C) Supporting data should be provided for products using nonlinear calibration models.

D) For the concentration unit, it is recommended to use an internationally recognized unit such as those proposed by the WHO, if there is any. If there isn't, it is recommended to use objective units such as copy number, mass, or molecular weight. However, an arbitrary unit may be used if the correlation between mass and activity is unclear or objective quantification is extremely difficult.

E) LoD can be defined in terms of pfu/mL, μg/mL, U/mL, or genomic DNA copy.

D. Strain Reactivity

1) General Information

A) Reactivity should be evaluated three subtypes of SARS-CoV-2 serotype antigen or antibody using the evaluated product.

B) A panel consisting of SARS-CoV-2 samples containing other SARS-CoV-2 virus sub-types should be evaluated.

C) In consideration of the outbreak and current status of SARS-CoV-2 at the time of the product's development, other types may be added other than the proposed SARS-CoV-2 virus.

D) If some of the SARS-CoV-2 sub-types were not evaluated in the test, valid data (literature, etc.) may be submitted to show that non-tested SARS-CoV-2 sub-types may be detected.

2) Test Methods

A) The sample types and the sample preparation processes (sample types, matrix, number of samples, number of measurements, concentration of analytes, and method used to verify concentration) should be provided.

B) The test method for evaluating the reactivity of the evaluated product should be described in detail (number of repetitions, measurement method, etc.).

C) In case of a genetic test product, the ability to detect SARS-CoV-2 nucleic acid sequence can be analyzed using the in silico method.

3) Test Results

A) The SARS-CoV-2 subtypes that can be detected with the evaluated product should be clearly described.

B) The LoDs that can be detected with the evaluated product should be described for each SARS-CoV-2 sub-type.

C) Information regarding the SARS-CoV-2 cell strains, the in silico method, and the results used for analysis should be provided.

2. Analytical Specificity

A. Cross-Reactivity

1) General Information

A) It is recommended to evaluate cross-reactivity with microorganisms (viruses, bacteria, etc.) and others causing respiratory infection.

B) It is recommended to test for the following coronaviruses:Human coronavirus NL63 and human coronavirus 229E of Alpha coronaviruses; and betacoronavirus (strain HCoV-OC43), human coronavirus HKU1 (HCOV-HKU1), Middle East respiratory syndrome–related coronavirus (MERS-CoV), and severe acute respiratory syndrome coronavirus (SARS-CoV) of Beta coronaviruses.

C) Viruses or bacteria should be evaluated at medically significant concentration levels. The recommended concentration levels for bacteria and viruses are 106 cfu/mL or higher, and 10^5 pfu/mL or higher, respectively.

2) Test Materials

A) Pathogen-positive samples with cross reactivity should be used.

B) Other microorganisms with phylogenetic proximity, and microorganisms causing conditions similar to those caused by the tested samples should be included.

C) In case of an antibody test product, materials should be used that contain antibodies (IgM and IgG) for the pathogens expected to be cross-reactive.

3) Test Methods

A) The types and concentration of the cross-reactive materials, the type of samples (e.g., samples added with the materials expected to be cross-reactive, or samples naturally containing the materials expected to be cross-reactive, etc.), the concentration of the analyte and the results should be described in detail.

- Genetic Products: The test methods should be provided in a way that allows for verification of the gene extraction reagents and the PCR equipment.

B) It is recommended to test samples for cross-reactivity evaluation at least three times.

4) Results

A) The type of positive materials used for the cross-reactivity evaluation (strain type, subtype, etc.) should be provided.

B) The type and concentration of the cross-reactive materials and the existence of cross-reactivity should be provided.

※ Example. Types of cross-reactive microorganisms

Test Organism
Bacteria
Legione la spp.
Mycoplasma spp.
Virus
Human coronavirus NL63
Human coronavirus 229E
Betacoronavirus(strain HCoV-OC43)
Human coronavirus HKU1(HCOV-HKU1)
Middle East respiratory syndrome-related coronavirus(MERS-CoV)
SARS
Influenza A(H1N1/09, H3N2)
Influenza B(H5N1)
Rhinovirus/Enterovirus
Respiratory syncytial virus A/B
Parainfluenza 1, 2, 3 virus
Parainfluenza A, B virus
Human metapneumovirus
Adenovirus
Human Bocavirus

B. 1) Interference

1) General Information

A) Possible interference in the use of the evaluated product should be comprehensively tested.

B) It is recommended to perform the test at the highest concentration level where the Interfering materials can exist in the sample,assuming the worst-case scenario.

2) Test Materials

A) Samples with matrix compatible with the measured samples should be used.

B) Interfering substances may be an internal factor in the samples or an external factor, which may vary depending on the measurement method. Therefore, it is recommended to perform interference tests on the following materials expected to affect test results depending on the method used.

- Substances likely to be consumed by the patient: Medicine, alcoholic beverage, vitamins, foods, etc.
- Substances added for sample treatment: Preservative, stabilizer, anticoagulant, etc.
- Substances likely to be included in the samples: Hemoglobin, white cells, protein, mucin, lipid, bilirubin, etc.

※ Examples of Interfering materials

Serial No.	Substance
1	Mucin
2	Blood
3	Antiviral agent
4	Heparin
5	Na citrate
6	EDTA
7	Albumin
8	Hemoglobin
9	Human DNA
10	Conjugated bilirubin
11	Lipid
12	ANA
13	Rheumatoid factor

3) Test Methods

A) Interfering materials should be selected based on the samples and testing methods.

B) The test methods should be described in detail, including the sample types, the type of interfering materials, the concentration of the interfering materials, the concentration of the analytes, the manufacturing method of the samples (e.g., samples mixed with the interfering materials, or samples naturally containing a high concentration of the interfering materials).

C) The concentration of the sample material should be near the cut-off value.

D) The concentration of the interfering materials should be higher than the highest concentration that can be observed in the clinical sample.

E) Each sample should be tested for three times or more.

F) The samples containing the interfering materials should be compared with those not containing the interfering substance.

G) If there is no effect from high-concentration interfering materials, additional evaluations is not required. However, if there is, a dose-response test should be performed to verify how interfering materials may affect at different concentration levels.

H) It is recommended to perform tests in accordance with the CLSI EP7-A2 guidelines.

4) Results

A) The results for samples containing the interfering materials and those not containing the interfering substance should be provided.

B) For materials identified as interfering materials, the specific concentration levels and results should be described.

C) The effect of the interfering materials on the analyte result should be described, if any (e.g., a high concentration of substance X reduces the test result for the analyte).

3. Precision

A. Within-Laboratory Precision/Repeatability

1) General Information

A) The same samples should be tested repeatedly, and the results should be analyzed and submitted as precision data.

B) For the repeatability data, the results from a single body (within laboratory) should be analyzed and submitted.

C) An evaluation body should perform evaluation after familiarizing themselves with the test method.

D) In case of a qualitative test method not requiring measurement equipment (e.g., immunochromatography), repeatability evaluation data may be not required.

2) Test Materials

A) Four or more samples should be used for the test, and the concentration of the samples should be near the cutoff value.

B) The test materials to be used should be specified (e.g., positive control materials, negative control materials, high-concentration negative samples, and low-concentration positive samples).

3) Test Methods

A) The test methods should be provided in detail including the sample type, the number of samples, measuring method and the number of measurements.

B) A single-lot product should be tested for twice per day for at least five days. For each test, it is recommended to test each sample twice.

4) Test Results

A) Information on intra-assay, inter-assay, and inter-lot should be provided.

B. Between-Laboratory Precision/Reproducibility

1) General Information

A) The same samples should be tested repeatedly, and the results should be analyzed and submitted as precision data.

B) Reproducibility data should be submitted by analyzing test results from multiple bodies.

C) An evaluation body should perform evaluation after familiarizing themselves with the test method.

2) Test Materials

A) Three or more samples should be used for the test, and the concentration of the samples should be near the cutoff value.

B) The test materials to be used should be specified (e.g., negative control materials, high-concentration negative samples, and low-concentration positive samples).

3) Test Methods

A) The test methods should be provided in detail including the sample type, the number of samples, measuring method and the number of measurements.

B) Two or more testers should perform two tests or more per day, for five days or longer at two test labs (including the manufacturer) using two-lot products. It is recommended to test each test sample at least twice.

C) It is recommended to refer to CLSI EP05-A2, CLSI EP12-A2, and CLSI EP15-A2 Guidelines

4) Test Results

A) Repeatability results should be provided for each test lab.

B) Repeatability results for all test labs and between-site results should be provided.

4. Accuracy

A. Test Materials

1) If there exist reference materials, international standard materials, and other materials with specified characteristics, it is recommended to use those materials.

B. Test Methods

1) If there exist reference materials, international standard materials, and other materials with specified characteristics, it is recommended to use those materials for the evaluation. Measurement should be taken at least two times.

C. Results

1) The target results for the reference materials and actual measurements should be provided.

2) The method used for standardizing the reagents should be described.

3) The fixed concentration of the calibration materials and their traceability should be described.

4) The manufacturing method of the control materials, the fixed concentration, and the results of the repeated measurements should be described.

5) If reference materials are not available, the measurements for the analyte using the standard method can be compared with the measurements taken using the applied device (e.g., compare the results with the PCR positive results to evaluate the accuracy of the antigen and antibody tests).

5. Carry-Over and Cross-Contamination

A. General Information

1) In case of a product that uses a device to test multiple samples, it should be tested for carry-over and cross-contamination.

B. Test Materials

1) Positive samples and negative samples should be used.

2) An appropriate concentration level should be determined considering the performance of the product and the purpose of the test.

C. Test Methods

1) Tests should be performed using either positive or negative samples depending on the performance of the device.

2) Tests should be repeated at least five times alternating between positive and negative samples.

D. Results

1) The proportion of negative results from measurement of high-concentration negative samples should be expressed as percentage.

2 Submissions on Clinical Performance Test Data

□ The following should be considered when preparing submissions on clinical performance test.

1. General Information

   A. A clinical trial plan should be prepared in accordance with Article 13 of the Enforcement Rule of the In Vitro Diagnostic Medical Device Act.

   B. The purpose (diagnosis, diagnostic support, etc.) and users (healthcare professionals) of the clinical trial should be specified, and the clinical test should be designed accordingly.

2. Inclusion and Exclusion Criteria for Subjects

   A. The inclusion and exclusion criteria for samples should be clearly defined.

   B. In principle, samples taken from humans should be tested without dilution, concentration, or any other manipulation. However, for some positive samples (not more than 30% of the total samples), evaluation data acquired by spiking positive samples with negative clinical samples taken from different persons are acceptable as well.
   - In cases where information exists regarding sample types and RNA extraction/storage methods, RNA tests may be performed. It is recommended to use RNA extracted using a single method. In such cases, 30% of the overall samples should be evenly distributed at concentration levels ranging from 1× LoD to 3 × LoD.

   C. For genetic tests (PCR) and antigen tests, if some of the samples used for the tests are artificial samples, the tests should use samples of which concentration levels are evenly distributed between 1× LoD and 3 × LoD.

   D. Information regarding the method used for verifying the existence/nonexistence of conditions (“clinical true”), the control group (Inclusion/exclusion criteria and number of patients), and sample types should be provided in detail.

※ Example

A. Inclusion Criteria for Subjects
   1) Adult males and females aged 19 or older
   2) Patients suspected of respiratory infection under the CDC Guidelines, symptoms including fever, throat pain, dyspnea and ranging from minor to serious symptoms

B. Inclusion Criteria for Samples
   1) Remaining nasopharyngeal swab from patients diagnosed with COVID-19 under the CDC Guidelines at OO Hospital until March 2020
   2) Samples stored in MFDS-VTM 3 mL at –20°C for a year or less
   3) Remaining samples that can be used to confirm definite diagnosis

4) Uncontaminated samples
5) In case of samples stored as RNA, samples that can be verified as the samples extracted with Jesin No. 00-000 (the gene extraction reagent indicated in the user instruction)

3. Calculation of Sample Size

A. Estimation of Clinical Sensitivity and Specificity of the applied device

1) Valid data supporting the clinical effectiveness (sensitivity and specificity) to be verified in the confirmatory clinical trial should be provided. If possible, it is recommended to calculate the clinical sensitivity and specificity to be verified through an exploratory clinical trial.

A) Sensitivity and specificity should be calculated based on the clinical efficacy criteria and the general clinical sensitivity and specificity of the reagents.

B) If other methods (journal articles, real-world data, etc.) are available to calculate the sensitivity and specificity estimation, such methods may be used as well.

B. Clinical Efficacy Criteria

1) Clinical efficacy should be determined based on valid supporting data (clinical sensitivity and specificity estimations proposed by previously approved products, articles, and textbooks). However, if such supporting data is not readily available, such as in the case of COVID-19, the clinical efficacy may be determined as follows considering the characteristics of the existing genetic test reagents: sensitivity at 95%; lower limit of the confidence interval for sensitivity at 90%; specificity at 97%; and lower limit of confidence interval for sensitivity at 95%. In case of an existing genetic test product, in reference to the US FDA criteria for influenza viruses, the clinical efficacy may be determined as follows: sensitivity at 80% or higher; lower limit of the confidence interval for sensitivity at 70%; specificity at 95%; and lower limit of confidence interval for sensitivity at 90%.

2) Calculation of the numbers of samples

A) The number of samples can be calculated using the following equation.

The following equation can be used to calculate sample size for clinical sensitivity and specificity analysis.

$$n = \frac{(Z_{\alpha/2} + Z_{\beta})^2 \times P_1(1-P_1)}{(P_1 - P_0)^2}$$

P1: estimated sensitivity (or specificity) of the device
P0: Lower limit of confidence interval for clinical target sensitivity (or specificity)
$Z_{\frac{\alpha}{2}}$: t value of type 1 error (α)
Z_{β}: t value of type 2 error (β)

※ Example) Calculation of the numbers of samples

- Estimated sensitivity of the device: 95%
- Lower limit of confidence interval for clinical target sensitivity: 90%
- t value of type 1 error (α) at 0.05 significance level (α): 1.96
- t value of type 2 error (β) at 80% power: 0.84

$$149 = \frac{(1.96 + 0.84)^2 \times 0.95(1-0.95)}{(0.95-0.90)^2}$$

149 ≒ 150

B) In case of setting the estimated sensitivity or specificity of the applied device at a value higher than 95%, it is recommended to estimate the value using simulation and other methods to ensure that the 95% confidence interval is larger than the success criteria.

* If applicant assume the estimated sensitivity (or specificity) extreme value near 1, the supporting documents (including exploratory clinical trial) are required. In addition, the numbers of samples shall be calculated to verify the risk of false negative or false positive.

3) Considerations for calculation of the numbers of samples

A) The purpose of calculation of the numbers of samples is to identify the optimal number of samples for verifying the efficacy of the device's clinical specificity and sensitivity. Moreover, 80% power is not a fixed value.

B) Even when conducting a clinical trial with the estimated sample size, the measurements may be lower than the estimated sensitivity and specificity, in which case clinical efficacy is not achieved. Given the possibility of eliminated samples, it is recommended to use samples exceeding the estimated the numbers of samples

4. Clinical Trial Methods

A. Clinical sensitivity and clinical specificity compared with the reference standard methods and the clinical diagnosis results should be provided in detail. In addition, an evaluation should be carried out, including the following items, to provide users with accurate information regarding the product's performance.

1) For a genetic test product or an immunological test product (antigen)

A) A summary of case report form (CFR) should be provided for verification of results (Ct value, etc.) after the end of the clinical trial.

2) For an immunological test product (antibody)

A) Evaluation should be performed using a certain number of seroconversion samples. Seroconversion samples separated from the same patient and evaluated by comparison against the genetic test method (EUA or approved products) should be used for the evaluation. A valid reason for the unavailability should be provided if a sufficient number of samples are not available.

B) However, the following should be considered for antibody test products, depending on their intended use.

- It is recommended to test samples sharing the same infection time (±1 day).

- It is recommended to test samples with different infection times. In such cases, the sample sizes calculated for the different infection times should be applied for the test (e.g., samples within __ days from symptom manifestation).

5. Criteria for Performance Evaluation

A. Clinical sensitivity, specificity, positive prediction, and negative prediction ratio should be determined as the primary efficacy evaluation variables

1) The criteria for clinical sensitivity and specificity should be determined based on valid supporting data.

2) If applicable, the positive match ratio and the negative match ratio should be proposed.

B. As for the secondary indicators for efficacy evaluation, the following should be included.

1) If artificial samples were used in a genetic test, a comparison result between the aforementioned definite diagnosis method and the samples diluted to 1 × LOD – 3 × LOD should be added.

2) If all of the samples used were patient samples, data should be submitted regarding an evaluation where samples corresponding to 10 percent of the total samples were diluted using serial decimal dilution, etc. until positive results were replaced by negative results.

3) In case of a serological test product, evaluation results for seroconversion samples, consecutively derived samples, and samples with different infection times should be added.

6. Evaluation and Interpretation Methods

A. Determination of the Reference Standard Method

1) The reference standard method that verified the existence of a condition may be either a single method implemented to verify the existence of a target material, or a combination of multiple methods. In case of combined methods, the diagnosis method defined as the true value and the supporting data for the method should be described.

2) For the purpose of evaluating the applied product, EUA products in Korea may be used as the reference standard method. In case of conducting a clinical performance test for an EUA product (A), another EUA product (B) can be used as a comparison test method.

3) Additional tests may be implemented using a third EUA product, methods used at the KCDCP, and nucleic acid sequencing if the genetic test result of the evaluated product does not match the results of the definite diagnosis method. The results should be used only to verify the reason for non-match.

B. Clinical efficacy Determination

1) Clinical efficacy should be established by verifying whether the lower limit of the 95% confidence interval for the clinical sensitivity and specificity verified by a clinical trial is higher than the lower limit of the confidence interval for the clinical target sensitivity and specificity.

2) Clinical significance is not established even if the tested sensitivity is higher than the target sensitivity if the lower limit of the 95% confidence interval is lower than the lower limit of the confidence interval for the clinical targets.

※ Example) Clinical efficacy Result Example
- Clinical target sensitivity: 95%
- Lower limit of confidence interval for clinical target sensitivity: 90%
- Clinical target specificity: 97%
- Lower limit of confidence interval for clinical target specificity: 95%

1) In case of using 100 positive samples and 200 negative samples:

		Confirmation Method		Total
		Positive	Negative	
Applied Device	Positive	96	4	100
	Negative	4	196	200
Total		100	200	300

- Sensitivity: 96% (CI, 95%: 90.2–98.4)
- Specificity: 98% (CI, 95%: 95.0–99.2)
- Clinical Result Analysis: Clinical efficacy exists, because the lower limit of the confidence interval for sensitivity and specificity is higher than the lower limit of the confidence interval for clinical targets (sensitivity: 90%, specificity: 95%).

2) In case of using 70 positive samples and 110 negative samples:

		Confirmation Method		Total
		Positive	Negative	
Applied Device	Positive	67	2	69
	Negative	3	108	111
Total		70	110	180

- Sensitivity: 95.7% (CI, 95%: 88.1–98.5)
- Specificity: 98.2% (CI, 95%: 93.6–99.5)
- Clinical Result Analysis: Clinical efficacy does not exist, because the lower limit of the confidence interval for sensitivity and specificity is lower than the lower limit of the confidence interval for clinical targets (sensitivity: 90%, specificity: 95%).

3) In case of using 70 positive samples and 110 negative samples:

		Confirmation Method		Total
		Positive	Negative	
Applied Device	Positive	68	1	69
	Negative	2	109	111
Total		70	110	180

- Sensitivity: 97.1% (CI, 95%: 90.5–99.2)
- Specificity: 99.1% (CI, 95%: 95.0–99.8)
- Clinical Result Analysis: Clinical efficacy exists, because the lower limit of the confidence interval for sensitivity and specificity is higher than the lower limit of the confidence interval for clinical targets (sensitivity: 90%, specificity: 95%).

The Number of Samples for Clinical Performance Test and Efficacy Evaluation **Criteria by Product Type (for Reference)**

- Genetic test product

Clinical sensitivity
Clinical efficacy criteria: 95%
Lower limit of confidence interval: 90%

Calculation of the number of samples	Sensitivity (estimate)	95%	96%	97%
	Positive samples	150	100	70
Clinical Result	Sensitivity (result)	95.3%	96.0%	97.1%
	Positive samples	143	96	68
	Confidence interval	90.7–97.7	90.2–98.4	90.2–99.2

Clinical specificity
Clinical efficacy criteria: 97%
Lower limit of confidence interval: 95%

Calculation of the number of samples	Specificity (estimate)	97%	98%	99%
	Negative samples	500	200	110
Clinical Result	Specificity (result)	97.2%	98%	99.1%
	Negative samples	486	196	109
	Confidence interval	95.4–98.3	95.0–99.2	95.0–99.8

- Immunological test product

Clinical sensitivity
Clinical efficacy criteria: 80%
Lower limit of confidence interval: 70%

Calculation of the number of samples	Sensitivity (estimate)	80%	85%	90%
	Positive samples	130	55	30
Clinical Result	Sensitivity (result)	80.8%	85.5%	90.0%
	Positive samples	105	47	27
	Confidence interval	73.2–86.6	73.8–92.4	74.4–96.5

Clinical specificity
Clinical efficacy criteria: 95%
Lower limit of confidence interval: 90%

Calculation of the number of samples	Specificity (estimate)	95%	96%	97%
	Negative samples	150	100	70
Clinical Result	Specificity (result)	95.3%	96.0%	97.1%
	Negative samples	143	96	68
	Confidence interval	90.7–97.7	90.2–98.4	90.2–99.2

3 Reports and Submissions on Quality Management Test of Finished Products

1. Report and submissions on Quality Management Test of finished products (one or more test of three batches; or three or more tests of one batch) according to the manufacturer's test standards should be submitted to ensure the uniformity of the products.

2. In case of using the criteria conforming to the manufacturer's test standards, data regarding test methods, and reference materials, the relevant data should be submitted.

3. Test items should be selected among items capable of establishing quality equivalence (sensitivity, specificity, and precision, etc.).

4 Submissions on Standard Materials and Sample Storage

1. The following data should be submitted if reference materials or other companies' reference materials were purchased for use.

   A. Certificates for the standard product or other reference materials used

   B. Sources and supporting data

2. In case of a company manufacturing its own reference material for use, the following data should be submitted.

   A. Test data and result analysis data for verifying the criteria at different concentration levels of the reference materials

   B. Management method and records for the reference materials (including quality control) and certificates for the reference materials

3. Based on the test results, the sample handling methods, storage conditions and methods, period of use, and other cautions should be provided. These include the pretreatment processes including centrifugal conditions, applicability of frozen and unfrozen samples, and limitations.

4. The test results regarding sample handling and storage conditions should be provided. It should be verified that the proposed time, temperature, and result are achieved. The test results should be the results evaluated using the same or higher test values for several intervals among those suggested as valid in terms of marginal humidity at both ends and other items. Moreover, the changes in the results caused by conditional changes should be proposed, along with the satisfaction criteria used for the evaluation.

5 Correlation Evaluation

1. General Information

   A. A comparative test report should be included that allows for verification of correlation between the applied product and comparator for in vitro diagnosis approved in and outside of Korea. However, the product may be compared against a product with the same intended use, if the product's measurement principles and items are unprecedented.

   B. If, in a test performed for clinical sensitivity and specificity calculation, and an existing test method (previously approved product) was used as well, the two test results may be submitted as correlation data. Any comparison data with existing test methods acquired during analytical performance test may be submitted as additional correlation data.

2. Test Material Samples

   A. The number of samples which is statistically interpretable should be proposed for the comparative test.

   B. It is recommended to use clinical samples of which history, etc. has been verified through tests using previously approved or verified methods.

3. Test Methods

   A. A comparative test should be performed with a product approved in Korea or another country (if no product has been approved in Korea) of which the measuring principles and items are the most similar to those of the evaluated product.

   B. The compared products should be tested using the user instructions of each product.

   C. It is recommended to perform other tests to analyze the cause of the discrepancy, and provide the data regarding the latter tests if the results do not match.

4. Results

   A. If there is a group of special cases, group-specific results should be provided along with the overall results.

   B. The positive match ratio, negative match ratio, and total match ratio of the comparative test should be provided at 95% confidence interval.

   C. Data should be provided regarding the analysis of the cause of the discrepancy if the results do not match.

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