CE 1023

IVD For *inVitro* Diagnostic Use

For Professional Use Only

CMV/EBV/HHV6 Quant Real-TM

Handbook

Multiplex Real Time PCR Kit for quantitative detection and differentiation of Cytomegalovirus (CMV), Epstein Barr Virus (EBV) and Human Herpes 6 Virus (HHV6)

REF V48-100FRT

Σ **100**

NAME

CMV/EBV/HHV6 Quant Real-TM

INTENDED USE

The **CMV/EBV/HHV6 Quant Real-TM** PCR kit is an in vitro nucleic acid amplification test for qualitative and quantitative detection of human cytomegalovirus (CMV) DNA, Epstein-Barr virus (EBV) DNA and Human Herpes virus type 6 (HHV6) DNA in clinical material (whole blood, white blood cells, viscera biopsy material and cerebrospinal fluid) using real-time hybridization-fluorescence detection of amplified products.

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

PRINCIPLE OF PCR DETECTION

CMV, EBV and HHV6 detection by polymerase chain reaction (PCR) with hybridization-fluorescence detection includes DNA extraction from clinical samples and PCR amplification of pathogen genome specific region with real-time hybridization-fluorescence detection. During DNA extraction from clinical material, human genomic DNA (endogenous internal control) is amplified. Endogenous internal control (IC Glob) allows controlling both PCR-analysis stages (DNA extraction and PCR amplification), material sampling, and storage adequacy. Then, the obtained samples are amplified using specific primers and polymerase (TaqF). In real-time PCR, the amplified product is detected using fluorescent dyes. These dyes are linked to oligonucleotide probes which bind specifically to the amplified product during thermocycling. The real-time monitoring of the fluorescence intensities during the real-time PCR allows the detection of accumulating product without re-opening the reaction tubes after the PCR run.

MATERIALS PROVIDED

Reagent	*Description*	*Volume, ml*	*Quantity*
PCR-mix-1-FRT *EBV* / *CMV* / *HHV-6* / Glob	colorless clear liquid	0.6	2 tubes
PCR-mix-2-FRT	colorless clear liquid	0.3	2 tubes
Polymerase (TaqF)	colorless clear liquid	0.03	2 tubes
RNA-buffer	colorless clear liquid	0.6	1 tube
DNA calibrator KSG1	colorless clear liquid	0.2	1 tube
DNA calibrator KSG2	colorless clear liquid	0.2	1 tube
Negative Control (C-) *	colorless clear liquid	1.2	2 tubes
Positive Control DNA *EBV* / *CMV* / *HHV-6* and human DNA **	colorless clear liquid	0.1	2 tubes

Contains reagents for 110 tests.

* *must be used in the extraction procedure as Negative Control of Extraction.*
** *must be used in the extraction procedure as Positive Control of Extraction (PCE).*

MATERIALS REQUIRED BUT NOT PROVIDED

- DNA extraction kit.
- Transport medium.
- Disposable powder-free gloves.
- Pipettes (adjustable).
- Sterile pipette tips with aerosol barriers.
- Disposable polypropylene 1,5/2,0 ml tubes.
- Tube racks.
- Vortex mixer.
- Desktop centrifuge with rotor for 1,5/2,0 ml tubes.
- PCR Workstation.
- Real Time Thermal cycler.
- Disposable polypropylene microtubes for PCR.
- Refrigerator for 2–8 °C.
- Deep-freezer for ≤ –16 °C.
- Waste bin for used tips.

QUALITY CONTROL

In accordance with Sacace's ISO 13485-Certified Quality Management System, each lot is tested against predetermined specifications to ensure consistent product quality.

PRODUCT USE LIMITATIONS

All reagents may exclusively be used in in vitro diagnostics. Use of this product should be limited to personnel trained in the techniques of DNA amplification (UNI EN ISO 18113-2:2012). Strict compliance with the user manual is required for optimal PCR results. Attention should be paid to expiration dates printed on the box and labels of all components. Do not use a kit after its expiration date.

WARNINGS AND PRECAUTIONS

IVD ***In Vitro* Diagnostic Medical Device**

For *In Vitro* Diagnostic Use Only

1. Wear disposable gloves, laboratory coats and eye protection when handling specimens and reagents. Thoroughly wash hands afterward.
2. Do not pipette by mouth.
3. Do not eat, drink, smoke, apply cosmetics, or handle contact lenses in laboratory work areas.
4. Do not use a kit after its expiration date.
5. Dispose of all specimens and unused reagents in accordance with local regulations.
6. Biosafety Level 2 should be used for materials that contain or are suspected of containing infectious agents.
7. Clean and disinfect all spills of specimens or reagents using a disinfectant such as 0,5% sodium hypochlorite, or other suitable disinfectant.
8. Avoid contact of specimens and reagents with the skin, eyes and mucous membranes. If these solutions come into contact, rinse immediately with water and seek medical advice immediately.
9. Material Safety Data Sheets (MSDS) are available on request.
10. Use of this product should be limited to personnel trained in the techniques of DNA amplification.
11. PCR reactions are sensitive to contamination. Measures to reduce the risk of contamination in the laboratory include physically separating the activities involved in performing PCR in compliance with good laboratory practice.
12. Workflow in the laboratory must proceed in a uni-directional manner, beginning in the Extraction Area and moving to the PCR and Detection Area. Do not return samples, equipment and reagents in the area where you performed previous step.

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

Sampling of biological materials for PCR-analysis, transportation, and storage are described in details in the handbook of the manufacturer. It is recommended that this handbook is read before beginning of the work.

STORAGE INSTRUCTIONS

The components of **CMV/EBV/HHV6 Quant Real-TM** PCR kit must be stored at 2–8 ºC excepting **Polymerase (TaqF), PCR-mix-1-FRT *EBV/CMV7HHV-6/*Glob** and **PCR-mix-2-FRT** that must be stored at -16°C or below.

The kit can be shipped at 2-8°C for no longer than 5 days but should be stored at 2-8°C and -16°C or below immediately on receipt.

STABILITY

CMV/EBV/HHV6 Quant Real-TM is stable up to the expiration date indicated on the kit label. The product will maintain performance through the date printed on the label. Exposure to light, heat or humidity may affect the shelf life of some of the kit components and should be avoided. Repeated thawing and freezing of these reagents should be avoided, as this may reduce the sensitivity.

The shelf life of reagents before and after the first use is the same, unless otherwise stated.

SAMPLE COLLECTION, STORAGE AND TRANSPORT

CMV/EBV/HHV6 Quant Real-TM can analyze DNA extracted from:

- *whole peripheral and umbilical cord blood* collected in either ACD or EDTA tubes;
- *white blood cells (buffy coat)*;
- *biopsy material* homogenized with mechanical homogenizer and dissolved in PBS sterile;
- *CSF (Liquor);*

It is recommended to process samples immediately after collection. Store samples at 2–8 °C for no longer than 24 hours, or freeze at –20/80°C. Transportation of clinical specimens must comply with country, federal, state and local regulations for the transport of etiologic agents.

DNA ISOLATION

Any commercial RNA/DNA isolation kit, if IVD-CE validated for the specimen types indicated herein at the “SAMPLE COLLECTION, STORAGE AND TRANSPORT” paragraph, could be used.

Sacace Biotechnologies recommends to use the following kits:

⇒ **DNA-Sorb-B** (Sacace, REF K-1-1/B/100);

⇒ **DNA/RNA-Prep** (Sacace, REF K-2-9);

Please carry out the DNA extraction according to the manufacturer’s instructions.

REAGENTS PREPARATION (REACTION VOLUME 25 µL):

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

1. Prepare the required number of the tubes for amplification of DNA from clinical and control samples.
2. Prepare in a new sterile tube the **Reaction Mix.** For each sample mix **10*N µl** of **PCR-mix-1-FRT *EBV/CMV7HHV-6/*Glob**, **5,0*N µl** of **PCR-mix-2-FRT** and **0,5*N µl** of **Polymerase (TaqF).** Vortex and centrifuge for 2-3 sec.
3. Add **15 µl** of **Reaction Mix** and **10 µl** of **extracted DNA** sample to appropriate tube. Mix by pipetting.
4. Carry out the control amplification reactions:

For qualitative analysis:

NCA - Add **10 µl** of **RNA-buffer** to the tube labeled NCA (Negative Control of Amplification).

C+ - Add **10 µl** of **DNA calibrator KSG2** to the tube labeled C+ (Positive Control of Amplification).

For quantitative analysis:

NCA - Add **10 µl** of **RNA-buffer** to the tube labeled NCA (Negative Control of Amplification).

Calibrators - Add **10 µl** of **DNA calibrator KSG1** into two tubes.

- Add **10 µl** of **DNA calibrator KSG2** into two tubes.

Close tubes and transfer them into the instrument in this order: samples, negative controls, positive control, calibrators.

Amplification

Create a temperature profile on your instrument as follows:

Step	Rotor type instruments[1]			Plate or modular type instruments[2]		
	Temperature, °C	*Time*	*Cycles*	*Temperature, °C*	*Time*	*Cycles*
Hold	95	15 min	1	95	15 min	1
Cycling	95	5 sec	5	95	5 sec	5
	60	20 sec		60	20 sec	
	72	15 sec		72	15 sec	
Cycling 2	95	5 sec	40	95	5 sec	40
	60	**20 sec fluorescence detection**		60	**30 sec fluorescence detection**	
	72	15 sec		72	15 sec	

1 For example, Rotor-Gene™ 3000 / Rotor-Gene™ 6000 (Qiagen) or equivalent.
2 For example iCycler iQ™,/ iQ5™(BioRad), Mx3000P™ (Stratagene) or equivalent.

Fluorescence is detected at the 2nd step of Cycling 2 stage (60 °C) in FAM/Green, JOE/Yellow/HEX/Cy3, ROX/Orange/Texas Red, and Cy5/Red fluorescence channels.

INSTRUMENT SETTINGS (Rotor-Gene 6000/Q)

Rotor-type instruments

Channel	Calibrate/Gain Optimization…	Threshold	More Settings/ Outlier Removal	Slope Correct
FAM/Green	*from 5 Fl to 10 Fl*	*0.03*	*10 %*	*On*
JOE/Yellow	*from 5 Fl to 10 Fl*	*0.03*	*10 %*	*On*
Rox/Orange	*from 5 Fl to 10 Fl*	*0.03*	*10 %*	*On*
Cy5/Red	*from 5 Fl to 10 Fl*	*0.03*	*10 %*	*On*

Plate- or modular type instruments

The threshold line should cross only sigmoid curves of signal accumulation of positive samples and should not cross the baseline; otherwise, the threshold level should be raised. Set the threshold at a level where fluorescence curves are linear and do not cross curves of the negative samples.

DATA ANALYSIS

- **β-Globin gene DNA (IC)** is detected in the **FAM/Green** channel,
- ***EBV* DNA** is detected in the **JOE/HEX/Cy3/Yellow** channel,
- ***CMV* DNA** is detected in the **ROX/Texas Red/Orange** channel,
- ***HHV6* DNA** is detected in the **Cy5/Red** channel.

RESULTS INTERPRETATION

The results are interpreted by the software of the used Instrument by the crossing (or not) of the fluorescence curve with the threshold line.

1. The sample is considered to be **positive** for ***EBV*** **DNA** if its Ct value in the results grid on the JOE/HEX/Cy3/Yellow channel is detected and does not exceed the boundary value.
2. The sample is considered to be **positive** for ***CMV*** **DNA** if its Ct value in the results grid on the ROX/Orange/Texas Red channel is defined and does not exceed the boundary value.
3. The sample is considered to be **positive** for ***HHV6*** **DNA** if its Ct value in the results grid on the Cy5/Red channel is defined and does not exceed the boundary value.
4. For qualitative analysis, the sample is considered to be **negative** if its Ct value in the results grid in the FAM/Green channel does not exceed the Ct value indicated in the **Boundary Ct values** table.
5. For quantitative analysis, the quantity of **IC Glob DNA** should be greater than 2000 copies per reaction for whole blood, white blood cells, viscera biopsy material or more than 500 copies per reaction for saliva and oropharyngeal swabs.

For cerebrospinal fluid (liquor), the Ct value can be greater than the Ct value indicated in the ***Boundary Ct values*** *table in the results grid in the FAM/Green channel or the quantity of IC Glob DNA can be less than 500 copies per reaction in case of quantitative analysis because the cerebrospinal fluid samples may contain a very small number of cells.*

For **qualitative** analysis, the result of analysis is considered to be **invalid** if the Ct value is not detected in the results grid (the fluorescence curve does not cross the threshold line) or if it is greater than the threshold value in the JOE/HEX/Yellow, ROX/Orange, or Cy5/Red channel and the Ct value in the results grid in the FAM/Green channel exceeds the Ct value indicated in the **Boundary Ct values** table.

For **quantitative** analysis, the analysis result is considered to be **invalid** if the Ct value is not detected in the results grid (the fluorescence curve does not cross the threshold line) or if it is greater than the boundary value in the JOE/Yellow/HEX, ROX/Orange, or Cy5/Red channel and the quantity of IC Glob DNA is less than 2000 copies per reaction for whole blood, white blood cells, viscera biopsy material or if it is less than 500 copies per reaction for saliva and oropharyngeal swabs. In such cases, PCR analysis of the sample should be repeated.

For qualitative analysis, results of analysis are considered reliable only if the results obtained for both Positive and Negative Controls of amplification as well as for the Negative Control of extraction are correct. For quantitative analysis, results on C+ should fall in range of concentrations indicated in the **Product Data Card.**

Results for controls

Control	Stage for control	Expected result				Interpretation
		FAM/Green	JOE/HEX/ Cy3/Yellow	ROX/Orange/ Texas Red	Cy5/Red	
NCE	DNA extraction, PCR	Neg	Neg	Neg	Neg	OK
NCA	PCR	Neg	Neg	Neg	Neg	OK
C+	DNA extraction, PCR	Pos	Pos	Pos	Pos	OK
KSG1 KSG2	PCR	Pos	Pos	Pos	Pos	OK

Boundary Ct values for Rotor-type instruments

Sample	FAM/Green	Joe/HEX/Yellow	ROX/Orange	Cy5/Red
NCE	Absent	Absent	Absent	Absent
NCA	Absent	Absent	Absent	Absent
C+	< 30	< 30	< 30	< 30
KSG2	< 30	< 30	< 30	< 30
Clinical samples	< 23	< 30	< 31	< 31

Boundary Ct values for Plate type instruments

Sample	FAM/Green	Joe/HEX/Yellow	ROX/Orange	Cy5/Red
NCE	Absent	Absent	Absent	Absent
NCA	Absent	Absent	Absent	Absent
C+	< 35	< 35	< 35	< 35
KSG2	< 35	< 35	< 35	< 35
Clinical samples	< 28	< 35	< 36	< 36

Quantitative results

In quantitative analysis, if total DNA is extracted **from human whole blood, white blood cells** and **biopsy material**, the concentration in log of DNA copies per standard cell quantity (10^5) in control and test samples is calculated by the following formula:

For *CMV*:

$$\log \{\frac{\textit{CMV}\text{ DNA copies in PCR sample}}{\text{Glob DNA copies in PCR sample}} \times 2*10^5\} = \log \{\textit{CMV}\text{ DNA copies}/10^5\text{ of cells}\}.$$

For *EBV*:

$$\log \{\frac{\textit{EBV}\text{ DNA copies in PCR sample}}{\text{Glob DNA copies in PCR sample}} \times 2*10^5\} = \log \{\textit{EBV}\text{ DNA copies}/10^5\text{ of cells}\}.$$

For *HHV6*:

$$\log \{\frac{\textit{HHV6}\text{ DNA copies in PCR sample}}{\text{Glob DNA copies in PCR sample}} \times 2*10^5\} = \log \{\textit{HHV6}\text{ DNA copies}/10^5\text{ of cells}\}.$$

If total DNA is extracted from **saliva, oropharyngeal swabs** and **cerebrospinal fluid (liquor)**, the concentration of DNA per ml of sample (Conc $_{DNA}$) is calculated by the following formula:

$$\text{Conc}_{DNA} = C_{DNA} \times 100 \text{ (copies/ml)}$$

C $_{DNA}$ is the number of *EBV* DNA copies, or the number of *CMV* DNA copies, or the number of *HHV6* DNA copies in DNA sample.

Example of Qualitative Analysis (plate-type instrument)

Ct limits (for plate type instruments)			
IC	**EBV**	**CMV**	**HHV6**
28	35	36	36

No.	Desription	Fam (IC)	Joe (EBV)	Rox (CMV)	Cy5 (HHV6)	Result	EBV	CMV	HHV6
	Name	Ct	Ct	Ct	Ct				
1	344	27,18			28	*HHV6*	**-**	**-**	**+**
2	445	26,41		34,12	32,1	*CMV, HHV6*	**-**	**+**	**+**
3	451	29,81				*Invalid*	**?**	**?**	**?**
4	456	23,3	28,48		27,7	*EBV, HHV6*	**+**	**-**	**+**
5	461	29,02		35,08		*Invalid-?, (low CMV)*	**?**	**low**	**?**
6	472	24,83	33,28			*EBV*	**+**	**-**	**-**
7	477	17,51	24,06		34,95	*EBV, HHV6*	**+**	**-**	**+**
8	489	21,32	21,85		27,2	*EBV, HHV6*	**+**	**-**	**+**
9	491	23,47	28,15			*EBV*	**+**	**-**	**-**
10	494	29,88				*Invalid*	**?**	**?**	**?**
11	497	16,29	31,06		34,18	*EBV, HHV6*	**+**	**-**	**+**
12	501	18,5		32,64		*CMV*	**-**	**+**	**-**
13	C+	27,23	30,18	28,47	27,25	*OK*			
14	C+	26,06	30,45	27,95	26,58	*OK*			
15	C+	26,37	30,8	28,17	26,73	*OK*			
16	C- (Neg. Control)					*OK*			
17	C- (DNA-buffer)					*OK*			
18	C- (DNA-buffer)					*OK*			

QUALITY CONTROL PROCEDURE

CMV/EBV/HHV6 Quant Real-TM PCR contains the Internal Control IC (human beta-globine gene), which allows to control the presence of cellular material in the sample. If the sample is not correctly prepared or it is an insufficient quantity of epithelial cells the Internal Control will not be detected.

A negative control of extraction (NCE), negative amplification control (NCA), positive amplification control (C+) are required for every run to verify that the specimen preparation, the amplification and the detection steps are performed correctly.

If the controls are out of their expected range (see table Results for Controls), all of the specimens and controls from that run must be processed beginning from the sample preparation step.

PERFORMANCE CHARACTERISTICS

Sensitivity

The analytical sensitivity of **CMV/EBV/HHV6 Quant Real-TM** PCR kit is specified in the table below.

Type of clinical material	Nucleic acid extraction kit	Sensitivity
Cerebrospinal fluid (liquor)	**DNA/RNA-Prep**	400 copies/ml
Whole blood, white blood cells, viscera biopsy material	**DNA/RNA-Prep**	5 DNA copies per 10^5 cells

Specificity

CMV/EBV/HHV6 Quant Real-TM PCR kit is intended for *Epstein-Barr virus* (*EBV*) DNA, *Human Herpes Virus* type 6 (*HHV6*) DNA and *human cytomegalovirus* (*CMV*) DNA detection. Specific activity of **CMV/EBV/HHV6 Quant Real-TM** PCR kit was confirmed by analysis of reference *CMV* strain AD 169, QCMD panel for *Epstein-Barr virus,* as well as by analysis of clinical material with subsequent confirmation of results by sequencing the amplified fragments. The activity of the PCR kit components with respect to DNA of other viruses (herpes simplex virus types 1 and 2, human herpes virus type 8, Varicella Zoster Virus, Parvovirus B19, and others), bacterial pathogens (*Staphylococcus aureus, Streptococcus pyogenes, Streptococcus agalactiae,* and others) and human DNA was absent. The clinical specificity of **CMV/EBV/HHV6 Quant Real-TM** PCR kit was confirmed in laboratory clinical trials.

Target region

Channel for fluorophore	FAM	JOE	ROX	Cy5
DNA-target	IC Glob DNA	EBV DNA	CMV DNA	HHV6 DNA
Target gene	β-globin gene	LMP-gene	exon 4 of MIE (major immediate early) gene	DNA polymerase catalytic subunit

TROUBLESHOOTING

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

1. The presence of any Ct value on JOE/Yellow/HEX, FAM/Green, ROX/Orange and Cy5/Red channels in the results grid for the Negative Control of Amplification (NCA) and for the Neg. Control of Extraction (C-) indicates contamination of reagents or samples. In this case, PCR analysis should be repeated for all samples in which pathogen DNA was detected starting from the DNA extraction stage.
2. For qualitative analysis, if the Ct value in the results grid for the Positive Control of PCR on the JOE/Yellow/HEX, FAM/Green, ROX/Orange, or Cy5/Red channels is absent, it is necessary to repeat amplification for all samples where pathogen DNA was not detected.
3. If the Ct value for the sample is not detected on JOE/Yellow/HEX/Cy3, ROX/Orange/Texas Red, Cy5/Red channel or it exceeds the boundary Ct value specified in the Boundary Ct values table and the Ct value for the sample is greater than the maximum Ct value for IC in the FAM/Green channel, analysis should be repeated starting from the DNA extraction stage. This error may be caused by incorrect treatment of clinical material, which resulted in the loss of DNA, or by the presence of PCR inhibitors.
4. If the Ct value for the sample is detected in JOE/Yellow/HEX/Cy3, ROX/Orange/Texas Red or Cy5/Red channel and it is greater than the boundary Ct value specified in the Boundary Ct values table**,** the result is considered to be equivocal. It is necessary to repeat analysis of such sample in duplicate. If a reproducible positive Ct value is obtained, the result is considered to be positive; otherwise, the result is considered to be equivocal.

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KEY TO SYMBOLS USED

REF	List Number		Caution!
LOT	Lot Number		Contains sufficient for <n> tests
IVD	For *in Vitro* Diagnostic Use	VER	Version
	Store at	**NCA**	Negative Control of Amplification
	Manufacturer	**C–**	Negative control of Extraction
	Consult instructions for use	**C+**	Positive Control of Amplification
	Expiration Date	**IC**	Internal Control

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