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For Professional Use Only

# eSens M.genitalium ML/FQ resistance QT PCR kit

**REF ES3009B**

## Instructions for Use

## 1 INTENDED USE

**eSens M.genitalium ML/FQ resistance QT PCR kit** is an *in vitro* nucleic acid amplification test for detection of mutations in *M.genitalium* DNA associated with resistance to macrolides (in domain V of the 23S rRNA gene) and fluoroquinolones (in QRDR of the ParC gene) in DNA samples extracted from biological material (urethral, cervical, vaginal swabs and urine samples), using real-time hybridization-fluorescence detection of amplified products.

The PCR kit is recommended for use after the detection of *M.genitalium* DNA in the test samples.

***Indications and contra-indications for use of the reagent kit***

The reagent kit is used in clinical laboratory diagnostics for the analysis of biological material taken from the persons infected with *M.genitalium* in order to prescribe the correct and timely therapy of the infection caused by *M.genitalium*.

There are no contra-indications with the exception of cases when the material cannot be taken for medical reasons.

**NOTE:** The results of PCR analysis are taken into account in complex diagnostics of disease.

## 2 PRINCIPLE OF PCR DETECTION

Principle of testing is based on simultaneous amplification of *M.genitalium* DNA fragments, including the location of the mutations associated with *M.genitalium* resistance to macrolides and fluoroquinolones, and DNA of the exogenous internal control sample (Internal Control (IC)*) with real-time hybridization-fluorescence detection. IC allows to control all PCR-analysis stages of each individual sample and to identify possible reaction inhibition.

Amplification of DNA fragments with the use of specific primers and Taq-polymerase enzyme are performed with the DNA samples obtained at the extraction stage. In the real- time PCR, the amplified

product is detected with the use of fluorescent dyes. These dyes are linked to oligonucleotide probes, which bind specifically to the amplified product during thermocycling. The real-time monitoring of fluorescence intensities during the real-time PCR allows the detection of accumulating product without re-opening the reaction tubes after the PCR run.

Oligonucleotide probes complementary to wild type *M.genitalium* DNA are used for mutation detection. The maximum range of target mutations can be detected with this approach.

**eSens M.genitalium ML/FQ resistance QT PCR kit** uses "hot-start", which greatly reduces the frequency of nonspecifically primed reactions. "Hot-start" is guaranteed by using chemically modified polymerase (TaqF). The chemically modified polymerase (TaqF) is activated by heating at 95 °C for 15 min.

Detection of mutations associated with *M.genitalium* resistance to macrolides and fluoroquinolones for one sample is performed in two tubes. In the first tube, *M.genitalium* DNA (gyrB gene) and the presence (or absence) of macrolide resistance mutations (in domain V of the 23S rRNA gene) are detected; in the second tube, IC DNA and the presence (or absence) of fluoroquinolone resistance mutations (in QRDR of the ParC gene) are detected.

The results of amplification are registered in the following fluorescence channels:

* IC is added at the stage of *M.genitalium* DNA extraction when analyzing samples with PCR kits for *M.genitalium* DNA detection manufactured by FBIS CRIE.

**Table 1**

| **Channel for fluorophore** | **FAM** | **JOE** | **ROX** |
|---|---|---|---|
| **Name of PCR-mix-FL** | **DNA-target** | | |
| PCR-mix-FL *Mg*/ML | domain V of 23S rRNA gene (wild type) | - | gyrB gene |
| PCR-mix-FL *Mg*/FQ | - | QRDR of ParC gene (wild type) | IC DNA (artificially synthesized sequence) |

# 3 CONTENT

**eSens M.genitalium ML/FQ resistance QT PCR kit** (ES3009B) includes:

| Reagent | Description | Volume, ml | Quantity |
|---|---|---|---|
| **PCR-mix-FL *Mg*/ML** | clear liquid from colorless to light lilac colour | 0.6 | 1 tube |
| **PCR-mix-FL *Mg*/FQ** | clear liquid from colorless to light lilac colour | 0.6 | 1 tube |
| **PCR-buffer-B** | colorless clear liquid | 0.6 | 1 tube |
| **Polymerase (TaqF)** | colorless clear liquid | 0.06 | 1 tube |
| **TE-buffer** | colorless clear liquid | 0.2 | 1 tube |
| **C1 *Mg*/ML** | colorless clear liquid | 0.2 | 1 tube |
| **C2 *Mg*/ML** | colorless clear liquid | 0.2 | 1 tube |
| **C1 *Mg*/FQ** | colorless clear liquid | 0.2 | 1 tube |
| **C2 *Mg*/FQ** | colorless clear liquid | 0.2 | 1 tube |

**eSens M.genitalium ML/FQ resistance QT PCR kit** is intended for 55 reactions (including controls).

**eSens M.genitalium ML/FQ resistance QT excel** (version 1.0) for automated data processing and Operator manual.

# 4 ADDITIONAL REQUIREMENTS

- Sterile pipette tips with aerosol filters (up to 10, 100, 200 and 1,000 µl).
- Tube racks.
- Vortex mixer.
- PCR box.
- Real-time instruments (for example, Rotor-Gene Q (QIAGEN, Germany)).
- Disposable polypropylene tubes:
  a) screwed or tightly closed 1.5-ml tubes for reaction mixture preparation.
  b) thin-walled 0.2-ml PCR tubes with flat caps or strips of four 0.1-ml Rotor-Gene PCR tubes.
- Pipettes (adjustable).
- Refrigerator for 2–8 °C.
- Deep-freezer at the temperature from minus 24 to minus 16 °C.
- Reservoir for used tips.
- Disposable powder-free gloves and a laboratory coat.

# 5 GENERAL PRECAUTIONS

The user should always pay attention to the following:

- Use sterile pipette tips with aerosol filters and use a new tip for every procedure.
- Store all extracted positive material (specimens, controls and amplicons) away from all other reagents and add it to the reaction mix in a distantly separated facility.
- Thaw all components thoroughly at room temperature before starting an assay.

- When thawed, mix the components and centrifuge briefly.
- Use disposable protective gloves and laboratory cloths, and protect eyes while samples and reagents handling. Thoroughly wash hands afterwards.
- Do not eat, drink, smoke, apply cosmetics, or handle contact lenses in laboratory work areas.
- Do not use the PCR kit if the internal packaging was damaged or its appearance was changed.
- Do not use the PCR kit if the transportation and storage conditions according to the Instruction Manual were not observed.
- Do not use a kit after its expiration date.
- Dispose of all specimens and unused reagents in accordance with local regulations.
- Samples should be considered potentially infectious and handled in biological cabinet in compliance with appropriate biosafety practices.
- Clean and disinfect all samples or reagents spills using a disinfectant, such as 0.5 % sodium hypochlorite or another suitable disinfectant.
- Avoid inhalation of vapors, samples and reagents contact with the skin, eyes, and mucous membranes. Harmful if swallowed. If these solutions come into contact, rinse the injured area immediately with water and seek medical advice if necessary.
- While observing the conditions of transportation, operation and storage, there are no risks of explosion and ignition.
- Safety Data Sheets (SDS) are available on request.
- The PCR kit is intended for single use for PCR analysis of specified number of samples (see the section “Content”).
- The PCR kit is ready for use in accordance with the Instruction Manual. Use the PCR kit strictly for intended purpose.
- Use of this product should be limited to personnel trained in DNA amplification techniques.
- Workflow in the laboratory must be one-directional, beginning in the Extraction Area and moving to the Amplification and Detection Area. Do not return samples, equipment and reagents in the area where the previous step was performed.

⚠ Some components of this kit contain sodium azide as a preservative. Do not use metal tubing for reagent transfer.

# 6 SAMPLING AND HANDLING

**eSens M.genitalium ML/FQ resistance QT PCR kit** is intended for analysis of the DNA samples obtained earlier at the extraction stage from the test material in which *M.genitalium* DNA was detected.
*M.genitalium* DNA samples can be stored before PCR-analysis:

- at the temperature from 2 to 8 °C – for 1 week,
- at the temperature from minus 24 to minus 16 °C – for 1 year.

Only one freeze-thawing cycle is required.
Samples can be transported at the temperature from 2 to 8 °C for 1 day.

***Interfering substances and limitations of using test material samples***

In the course of the risk analysis, the following features of PCR kit content and analysis configuration which allow to exclude the influence of potentially interfering substances on the PCR method were determined:

- the DNA samples obtained earlier at the extraction stage from the test material and in which *M.genitalium* DNA has already been detected are used as test samples;

- use of specific primers and fluorescent-labeled oligonucleotides complementary to detected DNA targets;
- detection of IC DNA artificially synthesized sequence as exogenous internal control.

If the signal of IC DNA and *M.genitalium* DNA is absent, the result of this analysis is invalid. Due to the indicated features of the PCR kit content and analysis configuration, it is not necessary to study the interfering properties of individual components of a biological sample.

# 7 WORKING CONDITIONS

**eSens M.genitalium ML/FQ resistance QT PCR kit** should be used at the temperature from 20 to 28 °C and relative humidity from 15 to 75 %.

# 8 PROTOCOL

## 8.1 DNA extraction

Any commercial nucleic acid extraction kit, if IVD-CE validated for the indicated specimen types, could be used.

**Ecoli Dx, s.r.o. recommends:**

- For the manual extraction

- **DNA-sorb-AM** (K1-12-100-CE)

- For the automatic extraction

- **ePure STD DNA Extraction Kit** (E2007)

## 8.2 Preparing PCR

### 8.2.1 Preparing tubes for PCR

The type of tubes depends on the PCR instrument used for analysis. Use disposable filter tips for adding reagents, DNA and control samples into tubes.

The total reaction volume is **25 µl**, the volume of the **DNA** sample is **10 µl**.

1. Calculate the required quantity of each reagent for reaction mixture preparation. For one reaction:

   **10 µl** of **PCR-mix-FL *Mg*/ML** or **PCR-mix-FL *Mg*/FQ,**
   **5 µl** of **PCR-buffer-B,**
   **0.5 µl** of **polymerase (TaqF)**.

Prepare the reaction mixture for the total number of test and control samples plus some extra reaction. See numbers of control samples in item 7.

**NOTE:** Prepare the reaction mixture just before use.

2. Mix the content of the tubes with **PCR-mixes-FL**, **PCR-buffer-B** and **polymerase (TaqF)**. Sediment the drops by vortex.
3. In the two new tubes prepare two reaction mixtures. Mix the required quantities of **PCR- mix-FL *Mg*/ML** or **PCR-mix-FL *Mg*/FQ, PCR-buffer-B** and **polymerase (TaqF)**. Sediment the drops by vortex.

4. Take the required (twofold) number of the tubes or strips for PCR of DNA of test and control samples, place them in two rows.
5. Transfer **15 µl** per sample of one of the two prepared reaction mixtures to each row of tubes. Discard the unused reaction mixture.
6. Add **10 µl** of **DNA samples** obtained by extraction of the test samples to the two tubes with different reaction mixtures.

**NOTE:** The volume of the extracted *M.genitalium* DNA sample for the study should be at least **20 µl**.

7. Carry out the control amplification reactions:

| | | |
|---|---|---|
| For **PCR-mix-FL *Mg*/ML:** | | |
| **DNA-calibrator C1** | – | Add **10 µl** of **C1 *Mg*/ML** to the tube labeled **DNA-calibrator C1.** |
| **DNA-calibrator C2** | – | Add **10 µl** of **C2 *Mg* /ML** to the tube labeled **DNA-calibrator C2.** |
| **NCA** | – | Add **10 µl** of **TE-buffer** to the tube labeled **NCA** (Negative Control of Amplification). |
| For **PCR-mix-FL *Mg*/FQ:** | | |
| **DNA-calibrator C1** | – | Add **10 µl** of C1 ***Mg*/FQ** to the tube labeled **DNA-calibrator C1.** |
| **DNA-calibrator C2** | – | Add **10 µl** of C2 ***Mg*/FQ** to the tube labeled **DNA-calibrator C2.** |
| **NCA** | – | Add **10 µl** of **TE-buffer** to the tube labeled **NCA** (Negative Control of Amplification). |

### 8.2.2 Amplification

1. Create a temperature profile on your instrument as follows:

**Table 2**

**eSens-1 amplification and detection program of fluorescent signal for rotor-type instruments**

| | **Rotor-type Instruments** (e.g Rotor-Gene Q or equivalent) | | |
|---|---|---|---|
| **Step** | **Temperature, °C** | **Time** | **Cycles** |
| **1** | **95** | **15 min** | **1** |
| **2** | **95** | **5 s** | **5** |
| | **60** | **20 s** | |
| | **72** | **15 s** | |
| **3** | **95** | **5 s** | **40** |
| | **60** | **20 s** | |
| | **72** | **15 s** | |

**NOTE:** If several tests are carried out simultaneously, the detection is enabled in other used channels except for the specified ones.

Fluorescent signal is detected in the channels for the **FAM, JOE** and **ROX** fluorophores.

2. Adjust the fluorescence channel sensitivity according to the *Technical Sheet*.
3. Insert tubes into the reaction module of the device.
4. Run the amplification program with fluorescence detection.
5. Analyze results after the amplification program is completed.

# 9 DATA ANALYSIS

**NOTE:** Data analysis is performed automatically by **eSens M.genitalium ML/FQ resistance QT excel** (version 1.0). The operation procedure for **eSens M.genitalium ML/FQ resistance QT excel** (version 1.0) is described in the Operator manual.

The curves of fluorescent signal accumulation are analyzed in three channels:

**Table 3**

| **Name of PCR-mix-FL** | **Channel for fluorophore** | | |
|---|---|---|---|
| | **FAM** | **JOE** | **ROX** |
| **PCR-mix-FL *Mg*/ML** | **domain V of 23S rRNA gene (wild type)** | **-** | **gyrB gene** |
| **PCR-mix-FL *Mg*/FQ** | **-** | **QRDR of ParC gene (wild type)** | **IC DNA (artificially synthesized sequence)** |

Results are interpreted by the crossing (or not-crossing) the fluorescence curve with the threshold line set at the specific level, as well as using F, K, d Lg(C) coefficients calculated automatically by **eSens M.genitalium ML/FQ resistance QT excel** (version 1.0).

Principle of interpretation is the following:

**Table 4**

**Results interpretation**

| Name of PCR-mix-FL | *Ct* values and values for F, K, d Lg(C) coefficients in the channel for fluorophore | | | Result |
|---|---|---|---|---|
| | **FAM** | **JOE** | **ROX** | |
| **Variant 1** | | | | |
| ***Mg*/ML** | absent | not taken into account | absent | ***M.genitalium* DNA is NOT detected** |
| ***Mg*/FQ** | not taken into account | absent | < boundary value | |
| **Variant 2** | | | | |
| ***Mg*/ML** | determined or absent | not taken into account | Determined or absent* | **Low concentration of *M.genitalium* DNA. No mutations could be detected** |
| ***Mg*/FQ** | not taken into account | determined or absent | determined or absent | |
| **Variant 3** | | | | |
| ***Mg*/ML** | 1. absent<br>2. determined and at least one of the conditions is fulfilled: F < boundary value and/or d Lg(C) > boundary value and/or K < boundary value | not taken into account | determined** | **Mutations ARE DETECTED in the region associated with MACROLID resistance** |
| ***Mg*/FQ** | not taken into account | determined or absent | determined or absent | |
| **Variant 4** | | | | |
| ***Mg*/ML** | determined or absent | not taken into account | determined** | **Mutations ARE DETECTED in the region associated with FLUOROQUINOLONES resistance** |
| ***Mg*/FQ** | not taken into account | 1. absent<br>2. determined and at least one of the conditions is fulfilled: F < boundary value and/or d Lg(C) > boundary value and/or K < boundary value | determined or absent | |

| | | | | |
|---|---|---|---|---|
| **Variant 5** | | | | |
| ***Mg*/ML** | determined and the conditions are fulfilled: F ≥ boundary value and d Lg(C) ≤ boundary value and K ≥ boundary value | not taken into account | determined** | **Mutations ARE NOT DETECTED in the regions associated with MACROLID and FLUOROQUINOLONES resistance** |
| ***Mg*/FQ** | not taken into account | determined and the conditions are fulfilled: F ≥ boundary value and d Lg(C) ≤ boundary value and K ≥ boundary value | determined or absent | |
| **Variant 6** | | | | |
| ***Mg*/ML** | absent | not taken into account | absent | **Invalid*** ** |
| ***Mg*/FQ** | not taken into account | absent | absent or > boundary value | |

* *M.genitalium* concentration is < 1x103 GE/ml.

** *M.genitalium* concentration is ≥ 1x103 GE/ml.

*** In case of invalid result, the PCR analysis should be repeated for the corresponding test sample starting from the DNA extraction stage.

**The result of the analysis is considered reliable only if the results obtained for the controls of amplification are correct (according to Table 5 and *Technical Sheet*).**

**Table 5**

**Results for controls**

| Control | Name of PCR-mix-FL | *Ct* value in the channel for fluorophore | | |
|---|---|---|---|---|
| | | FAM | JOE | ROX |
| NCA | *Mg*/ML | absent | not taken into account | absent |
| | *Mg*/FQ | not taken into account | absent | absent |
| C1 | *Mg*/ML | < boundary value | not taken into account | < boundary value |
| | *Mg*/FQ | not taken into account | < boundary value | < boundary value |
| C2 | *Mg*/ML | determined | not taken into account | determined |
| | *Mg*/FQ | not taken into account | determined | determined |

# 10 TROUBLESHOOTING

Results of analysis are not taken into account in the following cases:

1. For the Negative Control of amplification (NCA):
   a) The *Ct* value (*Ct*-1) is determined in the channels for the FAM and/or ROX fluorophores when using PCR-mix-FL *Mg*/ML and in the channels for the JOE and/or ROX fluorophores when using PCR-mix-FL *Mg*/FQ. The contamination of laboratory with amplification products or contamination of reagents, test samples is probable at any stage of PCR analysis. Measures for detecting and elimination of contamination source must be taken. The amplification and detection should be repeated for all samples in which specific DNA was detected;
   b) The *Ct* value (*Ct*-2) is determined in the channel for the FAM fluorophore when using PCR-mix-FL *Mg*/ML and in the channel for the JOE fluorophore when using PCR- mix-FL *Mg*/FQ. The contamination of laboratory with amplification products or contamination of reagents, test samples is probable at any stage of PCR analysis. Measures for detecting and elimination of contamination source must be taken. The amplification and detection should be repeated for all samples in which specific DNA was detected.
2. The *Ct* value (*Ct*-1 and/or *Ct*-2) is absent for the DNA-calibrators C1, C2 *Mg*/ML in any of the specified detection channels (see Table 5). The amplification and detection should be repeated for all the samples.
3. The *Ct* value (*Ct*-1 and/or *Ct*-2) is absent for the DNA-calibrators C1, C2 *Mg*/FQ in any of the specified detection channels (see Table 5). The amplification and detection should be repeated for all the samples.

4. The correlation coefficient $R^2$ is less than 0.9 when plotting the calibration line. Check the correctness of set concentrations of DNA-calibrators in accordance with the *Technical Sheet* enclosed to the PCR kit. If the improper result has been obtained again the amplification and detection should be repeated for all the samples.
5. The efficiency is less than 70 % or greater than 120 % when plotting the calibration line. Check the correctness of set concentrations of DNA-calibrators in accordance with the *Technical Sheet* enclosed to the PCR kit and the correctness of selected level of the threshold line. If set concentrations of DNA-calibrators and the threshold line level are correct but the efficiency does not fit in the required range, then the amplification and detection should be repeated for all the samples.

# 11 TRANSPORTATION

**eSens M.genitalium ML/FQ resistance QT PCR kit** should be transported at 2–8 °C for no longer than 5 days. PCR kit can be transported at 2–25 °C for no longer than 3 days.

# 12 STABILITY AND STORAGE

All components of the **eSens M.genitalium ML/FQ resistance QT PCR kit** are to be stored at 2–8 °C when not in use (except for PCR-buffer-B and polymerase (TaqF)).

All components of the **eSens M.genitalium ML/FQ resistance QT PCR kit** are stable until the expiry date stated on the label. The shelf life of reagents before and after the first use is the same, unless otherwise stated.

**NOTE:** PCR-buffer-B and polymerase (TaqF) are to be stored at the temperature from minus 24 to minus 16 °C.

**NOTE:** PCR-mix-FL *Mg*/ML and PCR-mix-FL *Mg*/FQ are to be kept away from light.

# 13 SPECIFICATIONS

## 13.1 Analytical sensitivity (limit of detection)

**Table 6**

| Test material | PCR kit | Analytical sensitivity (limit of detection), GE/ml |
|---|---|---|
| DNA sample extracted from biological material | ES3009B | $1x10^3$ |

## 13.2 Analytical specificity

The analytical specificity of **eSens M.genitalium ML/FQ resistance QT PCR kit** is ensured by the selection of specific primers and probes as well as stringent reaction conditions. The primers and probes have been checked for possible homologies to all sequences published in gene banks by sequence comparison analysis.

The PCR kit detects *M.genitalium* DNA fragments. The analytical specificity was proved when investigating the DNA of the following microorganisms/strains in concentration no less than $1x10^7$ GE/ml: *Lactobacillus* spp., *Gardnerella vaginalis*, *Enterococcus faecium*, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Mycoplasma hominis*, *Ureaplasma parvum*, *Ureaplasma urealyticum*, *Trichomonas vaginalis*, *Candida albicans*, *HSV* type 1 and 2, *CMV*, *Atopobium vaginae*, *Staphylococcus aureus*, *Staphylococcus saprophyticus*, *Staphylococcus epidermidis*, *Streptococcus agalactiae*,

*Streptococcus pneumoniae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Neisseria lactamica*, *Neisseria meningitidis*, *Enterobacter cloacae*, as well as human DNA in concentration no less than $1x10^7$ GE/ml.
The nonspecific reactions were not observed while testing the DNA samples of the above mentioned microorganisms, as well as human DNA. The specificity of testing was confirmed by sequencing of the detected amplification products.
The clinical specificity of **eSens M.genitalium ML/FQ resistance QT PCR kit** was confirmed in laboratory clinical trials.
The information about known interfering substances is specified in the *Interfering substances and limitations of using test material samples*.

## 13.3 Repeatability and reproducibility

Repeatability and reproducibility were determined by testing of positive and negative model samples. Positive samples were a mixture of quality control samples (QCS) containing *M.genitalium* DNA fragments with macrolide and fluoroquinolone resistance mutations at concentrations of $1x10^5$ copies/ml. Quality control samples (QCS) containing wild type *M.genitalium* DNA fragments at concentrations of $1x10^5$ copies/ml were used as samples with no target mutations.

Repeatability conditions included testing in the same laboratory, by the same operator, using the same equipment within a short period of time. Reproducibility conditions included testing in different laboratories, by different operators, using different equipment. The results are presented in Table 9.

**Table 7**

| Sample type | Repeatability | | Reproducibility | |
|---|---|---|---|---|
| | Number of samples | Agreement of results, % | Number of samples | Agreement of results, % |
| Positive | 20 | 100 | 40 | 100 |
| Negative | 20 | 100 | 40 | 100 |

## 13.4 Diagnostic characteristics

300 DNA samples containing *M.genitalium* DNA extracted from the urogenital tract and urine were tested to determine the diagnostic sensitivity of **eSens M.genitalium ML/FQ resistance QT PCR kit**. The samples were separately tested with **eSens M.genitalium ML/FQ resistance QT PCR kit** and by Sanger sequencing as a reference assay.

**Table 8**

**The results of testing eSens M.genitalium ML/FQ resistance QT PCR kit in comparison with the reference assay**

| Samples type | Antibiotic group | The results of application of eSens M.genitalium ML/FQ resistance QT PCR kit | | Results of using the reference Assay* | |
|---|---|---|---|---|---|
| | | | | Antibiotic resistance mutations are detected (positive) | Antibiotic resistance mutations are not detected (negative) |
| DNA samples extracted from biological material | Macrolides | 300 samples were tested | **Mutations are detected (positive)** | 25 | 0 |
| | | | **Mutations are not detected (negative)** | 0 | 275 |
| | Fluoroquinolones | 300 samples were tested | **Mutations are detected (positive)** | 15 | 0 |
| | | | **Mutations are not detected (negative)** | 0 | 285 |

***** Sanger sequencing method was used as a reference assay.

**Table 9**

**Diagnostic characteristics of eSens M.genitalium ML/FQ resistance QT PCR kit**

| Samples type | Antibiotic group | Diagnostic sensitivity* (with a confidence level of 95 %) | Diagnostic specificity** (with a confidence level of 95 %) |
|---|---|---|---|
| DNA samples extracted from biological material | Macrolides | 100 (88.7-100) % | 100 (98.9-100) % |
| | Fluoroquinolones | 100 (81.9-100) % | 100 (99-100) % |

***** Relative sensitivity in comparison with applied reference assay.

****** Relative specificity in comparison with applied reference assay.

# 14 QUALITY CONTROL

The production process, including batch release, is carried out in accordance with an established quality management system certified according to ISO 13485.

## 15 KEY TO SYMBOLS USED

| | | | |
|---|---|---|---|
| REF | Catalogue number | ⚠ | Caution |
| LOT | Batch code | Σ | Contains sufficient for <n> tests |
| IVD | *In vitro* diagnostic medical device | | Use-by Date |
| VER | Version | | Consult instructions for use |
| | Temperature limit | | Keep away from sunlight |
| | Manufacturer | **NCA** | Negative control of amplification |
| | Date of manufacture | **C1, C2** | DNA-calibrators |
| EC REP | Authorized representative in the European Community | **IC** | Internal control |
| **FBIS CRIE** | Federal Budget Institute of Science "Central Research Institute for Epidemiology" | | |

**List of Changes Made in the Instruction Manual**

| VER | Location of changes | Essence of changes |
|---|---|---|
| 01_04/2022 | | |


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