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INSTRUCTIONS FOR USE

Reagent kit for coronavirus (*SARS-CoV-2*) RNA qualitative detection by direct RT-PCR-RT "Cito-CoV-2-Test-L"

TS 21.20.23-062-97638376-2022

Version 3 dated July 11, 2024

Content

List of abbreviations

The following abbreviations and designations are used in these instructions:

PCR	polymerase chain reaction
RT	reverse transcription
cDNA	complementary DNA
RNA	ribonucleic acid
LRM	lyophilized reaction mixture
NC	negative control sample
PC	positive control sample
ICS	internal control sample
SC	specificity control sample
SenC	sensitivity control sample

Introduction

Target analyte: specific regions of SARS-CoV-2 (2019-nCoV, COVID-19) strain genomic RNA, highly conserved fragments of *N* and *RdRp* genes (open reading frame 1ab, *ORF1ab*).

The scientific validity of the target analyte lies in its specificity (RNA/DNA sequence uniqueness) in relation to SARS-CoV-2 (2019-nCoV, COVID-19) strain genome.

The new SARS-CoV-2 is a single-stranded RNA-containing virus, belonging to the Coronaviridae family and the Beta-CoV B lineage. The virus belongs to pathogenicity group II, as well as some other representatives of this family (SARS-CoV virus, MERS-CoV), and is presumably a recombinant virus between bat coronavirus and coronavirus of unknown origin. The COVID-19 emergence has given healthcare professionals the task of providing rapid diagnosis and patient medical care. Currently, an intensive study of the clinical and epidemiological disease features continues, as well as the development of new prevention and treatment means. The most common clinical manifestation of the new coronavirus infection variant is bilateral pneumonia (viral diffuse alveolar damage with microangiopathy), and acute respiratory distress syndrome (ARDS) has been registered in 3-4% of patients. In some patients hypercoagulable syndrome with thrombosis and thromboembolism develops, other organs and systems (central nervous system, myocardium, kidneys, liver, gastrointestinal tract, endocrine and immune systems) are also affected, sepsis and septic shock may develop.[1]

Early diagnostics of severe acute respiratory infection (atypical pneumonia) caused by SARS-CoV-2 is extremely important for proper and timely diagnosis and treatment.

The scope of the reagent kit: clinical laboratory diagnostics of infectious diseases.

Indications for use: SARS-CoV-2 RNA detection by RT-PCR is recommended for patients with clinical symptoms of a respiratory disease suspected of infection caused by SARS-CoV-2, especially those arriving from epidemiologically unfavorable regions immediately after initial examination, as well as for contact persons.

[1] Temporary guidelines "Prevention, diagnosis and treatment of new coronavirus infection (COVID-19). Version 18 (October 26, 2023)" (approved by the Ministry of Health of the Russian Federation)

Contraindications for use: when used by specially trained personnel and considering the intended use, there are no contraindications, except in cases when the biomaterial collection cannot be carried out for medical reasons.

Population, demographic aspects of the kit use: the detection of SARS-CoV-2 RNA is carried out in patients with clinical symptoms of respiratory disease, suspected of infection with SARS-CoV-2 virus, especially those arriving from epidemiologically unfavorable regions immediately after the initial examination, as well as contact persons.

Sterility: the product is not sterile.

1. Intended use

Intended use: Cito-CoV-2-Test-L reagent kit is designed for qualitative detection of SARS-CoV-2 (2019-nCoV, COVID-19) strain genomic RNA specific region – *N* and *RdRp* genes fragments (open reading frame 1ab, *ORF1ab*) by one-step reverse transcription - multiplex allele-specific polymerase chain reaction with hybridization-fluorescence detection in clinical samples (nasopharyngeal and oropharyngeal swabs) in order to diagnose severe acute respiratory viral infection caused by SARS-CoV-2 in patients with clinical symptoms of respiratory disease, as well as contact persons. A separate RNA isolation kit is not required, since the kit includes RT-PCR Buffer that provides viral particles lysis and is resistant to inhibitors.

Functional purpose: the results obtained can be used to diagnose severe acute respiratory viral infection caused by SARS-CoV-2. The results are taken into account in the comprehensive disease diagnosis.

Potential consumers of the medical device:

The kit is intended for professional use in medical centers and clinical diagnostic laboratories. The professional level of potential users is a clinical laboratory diagnostics doctor, a medical laboratory technician, and a laboratory technologist.

2. Method principle

Method

One-step reverse transcription - real-time multiplex allele-specific polymerase chain reaction (RT-PCR) with hybridization-fluorescence detection, which does not require RNA isolation (direct RT-PCR-RT).

Test sample type

The assay material is patient's clinical material taken from the upper respiratory tract (nasopharyngeal and oropharyngeal swab).

ATTENTION! To increase the virus concentration, place nasopharyngeal and oropharyngeal swabs in the same tube.

Detection principle

SARS-CoV-2 nucleic acids detection is based on the use of a reverse transcription reaction method followed by a real-time polymerase chain reaction in a single test tube.

The lyophilized reaction mixture (LRM-Cito) for RT-PCR is ready for use and contains a warm-start revertase, a thermostable hot-start DNA polymerase, dNTP and an optimized buffer, which allows to perform RT-PCR in the presence of inhibitors large number, as well as contains a mixture of cryoprotectants, a multiplex mixture of primers and probes.

The kit contains reagents for the multiplex detection of *SARS-CoV-2 N* and *RdRp* (open reading frame 1ab, *ORF1ab*) genes fragments RNA and an internal control sample (hereinafter - ICS): SARS-CoV-2 *N* and *RdRp* genes (open reading frame 1ab, *ORF1ab*) fragments amplification products are recorded in one channel, corresponding to the fluorophore FAM, the ICS amplification products – in HEX. (Table 1).

Table 1 – Test targets

Channel corresponding to the fluorophore	
FAM	HEX
SARS-CoV-2	ICS

ICS allows to evaluate the RT-PCR correctness and reaction inhibition degree.

Method limitations

A possible reason for obtaining a false positive result is contamination during the RT-PCR stage. A false positive result can be detected using a negative control sample.

Damage to the packaging integrity during transportation.

An expired kit use or kit storage conditions violation.

Samples storage and transportation conditions violation.

RT-PCR reaction time ranges from 80 to 100 minutes, depending on the used cycler model (excluding sample preparation).

3. Reagent kit components

Configuration form

Cito-CoV-2-Test-L reagent kit is designed in one configuration form.

Number of test samples

Each Cito-CoV-2-Test-L reagent kit is designed to perform 96 RT-PCR reactions, it equates to detection of 94 test samples, negative and positive control samples, or 32 single test samples detection with negative and positive control samples in each test.

Reagent kit components

Table 2 – Cito-CoV-2-Test-L reagent kit components

No.	Reagent name	Description	Quantity, volume
1.	LRM-Cito	White dry amorphous porous mass	96 test tubes connected with bridges in a plate, packed in a rack with a lid (lyophilizate)
2.	LRM-Cito reconstitution solution	Transparent colorless liquid	1 tube, 1800 µl
3.	PC	White dry amorphous porous mass	1 bottle (lyophilizate)
4.	Reconstitution solution for PC	Transparent colorless liquid	1 tube, 200 µl
5.	NC	Transparent colorless liquid	1 tube, 480 µl

The lyophilized reaction mixture (LRM-Cito) for RT-PCR contains a warm-start revertase, a thermostable hot-start DNA polymerase, dNTP and an optimized buffer that allows to performed RT-PCR in the presence of inhibitors large number, a mixture of cryoprotectants, and also contains a multiplex mixture of primers and probes:

1. Primers and a probe specific to coronavirus (SARS-CoV-2) N and RdRp genes (open reading frame 1ab, ORF1ab) fragments. Detection is carried out in the FAM channel.
2. Primers and a probe for the internal control sample. Detection - in the HEX channel.

Lyophilized reaction mixture (LRM-Cito) for RT-PCR contains an internal control sample (ICS), which is an NA preparation.

Positive control sample (PC) is a lyophilized mixture of a plasmid

vector with synthetic DNA insertions, complementary RNAs of the internal control sample and coronavirus (SARS-CoV-2) *N* and *RdRp* (open reading frame 1ab, *ORF1ab*) genes fragments, as well as cryoprotectants.

Negative control sample (NC) is ready for use and is deionized RNase-free water.

The kit contains no products for medical use, substances of human or animal origin.

4. Reagent kit characteristics

4.1 Technical and functional characteristics

Table 3 - Cito-CoV-2-Test-L reagent kit

Indicator name	Characteristics and standards
1. Technical characteristics	
1) Appearance	
LRM-Cito	White dry amorphous porous mass
Reconstitution solution for LRM-Cito	Transparent colorless liquid
PC	White dry amorphous porous mass
Reconstitution solution for PC	Transparent colorless liquid
NC	Transparent colorless liquid
1.2. Completeness	According to clause 1.4 TS 21.20.23-062-97638376-2022
1.3. Labelling	According to clause 4 TS 21.20.23-062-97638376-2022
1.4. Packaging	According to clause 5 TS 21.20.23-062-97638376-2022
2. Functional characteristics	
Positive result with PC	Fluorescence signal growth recorded in PC tubes in the FAM channel Ct≤30 and the HEX channel Ct≤32.
Negative result with NC	In NC tubes in the FAM channel, Ct >40 or is not indicated (i.e., there is no fluorescence accumulation curve), in the HEX channel, Ct≤32
Reaction with ESS-SC	In ESS-SC tubes Ct is not indicated in the FAM channel (that is, there is no fluorescence accumulation curve), and Ct≤32 in the HEX channel.
Reaction with ESS-SenC-1	In tubes with ESS-SenC-1 in the FAM and HEX channels in all repetitions (at least 3) Ct≤38 and with the standard deviation value in ESS-SenC-1 repetitions no more than 3%

Reaction with ESS-SenC-2	In tubes with ESS-SenC-2 in the FAM and HEX channels in all repetitions (at least 3) Ct≤38 and with the standard deviation value in ESS-SenC-2 repetitions no more than 3%

Note: during the control PCR, as ESS-SenC-1, ESS-SenC-2 and ESS-SC are used:

- as a control sample to determine ESS-SenC-1 sensitivity, a mixture of plasmids with synthetic insertions of sequences complementary to the targets of SARS-CoV-2 N gene fragment with 500 copies/ml concentration and to an internal control sample complementary RNA fragment with a concentration of 100000 copies per ml in a TE buffer (10 mM Tris, 1 mM EDTA) is used;
- as a control sample to determine ESS-SenC-2 sensitivity, a mixture of plasmids with synthetic insertions of sequences complementary to the targets of SARS-CoV-2 RdRp (open reading frame 1ab, ORF1ab) gene fragment with 500 copies/ml concentration and to an internal control sample complementary RNA fragment with a concentration of 100000 copies in ml in TE buffer (10 mM Tris, 1 mM EDTA) is used;
- a solution of human genomic DNA isolated from the U-937 cell line with 1000 copies per 20 µl (167000 copies/ml) concentration is used as specificity control sample (ESS-SC).

In case of the kit malfunction, deviations in its functioning that may affect safety, or changes in the kit analytical characteristics, stop using the kit immediately and inform the manufacturer (see Section 14).

4.1 Analytical efficiency characteristics

4.1.1 Analytical specificity

It is specific to the SARS-CoV-2 N and *RdRp* genes (open reading frame 1ab, *ORF1ab*) fragments.

4.1.1.1 Specificity confirmation in silico

The analytical specificity of SARS-CoV-2 *N* and *RdRp* (open reading frame 1ab, *ORF1ab*) genes target fragments was confirmed *in silico* using the BLAST resource *(https://blast.ncbi.nlm.nih.gov/Blast.cgi)*.

4.1.1.2 In vitro specificity confirmation using certified control materials

A standard NIBSC sample was used to assess the possibility of SARS-CoV-2 RNA detection:

- 1st WHO International Standard for SARS-CoV-2 RNA, NIBSC code: 20/146.

The WHO International standard after reconstitution was tested

twice in each analysis cycle.

Using a series of PCR, the International standard was assayed with Cito-CoV-2-test-L reagent kit. According to the WHO International Standard assay results:

- 1st WHO International Standard for SARS-CoV-2 RNA, NIBSC code: 20/146, the Cito-CoV-2-Test-L reagent kit specificity in relation to the SARS-CoV-2 (2019-nCoV, COVID-19 strain RNA was confirmed.

4.1.1.3 Analytical specificity: cross-reactivity evaluation

Analytical specificity assays: cross-reactivity evaluations were carried out during RNA/DNA assays of the following microorganisms/strains:

− strains from the ATCC collection (American Type Culture Collection, USA):

Streptococcus pneumoniae (ATCC® 49619™), *Pseudomonas aeruginosa* (ATCC® 9027™), *Mycoplasma pneumoniae*, Strain PI 1428 (ATCC® 29085™), *Chlamydophila pneumoniae*, Strain CM-1 (ATCC® VR-1360™), *Legionella pneumophila* subsp. pneumophila, Strain Philadelphia 1 (ATCC® 33152™), *Staphylococcus epidermidis*, FDA Strain PCI 1200 (ATCC® 12228 ™), Human Respiratory Syncytial Virus, Strain 9320 (ATCC® VR- 955™), Human Respiratory Syncytial Virus, Strain A-2 (ATCC® VR- 1540™), Human Parainfluenza Virus 1, Strain C35 (ATCC® VR-94™), Human Parainfluenza Virus 2, Strain Greer (ATCC® VR-92™), Human Parainfluenza Virus 3, Strain C243 (ATCC® VR-93™), Human Rhinovirus 17, Strain 33342 (ATCC® VR-1663™), Human Adenovirus 1, Strain Adenoid 71 (ATCC® VR-1™), Human Coronavirus, Strain OC43 (ATCC® VR-1558™), Human Coronavirus, Strain 229E (ATCC® VR-740™),

at a concentration of not more than $1x10^{9}$ geq/ml and not less than $1x10^{6}$ geq/ml;

− strains from the State Collection of Pathogenic Microorganisms:

Haemophilus influenzae 423, *Streptococcus pyogenes* Dick – I, *Bordetella pertussis* 703 L 6,

at a concentration of not more than $1x10^{9}$ geq/ml and not less than $1x10^{6}$ geq/ml;

− strains from the collection of Research Institute of Influenza named after A.A. Smorodintsev:

A/Saint Petersburg/NIIG-252/19 (Influenza A virus (H3N2)),

A/Kaliningrad/75/19 (Influenza A virus (H1N1)pdm09), B/Washington/02/19 (Influenza B virus lineage Victoria), B/Yakutsk/NIIG-06/2019 (Influenza B virus lineage Yamagata) at a concentration of not more than $1x10^{9}$ geq/ml and not less than $1x10^{7}$ geq/ml.

The purified DNA/RNA of the above-mentioned microorganisms was tested using Cito-CoV-2-Test-L reagents kit. According to the test results, nonspecific reactions were not detected.

4.1.2 Evaluation of interfering substances effects

The effect of potentially interfering substances on Cito-CoV-2-Test-L reagent kit performance was tested for potentially interfering substances (Table 4), which may originate from the following external and internal sources:

1) substances used in a patient's treatment (for example, medicines);

2) substances found in specific sample types - in this case, clinical sample contamination with a biological agent (mucin, hemoglobin) can inhibit RT-PCR.

The studied concentrations of interfering substances are shown in Table 4.

Table 4 - Conducted assay results analysis.

Type	Substance	Active component	Concentration
Endogenous	Biological agents	Mucin	2% m/v
		Hemoglobin	0.01% v/v
Exogenous	Over-the-counter nasal drops	Phenylephrine	15% v/v
	Over-the-counter nasal gel	Sodium chloride	5% v/v
	Over-the-counter nasal spray 1	Cromolin	15% v/v
	Over-the-counter nasal spray 2	Oxymetazoline	15% v/v
	Over-the-counter nasal spray 3	Fluconazole	5% m/v
	Throat lozenges	Benzocaine, menthol	0.15% m/v
	Over-the-counter homeopathic nasal spray 1	Galphimia glauca, Sabadilla	20% v/v
	Over-the-counter homeopathic nasal spray 2	Zinc gluconate	5% m/v
	Over-the-counter homeopathic nasal spray 3	Alkalol	10% v/v
	Over-the-counter homeopathic nasal spray 4	Fluticasone propionate	5% v/v
	Sore throat spray with phenol	Phenol	15% v/v
	Antiviral medicine	Tamiflu (oseltamivir phosphate)	0.5% v/v
	Antibiotic, nasal ointment	Mupirocin	0.25% v/v
	Antibacterial, systemic	Tobramycin	0.0004% m/v

Based on the assay results, these substances do not have an interfering effect on the kit operation and do not lead to PCR inhibition at concentrations not exceeding the permissible ones.

To reduce the PCR inhibitors number, it is required to follow clinical material sampling rules.

Limitations on the test material use:

- the test material cannot be used in case of storage and transportation conditions violation (temperature, duration, multiple freezing and thawing);

- it is not allowed to use samples contaminated with extraneous biological material.

4.1.3 Analytical sensitivity: limit of detection (LOD)

In accordance with GOST R 51352-2013 and taking into account **CLSI EP-17A2** international recommendations, the limit of detection (LOD) was determined by testing WHO International Standards dilutions:

- **1st WHO International Standard for SARS-CoV-2 RNA, NIBSC code: 20/146.**

in the range of the estimated detection limit in 1 ml test biosample: 200 copies/ml, 250 copies/ml, 300 copies/ml, 350 copies/ml, 400 copies/ml, 450 copies/ml, 500 copies/ml.

Each of the 7 dilutions was tested with Cito-CoV-2-Test-L kit for 3 different days in 30 repetitions to calculate the positive results percentage. The results were determined in accordance with **CLSI EP-17A2** international recommendations by probit analysis.

To conduct a RT-PCR assay with Cito-CoV-2-Test reagent kit, cyclers recommended by the test reagent kit manufacturer were used:

- Detecting cycler DTprime (NPO DNA Technology LLC, Russia);
- CFX 96 cycler (Bio-Rad, USA);
- QuantStudio 5 cycler (Thermo Fisher Scientific, USA);
- FLUORITE cycler (Xian TianLong Science and Technology Co, China).

In accordance with **CLSI EP-17A2** recommendations, statistical processing of the obtained results was carried out using probit analysis. To calculate SARS-CoV-2 RNA limit concentration with 95% confidence probability, a probit value (Y axis) of 6.64 was used (1.64 for the 95% limit, +5 for the probit scale).

According to the assay results, SARS-CoV-2 RNA detection limit in 1 ml biological samples with 95% detection rate for the DTprime cycler was 440 copies/ml (95% CI: 386.32–493.68), CFX 96 - 479 copies/ml (95% CI: 425.32–532.68), Quant Studio 5 - 464 copies/ml (95% CI: 410.32-517.68), FLUORITE – 448 copies/ml (95% CI: 394.32-501.68).

4.1.4 Precision under repeatability conditions

To evaluate precision under repeatability conditions, a positive control sample, an internal control sample were tested in 10 repetitions.

Repeatability data is obtained inside a laboratory for specific equipment and within a specific reagent kit batch.

To evaluate precision under repeatability conditions, the arithmetic mean of the sample, variance, standard deviation, and coefficient of variation are calculated based on the values obtained in control samples repetitions.

The assay results showed that the coefficient of variation under the kit repeatability conditions does not exceed 3%.

4.1.5 Precision under reproducibility conditions

The test system reproducibility is evaluated similarly to the calculation of precision under repeatability conditions (Section 4.1.4.), however, different batches of the reagent kit are used for testing, reactions are performed in different laboratories, by different operators, on different days, on different PCR cyclers (Reproducibility Unit 1, Reproducibility Unit 2, Reproducibility Unit 3, Reproducibility Unit 4).

When performing precision assay under reproducibility conditions, complete intra-assay, inter-assay and inter-series reproducibility was observed, the coefficient of variation does not exceed 3%.

4.1.6 Metrological traceability of calibration and the assigned value of the end–user calibrators – **PC,** included in Cito-CoV-2-Test-L reagent kit, and the used calibrators **ESS-SenC-1, ESS-SenC-2, ESS-SC** was carried out in accordance with GOST R ISO 17511-2022.

The calibration hierarchy of PC, ESS-SenC-1, **ESS-SenC-2** was carried out with an internationally accepted calibrator, which determines the measured value (clause 5.5 GOST R ISO 17511-2022):

- 1st WHO International Standard for SARS-CoV-2 RNA, NIBSC code: 20/146,

The common calibration hierarchy with indicated measurement uncertainty at each stage is shown in Table 5.

Table 5

Analyte	Sample	Sample type	Measurement uncertainty	Clinical material			
				Nasopharyngeal swab		Oropharyngeal swab	
				Combined standard uncertainty	Combined expanded uncertainty	Combined standard uncertainty	Combined expanded uncertainty
SARS-CoV-2 RNA	Internationally accepted SARS-CoV-2 RNA calibrator (from the NIBSC Collection: 20/146)	Internationally accepted calibrator	$u_{m.3} = 0.32$	$u(y) = 0.47$	$U(y) = 0.94$	$u(y) = 0.46$	$U(y) = 0.92$
	ESS-SenC-1, ESS-SenC-2	Used calibrator	$u_{p.4} = 0.07$				

	PC	End user IVD medical device calibrator	$u_{p.5} = 0.06$ $u_{cal} = 0.33$				

The assigned concentration of the **PC** end-user calibrator is 1x10 ^{5} copies/ml, the used calibrators **ESS-SenC-1**, **ESS-SenC-2** is 500 copies/ml.

In accordance with clause 4.7.1 GOST R ISO 17511-2022, the combined standard measurement uncertainty of the value assigned to the end user IVD medical device calibrator u_{cal} does not exceed the permissible proportion *Umax(y)* of specification for the IVD medical device, taking into account a coverage factor *k* (*k* = 2, for an approximate 95% confidence level):

$u_{cal} = 0.94 \leq \frac{1}{2}$ *Umax(y)* = 1 – in relation to SARS-CoV-2 RNA for nasopharyngeal swabs

$u_{cal} = 0.92 \leq \frac{1}{2}$ *Umax(y)* = 1 – in relation to SARS-CoV-2 RNA for oropharyngeal swabs

And in accordance with clause 4.1 GOST R ISO 17511-2022, the estimated combined expanded measurement uncertainty U(y) does not exceed the maximum permissible measurement uncertainty Umax(y):

U(y)=0.94 ≤ Umax(y)=2 – in relation to SARS-CoV-2 RNA for nasopharyngeal swabs

U(y)=0.92 ≤ Umax(y)=2 – in relation to SARS-CoV-2 RNA for oropharyngeal swabs

The calibration hierarchy of ESS-SC was carried out **with the primary reference measurement procedure, determining the measured value** (clause 5.3 GOST R ISO 17511-2022).

The total calibration hierarchy with indicated measurement uncertainty at each stage is shown in Table 6.

Table 6

Analyte	Sample	Sample type	Measurement uncertainty	Combined standard uncertainty	Combined expanded uncertainty
human genomic DNA isolated	Secondary CS - human genomic DNA isolated from the U937	Secondary CS	$u_{m.3} = 0.78$	$u(y) = 0.78$	$U(y) = 1.56$

from the U937 cell line	cell line (manufactured by SibEnzyme LLC, Russia)				
	ESS-SC	Used calibrator	$u_{p.4} = 0.1$		

The assigned concentration of the used calibrator **ESS-SC** is 1000 copies per 20 µl (167000 copies/ml).

4.2 Clinical efficiency characteristics

For clinical trials, 93 clinical material samples taken from the upper respiratory tract (nasopharyngeal and oropharyngeal swabs) were used from patients with clinical symptoms of a respiratory disease suspected of infection caused by SARS-CoV-2, which were obtained from a residual aliquots bank formed from a pool of samples submitted for testing in Samara State Medical University of the Ministry of Health of the Russian Federation.

This number of samples was collected in accordance with GOST R 51352-2013 recommendations and taking into account the International Guideline CLSI EP09-A3 recommendations.

Each test clinical sample was tested in two series using the test reagent kit Cito-CoV-2-Test-L and the obtained data were compared with the results obtained by Samara State Medical University of the Ministry of Health of the Russian Federation **using the registered medical device** "Reagent kit for qualitative detection of coronavirus *(SARS-CoV-2)* RNA by direct RT-PCR-RT "Cito-CoV-2-Test", manufactured by TestGene LLC, Russia, registration certificate No. RZN 2022/17319 dated May 24, 2022.

The results matched, proving that the tested medical device was functioning correctly.

To conduct a PCR assay with Cito-CoV-2-Test reagent kit, cyclers recommended by the test reagent kit manufacturer were used:

- CFX96 (BioRad, USA, RC No. FSZ 2008/03399 dated June 21, 2016),
- DTprime (NPO DNA Technology LLC, Russia, RC No. FSR 2011/10229 dated March 3, 2011),
- QuantStudio 5 (Thermo Fisher Scientific, USA, RC No. RZN 2019/8446 dated June 6, 2019),
- FLUORITE (Xian TianLong Science and Technology Co, China,

RC No. RZN 2022/16415 dated April 4, 2024).

The reproducibility results for all used cyclers - 100%.

Confidence intervals (CI) of diagnostic characteristics were calculated using the Clopper and Pearson Confidence Interval (Clopper, C., & Pearson, E. (1934). The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. Biometrika,26(4), 404-413. doi:10.2307/2331986). The diagnostic characteristics of the tested kit were calculated with 95% confidence probability (Table 7).

Table 7

Test material type	Number of observations with positive samples	Number of observations with negative samples	Diagnostic sensitivity with 95 % confidence probability	Diagnostic specificity with 95 % confidence probability
nasopharyngeal and oropharyngeal swab	96	90	100% (95% CI:96.23%-100%)	100% (95% CI:95.98%-100%)

To evaluate cross-reactivity in clinical assays with the tested reagent kit Cito-CoV-2-Test-L **35 nasopharyngeal and oropharyngeal swab samples** were tested. They did not contain SARS-CoV-2 RNA, but were with the confirmed genomic NA positive presence of the following organisms and viruses: *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Legionella pneumophila*, *Staphylococcus epidermidis*, Human Respiratory Syncytial Virus, Human Parainfluenza Virus 1, Human Parainfluenza Virus 2, Human Parainfluenza Virus 3, Human Rhinovirus, Human Adenovirus 1, Human Coronavirus, Strain OC43, Human Coronavirus, Strain 229E, *Haemophilus influenzae*, *Streptococcus pyogenes*, *Bordetella pertussis*, Influenza virus A (H3N2), Influenza A virus (H1N1)pdm09, Influenza B virus Victoria lineage, Influenza B virus Yamagata lineage. According to the assay results, no cross-reactivity was observed.

5. Risks associated with the reagent kit use

The border risk zone includes the following hazards:

1. Loss of functional properties of the reagents included in the kit due to transportation, storage or usage under inappropriate conditions,

2. Contamination of reaction mixtures with test material samples with contents from a PC tube or PCR products,

3. Failure to comply with the requirements for sample preparation, testing and disposal (failure to comply with the requirements for clinical material preliminary inactivation);

4. Use of an unusable kit (use after the expiration date or in case of damaged packaging).

No risks identified in the unacceptable risk zone.

The cumulative residual risk of using a reagent kit for coronavirus (SARS-CoV-2) RNA qualitative detection by direct RT-PCR-RT "Cito-CoV-2-Test-L" is acceptable, the benefits of its use exceed the risk.

6. Safety precautions

The class, depending on the potential risk of use - 3, in accordance with the medical devices nomenclature classification approved by the Order of the Ministry of Health of the Russian Federation No. 4n dated 06.06.2012.

ATTENTION! The clinical material must be pre-inactivated by heating at 70°C for 5 minutes in the working area 1[2].

All components and reagents included in Cito-CoV-2-Test-L reagent kit belong to hazard class 4 (low-hazard substances) according to GOST 12.1.007-76 "Occupational safety standards system. Harmful substances. Classification and general safety requirements".

The reagents included in Cito-CoV-2-Test-L reagent kit have low vapor elasticity and exclude the possibility of inhalation poisoning.

The reagents included in Cito-CoV-2-Test-L reagent kit are non-toxic, as they are prepared by mixing individual non-toxic components.

Specialists who have given written consent and have been instructed by employees of Rospotrebnadzor laboratories, which have a sanitary and epidemiological certificate to work with human infectious diseases pathogens of the pathogenicity group II, are allowed to work with test

[2] Temporary guidelines "Prevention, diagnosis and treatment of new coronavirus infection (COVID-19). Version 18 (October 26, 2023)" (approved by the Ministry of Health of the Russian Federation)

systems to diagnose COVID-19 in the organization laboratory.

Clinical material collection and its packaging is carried out by a medical organization employee trained in the requirements and rules of biological safety when working and collecting material suspected of infection with the pathogenicity group II microorganisms.

Placed each material sample in a separate transport container, to ensure the requirements of these guidelines.

All samples collected for laboratory testing should be considered as potentially infectious, and medical personnel who collect or transport clinical samples must comply strictly with biosafety requirements, as when working with pathogenicity group II microorganisms.

Transport samples in accordance with the requirements of sanitary legislation in relation to microorganisms of the pathogenicity group II.

All samples obtained for laboratory testing should be considered potentially infected, and the requirements of SanPiN 3.3686-21 "Sanitary and epidemiological requirements for the prevention of infectious diseases" should be taken into account when working with them. Healthcare workers who collect or transport clinical samples to a laboratory should be trained in safe biomaterial handling practices, observe strictly precautions and use personal protective equipment (PPE).

Work with material infected or suspected of being infected with SARS-CoV-2 is carried out in accordance with the requirements of sanitary and epidemiological rules for the safety of working with the pathogenicity groups I-II microorganisms (SanPiN 3.3686-21), temporary guidelines "Prevention, diagnosis and treatment of new coronavirus infection (2019-nCoV), as well as an Information Letter from the Federal Service for Surveillance of Consumer Rights Protection and Human Wellbeing (Rospotrebnadzor) dated 21.01.2020 No. 02/706-2020-27 "On the direction of temporary recommendations for the organization of laboratory diagnostics of a new coronavirus infection (2019-nCoV)".

It is necessary to simultaneously ensure and comply with the biological safety rules and requirements for the organization and conduct of these works by personnel in order to prevent premises and equipment contamination with nucleic acids and (or) amplicons of the tested samples.

The work should be carried out in a laboratory performing molecular biological (PCR) assays of clinical material in compliance with the sanitary and epidemiological rules of SanPiN 2.1.3684-21 "Sanitary and epidemiological requirements for the maintenance of urban and rural

settlements, water bodies, drinking water and drinking water supply, atmospheric air, soils, residential premises, operation of industrial and public premises, organization and conduct of sanitary and anti-epidemic (preventive) measures". Follow methodological recommendations MU 287-113.

The following requirements should always be met when working:

- remove unused reagents in accordance with SanPiN 2.1.3684-21 "Sanitary and epidemiological requirements for the maintenance of urban and rural settlements, water bodies, drinking water and drinking water supply, atmospheric air, soils, residential premises, operation of industrial and public premises, organization and conduct of sanitary and anti-epidemic (preventive) measures";

ATTENTION! When removing waste after amplification (tubes containing PCR products), it is unacceptable to open the tubes and splash the contents, as this may lead to contamination of the laboratory area, equipment and reagents with PCR products.

- use the kit strictly for its intended purpose, according to these instructions;
- do not use the kit after the expiration date;
- avoid contact with skin, eyes and mucosa. In case of contact, rinse immediately the affected area with water and seek medical assistance.

The necessary precautions regarding the influence of magnetic fields, external electrical influences, electrostatic discharges, pressure or pressure changes, overload, sources of thermal inflammation are not provided.

The kit contains no substances of human or animal origin with a potential infectious nature, therefore, precautions against any special, unusual risks during the product use or sale are not provided.

7. Required equipment and materials

Work with Cito-CoV-2-Test-L reagent kit for RT-PCR is carried out in working area 2 (for NA isolation) (MU 1.3.2569- 09).

RT-PCR equipment:

1. Class II and III biological safety box (for example, BMB-II-Laminar-C according to TS 32.50.50-010-51495026-2020, manufactured by Lamsystems CC, RC No. FSR 2012/13259 dated July 29, 2021 or DNA/RNA UV-Cleaner Box UVC/T-M-AR for sterile work, Biosan, Latvia, RC No. RZN 2023/19369 dated January 18, 2023);

2. Vortex (for example, a high-speed mini-centrifuge Microspin 12, BIOSAN SIA, Latvia, RC No. FSZ 2011/10116 dated July 11, 2011 or CM-70M centrifuge-mixer, manufactured by SIA ELMI, Latvia, RUCNo. RZN 2016/4616 dated May 31, 2023);

3. Variable volume dispensers that allow to take liquid volumes 0.5–10 µl, 10-100 µl or 20-200 µl, 100-1000 µl (for example, Eppendorf Research Plus, Germany, RC No. FSZ 2011/11028 dated November 15, 2011 or Biohit, Finland, RC No. FSZ 2012/12201 dated May 18, 2012);

4. Refrigerator from +2°C to +8°C with a freezer below -16°C (for example, laboratory combined refrigerator XL-250 POZIS, XL-250-1 POZIS according to TS 9452-203-07503307-2012, manufactured by POZIS JSC, RC No. RZN 2016/4043 dated May 8, 2019);

5. Cycler[3] with real-time fluorescence detection in channels corresponding to FAM, HEX fluorophores:

- CFX96 (BioRad, USA, RC No. FSZ 2008/03399 dated June 21, 2016),
- DTprime (NPO DNA Technology LLC, Russia, RC No. FSR 2011/10229 dated March 3, 2011),
- QuantStudio 5 (Thermo Fisher Scientific, USA, RC No. RZN 2019/8446 dated June 6, 2019),
- FLUORITE (Xian TianLong Science and Technology Co, China, RC No. RZN 2022/16415 dated April 4, 2024).

Materials and reagents not included in the kit:

ATTENTION! When working it is required to use only disposable sterile plastic RNase-free consumables.

1. Disposable pipette tips with an aerosol barrier up to 1000 µl,

[3] Cyclers must be maintained, calibrated and used according to the manufacturer's recommendations. Use of this kit in an uncalibrated device may affect the reagent kit performance.

200 µl, 20 µl and 10 µl (Axygen, USA, RC No. FSZ 2012/12077 dated February 27, 2014).

2. Separate lab coat and disposable talcum-free gloves.
3. Container with disinfectant solution.
4. Test tube racks for 0.1 or 0.2 ml tubes or for 0.1 or 0.2 ml tubes in strips (Axygen, USA, RC No. FSZ 2012/11892 dated August 26, 2014).
5. To take a swab from the nasopharynx and oropharynx, it is recommended to use a "Medical disposable sterile probe according to TS 32.50.13-002-28731857-2020", manufactured by PharmMedPolis RT LLC, Russia (registration certificate No. RZN 2021/13989 dated December 9, 2022).

8. Test samples

Test sample type

The material for the assay is clinical material taken from the upper respiratory tract (nasopharyngeal and oropharyngeal swabs).

ATTENTION! As tubes with transport medium use ONLY sterile 1.5-2.0 ml Eppendorf type tubes containing 500 µl of sterile saline solution (or phosphate buffered saline (PBS)). The use of transport medium with different components may result in an invalid result due to reaction inhibition.

ATTENTION! Use of 5-15 ml centrifuge tubes can lead to false positive results due to contamination when transferring clinical material into the RT-PCR tube. If it is impossible to refuse of 5-15 ml centrifuge tubes, it is recommended to pre-transfer the biomaterial into an Eppendorf type 1.5-2.0 ml tube using long tips per 1000 µl, and then add the biomaterial into RT-PCR with 10-20 µl tip from an Eppendorf type 1.5-2.0 ml tube.

ATTENTION! Do not repeat samples freezing and thawing.

8.1 Biological material sampling

ATTENTION! Diagnostic material sampling, its packaging, labeling and transportation are carried out in accordance with the requirements and rules for working with materials potentially infected with pathogens of pathogenicity group II, their storage and transportation in accordance with MU 1.3.2569-09 "Organization of laboratories work using NAAT when working with material containing microorganisms of pathogenicity groups I-IV" and Methodological recommendations of Rospotrebnadzor MU 3.1.0169-20 "Laboratory diagnostics of COVID-

19".

A medical worker, performing the diagnostic material collection, its labeling and packaging, must be instructed on sanitary and epidemiological requirements and biological safety rules when working with patients, potentially infected with microorganisms of pathogenicity group II.

Material sampling for testing

Nasopharyngeal swab

Nasal swab is taken with dry sterile cotton swabs on a plastic base. Insert a swab with a light movement along the outer nasal wall to 2-3 cm depth to the lower concha. Then lower slightly the swab, insert into the lower nasal passage, make a rotational movement and remove the swab along the outer nasal wall.

Oropharyngeal swab

Swabs are taken with dry cotton swabs on a plastic base with rotational movements from the surface of the tonsils, palatine arches and the posterior wall of the oropharynx.

After taking the material, place the swab (the applied part of the probe with a cotton swab) in a sterile disposable Eppendorf type tube with 500 µl of sterile saline solution (or phosphate buffered saline (PBS)) and brake off carefully the plastic rod at a distance up to 0.5 cm from the applied part, leaving the applied part of the probe with the material inside. Close the tube tightly with a lid.

ATTENTION! To increase the virus concentration place nasopharyngeal and oropharyngeal swabs in the same tube.

Transportation, storage and disposal conditions of initial clinical material:

Transport at 2-8°C. Samples can be stored before testing up to 5 days at 2-8°C, or longer at -20°C or -70°C.

Transport hermetically sealed containers with samples to a laboratory in special containers/dressing drums. Send referrals and other documentation in hard copy in a separate plastic bag.

If it is necessary to send samples to the laboratory of another medical institution, follow the requirements for the transfer of infectious materials of pathogenicity group II (SP 1.2.036-95 "Order of accounting, storage, transfer and transportation of the microorganisms pathogenicity groups I - IV").

Seal tubes / containers with samples, together with the lid with

various sealants (paraffin, parafilm, etc.); label the container. Place the samples of each patient in an individual sealed bag with an absorbent material and pack additionally in a common sealed bag. Two or more samples from the same patient can be packed in one plastic bag. It is forbidden to pack clinical material samples from different people in the same packaging.

Place the packaging with containers in a hermetically sealed container for biological material transportation. Place the container in a foam thermal container with ice packs. Seal and label the shipping container. It is recommended to place a disposable indicator in the container to monitor temperature compliance between 2°C... 8°C.

Place the accompanying documents in an individual packaging separately from the biological material and fasten securely to the outside of the container.

9. Kit components preparation for testing

Installation, assembling, adjustment, calibration of a kit is not required for commissioning.

ATTENTION! When working with RNA, it is required to use only disposable sterile plastic RNase-free consumables. It is mandatory to use a separate tip with an aerosol barrier for each reaction component.

ATTENTION! The clinical material must be pre-inactivated by heating at 70°C for 5 minutes in the working area 1[4].

ATTENTION! The lyophilized reaction mixture (LRM-Cito) for RT-PCR should be reconstituted right before testing.

Kit components preparation for RT-PCR

Before starting work, it is necessary to keep the kit components at 18-25°C for 30 minutes.

Open the PC bottle and add 200 µl of the PC reconstitution solution. Close the bottle tightly. Mix gently, keep at 18˚C... 25˚C for 15 minutes, then mix again. After dilution, store at -18˚C... -22˚C up to 1 year or at 2˚C... 8˚C up to 1 month.

Open the LRM-Cito packaging using a stationery knife or scissors, cut off the required number of LRM-Cito tubes (including control samples). The tubes should be cut off with a film covering them. Store

[4] Temporary guidelines "Prevention, diagnosis and treatment of new coronavirus infection (COVID-19). Version 18 (October 26, 2023)" (approved by the Ministry of Health of the Russian Federation)

unused LRM-Cito tubes in a packaging during the kit shelf life.

10. Testing procedure

Testing consists of the following stages:

1. RT-PCR preparation;

2. RNA reverse transcription and cDNA PCR amplification with hybridization-fluorescence detection of amplification products in real time;

3. Result interpretation (described in detail in Section 11).

1. RT-PCR preparation

To carry out one reaction, it is necessary to use:

1. LRM-Cito reconstitution solution– 20 µl.
2. Sample (test sample) – 5 µl
3. PC and NC sample – 5 µl.

Total reaction volume – 25 µl (including the lyophilized mixture volume).

ATTENTION! It is forbidden to change the reaction volume. When the volume changes, the method sensitivity decreases dramatically!

The reaction tubes must be prepared according to Table 8 in the following order:

1. Label the tubes in accordance with the protocol (taking into account PC and NC).
2. Add LRM-Cito reconstitution solution into the appropriate tubes according to Table 8.
3. Add 5 µl of the sample into the corresponding test tubes for the test samples. Do not add the sample into the tubes for PC and NC.
4. Add 5 µl of PC into the corresponding tube.
5. Add 5 µl of NC into the corresponding tube.
6. To remove drops from the walls, centrifuge the tubes for 1-3 seconds on a vortex microcentrifuge.
7. Leave the tubes for 3-5 minutes to reconstitute the reaction mixture at room temperature.

Table 8 – Example of the test tubes layout and PCR components introduction

Component	Sample 1		Sample 2		Controls	
	repetitions		repetitions		PC	NC
LRM-Cito restoration solution, µl	20	20	20	20	20	20
Sample, µl	5	5	5	5	-	-
PC, µl	-	-	-	-	5	-
NC, µl	-	-	-	-	-	5

Note: To increase accuracy, it is recommended to test each sample twice.

B) RNA reverse transcription and RNA PCR amplification with hybridization-fluorescence detection of amplification products in real time;

1. Place the tubes in the PCR device reaction module in "real-time". It is recommended to place the tubes in the thermoblock center to press evenly the tubes with the heating lid.

2. Program the device to perform the corresponding program of amplification and fluorescent signal detection, following the instructions for the device used. RT-PCR protocol is shown in Table 9.

Table 9 – RT-PCR protocol

Stage	**Temperature, °C**	**Time, min.:sec.**	**Detection channels**	**Total number of cycles**
1	52	25:00		
2	95	02:00		
3	95	00:15		5
	64	00:20		
4	95	00:15		45
	64	00:20	FAM HEX	

3. Specify the samples number and identifiers, mark the tubes location on the thermoblock matrix in accordance with their layout.

4. Make sure that the FAM/Green and HEX/Yellow detection channels are involved in the optical measurement parameters of the amplification program.

5. Start RT-PCR with a fluorescent signal detection.

6. Upon the program completion, start analyzing the results.

11 Result registration and interpretation

Results registration is carried out automatically upon RT-PCR completion with the used device software. The results interpretation is performed according to Ct values of the ICS (HEX channel) and Ct of the coronavirus targets (FAM channel).

First, the reaction and Ct values in the control samples are evaluated. The result interpretation in the test samples begins only in case of correct PC and NC reactions.

Result interpretation in control samples

The following results should be obtained for negative and positive control samples (Table 10).

Table 10 – Assay results for negative and positive control samples

Added material	Detection channel	
	FAM (coronavirus)	HEX (ICS)
NC	Ct >40 or absent	Ct ≤32
PC	Ct ≤30	Ct ≤32

When obtaining values for a negative control sample that differ from those indicated in Table 10, the results of the entire tested series are considered unreliable. In this case, special measures should be taken to eliminate possible contamination.

When obtaining values for a positive control sample that differ from those indicated in Table 10, repeated amplification of the entire samples batch is required.

Result interpretation in test samples

Result interpretation principle is shown in Table 11 and is performed in the following order:

1. Test quality is determined by the Ct value in the HEX channel, it should not exceed 32.
2. The reaction result is evaluated via the FAM channel.

Table 11 – Result interpretation principle.

The value of the threshold cycle (Ct) by channels		Result
FAM	HEX	
Absent	Ct ≤32	SARS-CoV-2 RNA not detected
Ct ≤38	not considered[5]	SARS-CoV-2 RNA detected
Ct >38 or absent	Ct >32 or absent	Invalid result
Ct >38	Ct ≤32	Doubtful result

Results interpretation principle:

SARS-CoV-2 RNA not detected "-" if Ct in the HEX channel does not exceed 32, and Ct in the FAM channel is not indicated (there is no fluorescence accumulation curve).

SARS-CoV-2 RNA is detected "+" if Ct in the FAM channel does not exceed 38. The result of the HEX channel is not taken into account.

The test result is invalid if Ct in the FAM channel is not indicated (there is no fluorescence accumulation curve) or more than 38, and Ct in the HEX channel is not indicated (there is no fluorescence accumulation curve) or more than 32.

The reason for obtaining an invalid result may be a low RNA concentration, a high inhibitor concentration in a clinical sample; incorrect implementation of the test protocol; non-compliance with the RT-PCR temperature regime, etc.

The test result is doubtful if Ct in the FAM channel is more than 38, and Ct in the HEX channel is not more than 32.

In case of an invalid and doubtful result, a conclusion is not issued, it is necessary to retake the biomaterial from the patient and retest it.

If a doubtful result is repeated, the sample is considered positive.

The diagnostic value of the obtained test result:

[5] At high SARS-CoV-2 RNA concentrations, HEX channel output may occur in late cycles or be absent.

The obtained test result can be used by a qualified specialist (doctor), considering the clinical picture and other test types in combination, to diagnose severe acute respiratory viral infection caused by SARS-CoV-2 in patients with clinical symptoms of respiratory disease, as well as in contact persons.

The results obtained using the kit should be used in combination with other data: symptoms, the general clinical picture, the test results by other test systems and the therapy used.

12. Kit storage, transportation and use conditions

Storage

Store Cito-CoV-2-Test-L reagent kit in the manufacturer's packaging at 2°C... 25°C during the kit entire shelf life. It is forbidden to freeze the unreconstituted lyophilized mixture. A reagent kit stored in violation of the regulated regime cannot be used.

Transportation

Transport Cito-CoV-2-Test-L reagent kit at 2°C... 25°C during the kit entire shelf life. During transportation, do not shake the kit to prevent the freeze dried (lyophilized) mixture destruction.

Reagent kits transported in violation of the temperature regime cannot be used.

Cito-CoV-2-Test-L reagent kit **shelf life** is 12 months from the acceptance date of the manufacturer's QCD, if all transportation, storage and usage conditions are met. A reagent kit with expired shelf life cannot be used.

Shelf life of the opened kit components

- after opening the original sealed packaging, the shelf life of tubes with reconstitution solution for LRM-Cito and NC at 2°C... 8°C - 12 months from the acceptance date of the manufacturer's QCD, if all transportation, storage and usage conditions are met;
- after reconstitution, store PC at -18... -22˚C up to 1 year or at 2˚C... 8˚C up to 1 month;
- tubes with lyophilized mixture LRM-Cito are designed for single use. Store LRM-Cito in its original sealed packaging at 2°C... 25°C during the kit entire shelf life. LRM-Cito should be reconstituted right before the testing.

A reagent kit with expired shelf life cannot be used.

13. Disposal

Reagent kits that have become unusable, including due to expiration dates, must be disposed in accordance with the requirements of SanPiN 2.1.3684-21 "Sanitary and epidemiological requirements for the maintenance of urban and rural settlements, water bodies, drinking water and drinking water supply, atmospheric air, soils, residential premises, operation of industrial, public premises, organization and conduct of sanitary and anti-epidemic (preventive) measures".

The consumer packaging and reagent tubes used are not related to human biological fluids and, according to the classification of medical waste, belong to Class A (epidemiologically safe waste, close in composition to solid household waste). Unused reagents in accordance with part X, paragraph 170 of SanPiN 2.1.3684-21 "Sanitary and epidemiological requirements for the maintenance of urban and rural settlements, for water bodies, drinking water and drinking water supply, atmospheric air, soils, residential premises, operation of industrial and public premises, organization and conduct of sanitary and anti-epidemic (preventive) measures" are collected in a disposable labeled packaging in any color (except yellow and red).

The remaining tubes and materials after the work completion are disposed of in accordance with MU 287-113 “Guidelines for disinfection, pre-sterilization cleaning and sterilization of medical devices”.

Liquid components (reagents) are destroyed by draining into the sewer with preliminary dilution of the reagent with tap water 1:100 and removal of remaining packaging as industrial or household waste.

Cito-CoV-2-Test-L reagent kit consumer packaging is subject to mechanical destruction with removal of residues as industrial or household waste.

Personnel destroying the reagent kit must comply with the safety rules for carrying out a particular destruction method.

14. Warranty, contacts

The manufacturer guarantees Cito-CoV-2-Test-L reagent kit compliance with TS requirements if all transportation, storage and usage established requirements are met.

In case of any complaints about the kit quality, undesirable events or incidents, submit information to:

Limited Liability Company TestGene (TestGene LLC),
9, 44th Inzhenerny Proezd, office 13, Ulyanovsk, 432072
Phone number: +7 (499) 705-03-75
www.testgene.com
Technical Support Service:
Phone number: +7 927 981 58 81
E-mail: help@testgen.ru

Annex A

Labelling symbols

Symbol	Symbol name
	Content is sufficient for n-number of tests
	Refer to the instructions for use
	In vitro diagnostics medical device
	Temperature range
	Batch code or Lot number
	Use before…
	Manufacture date
	Fragile, handle with care
	This way up Do not turn over or roll on its side. It must be stored and transported upright only.

Annex B

Designation	Document name
GOST ISO 14971-2021	Medical devices. Application of risk management to medical devices.
GOST R 51088-2013	In vitro diagnostic medical devices. Reagents, kits, test-systems, control materials, culture media. Requirements to devices and to supporting documentation.
GOST R ISO 23640-2015	In vitro diagnostic medical devices. Evaluation of stability of in vitro diagnostic reagents.
GOST R 51352-2013	In vitro diagnostic medical devices. Test methods.
GOST R EN 13612-2010	Performance evaluation of in vitro diagnostic medical devices.
GOST R ISO 18113-1-2015	In vitro diagnostic medical devices. Information supplied by the manufacturer (labelling). Part 1. Terms, definitions and general requirements.
GOST R ISO 18113-2-2015	In vitro diagnostic medical devices. Information supplied by the manufacturer (labelling). Part 2. In vitro diagnostic reagents for professional use.
GOST R ISO 15223-1-2023	Medical devices. Symbols to be used with information to be supplied by the manufacturer. Part 1. General requirements.
GOST ISO 13485-2017	Medical devices. Quality management systems. Requirements for regulatory purposes.
GOST R ISO 17511-2022	In vitro diagnostic medical devices. Requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human biological samples.