P0273
ViraQ Multi-Marker Check 75

CE
0483

IVD

REF P0273

The kit insert contains a detailed protocol and should be read carefully before testing the run control to ensure optimal performance

Table of contents

Intended Use....3
Key to Symbols Used....3
Principle of method....3
Traceability to viral nucleic acid copies and International Units....5
Stability of standards and run control....5
Kit Contents (materials provided)....7
Materials required but not supplied....7
Storage instructions....7
Warning and precautions....8
Reagent preparation....8
Test procedure and calculations....8
Interpretation of test results on run control in cobas MPX assay....11
Limitations....16
References....17

Intended Use

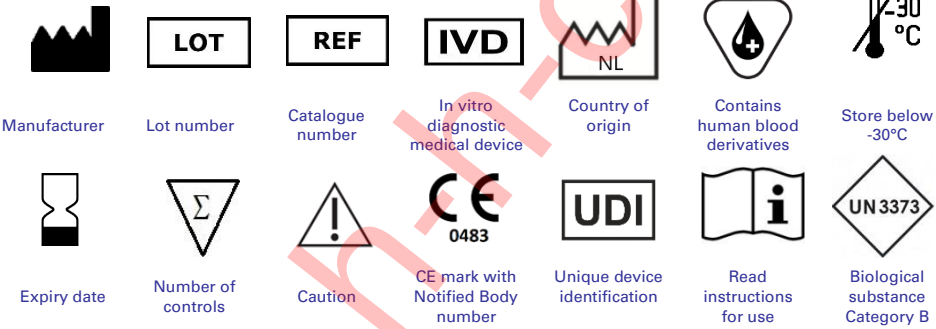
P0273 ViraQ Multi-Marker Check 75 is intended to be used as external run control for detection of hepatitis B virus (HBV)-DNA, hepatitis C virus (HCV)-RNA and human immunodeficiency virus type 1 (HIV-1) RNA by the cobas MPX multiplex amplification assay on the cobas 6800/8800 platforms (table1). The run control helps laboratories to ensure sufficient analytical sensitivity and consistent performance of this nucleic acid amplification technology (NAT) assay.

Table 1. Assay and platform covered by P0273 Multi-Marker Check 75 control

Assay (manufacturer)	Platform	Test environment
cobas MPX (Roche)	cobas 6800/8800	Blood screening

P0273 ViraQ Multi-Marker Check 75 should not be used to replace the internal controls or calibrators in the test kits. The test result on the run control should not be used to reject the run or delay the release of test results on donor or patient samples.

Key to Symbols Used



Principle of method

P0273 ViraQ Multi-Marker Check 75 control has been formulated to mimic natural plasma specimens with a low concentration of HBV-DNA, HCV-RNA and HIV-1 RNA. After thawing the run control tubes are ready for use and can be placed at random positions in sample racks on the NAT platforms. The run control contains 75 copies/mL of HBV-DNA, HCV-RNA and HIV-1 RNA which is equivalent to 14, 27 and 129 International Units (IU)/mL of the viruses respectively. The multi-marker run control has been designed to ensure sufficient analytical sensitivity and consistent performance of multi-dye real time polymerase chain reaction (PCR) tests in blood screening laboratories. The viral concentrations in the run control has been set at 4 to 5 times the 95% lower limit of detection (LOD) of the cobas MPX assay for HBV and HCV, but is somewhat higher for HIV (table 2, 3 and 4)[1]. The positioning of P0273 ViraQ Multi-Marker Check 75 control ensures reactivity rates above 99.9% in the cobas MPX assay and enables laboratories to be alerted in case of a significant reduction of analytical sensitivity of NAT test system. The run control is a mixture of dilutions of inactivated viral standards. The S0043 HBV-DNA genotype A and S0041 HIV-1 subtype B standards have been pasteurized at 65°C at low protein concentration before spiking in plasma[2-5]. The S0109 HCV-RNA genotype 3a standard has been prepared by inactivation of window period plasma with betapropiolactone)[2,6-8]. The plasma matrix in which the run control is diluted is manufactured from plasma units that tested negative for all relevant markers of blood borne viruses. The inactivated

BioQControl standards have been calibrated in copies/mL and IU/mL against the Viral Quality Control (VQC)-Sanquin and World Health Organization (WHO) International Standards (figure 1). The low concentration of HBV genotype A, HCV genotype 3 and HIV-1 subtype B are meant to be representative for other genotypes that are prevalent in different geographical regions of the world (and that should be detected with similar analytical sensitivity by the commercial NAT assays)[9-18]. The run control generates Ct values in the cobas MPX assay and other real time PCR assays. A non-reactive result on the run control or a significant shift to higher Ct values is indicative of reduced analytical sensitivity of the NAT system and should trigger investigation of the technical performance of the assay. Statistical analysis of Ct values generated over a certain period of time allows for comparison of analytical performance of NAT reagent lots and laboratory instruments.

Table 2. NAT detection limits on native and heat-inactivated HBV genotype A standard dilution panels

standard	panel	NAT method	n	50% LOD (CI) cp/mL	95% LOD (CI) cp/mL
S0043 BioQ HBV-DNA genot. A inact.	P0031	cobas MPX	12	2.4 (1.4-4.2)	18.6 (9.1-75.9)
	P0251	TaqScreen 2.0	12	2.8 (1.5-4.3)	23.8 (12.4-99.3)
S0011 VQC-Sanquin HBV-DNA genot. A	P0007	cobas MPX	24	1.9 (1.3-2.7)	13.0 (7.7-29.6)
S0010 Eurohep HBV-DNA genot. A	P0001	TaqScreen 1.0	12	2.3 (1.3-3.8)	14.1 (7.2-56.6)
	P0272	cobas MPX	48	1.7 (1.0-2.4)	10.3 (6.2-28.8)
WHO HBV-DNA 97/750#	P0023	cobas MPX	12	1.8 (0.93-2.8)	8.0 (4.4-37.4)

1 IU = 5.33 copies

Table 3. NAT detection limits on native and inactivated HCV standard dilution panels

standard	panel	NAT method	n	50% LOD (CI) cp/mL	95% LOD (CI) cp/mL
S0109 BioQ HCV-RNA genot. 3a inact.	P0020	TaqScreen 2.0	12	3.1 (2.0-4.7)	21.1 (11.6-68.3)
	P0020	cobas MPX	10	2.5 (1.7-3.6)	17.2 (12.3-24.6)
S0009 VQC-Sanquin HCV-RNA genot. 1	P0019	cobas MPX	60	2.9 (2.3-3.6)	20.4 (14.3-33.3)
	P0272	cobas MPX	48	2.9 (2.4-3.5)	15.1 (11.2-22.7)

1 IU = 2.73 copies

Table 4. NAT detection limits on native and inactivated HIV-1 subtype B standard dilution panels

standard	panel	NAT method	n	50% LOD (CI) cp/mL	95% LOD (CI) cp/mL
S0041 BioQ HIV-1 RNA subt. B inact.	P0026	cobas MPX	12	1.0 (0.6-1.60)	5.8 (3.0-23.2)
	P0251	TaqScreen 2.0	12	2.0 (1.3-2.8)	7.6 (4.9-21.4)
S0012 VQC-Sanquin HIV-1 RNA subt. B	P0272	cobas MPX	48	1.3 (1.0-1.6)	7.3 (5.3-11.8)
WHO HIV-1 RNA 97/650#	P0022	cobas MPX	12	2.7 (1.7-3.9)	5.8 (3.9-24.9)

1 IU = 0.58 copies

Traceability to viral nucleic acid copies and International Units

Figure 1, 2 and 3 shows the traceability chain for HBV-DNA, HCV-RNA and HIV-1 RNA between the ViraQ multi-marker run control, the BioQControl standards, the VQC-Sanquin standards and the 1st and 2nd WHO International Standards. The inactivated S0043 HBV-DNA, S0109 HCV-RNA and S0041 HIV-1 RNA standards (used for preparation of the P0273 ViraQ Multi-Marker Check 75 control) have been calibrated in copies/mL by replicate testing in the Siemens Versant bDNA 3.0 assay[19] against the historically established VQC-Sanquin S0011 HBV-DNA, S0009 HCV-RNA and S0012 HIV-1 standards[20]. However, when the inactivated S0109 HCV-RNA genotype 3 standard was later recalibrated against the native S0009 HCV genotype 1 standard using five different quantitative NAT methods it was decided to adjust the originally measured HCV concentration to a 1.67-fold lower value[21].

The primary native VQC-Sanquin standards have been calibrated at:

- 5.33 (5.11-5.55) and 5.20 (4.61-5.80) copies per IU against the first and second WHO HBV-DNA (97/746 and 97/750) standards respectively in two experiments[21,22].
- 2.73 (1.4-4.8) copies per IU against the first and second WHO HCV-RNA (96/790 and 96/798) standards according to data from different studies[21,23,24].
- 0.39 (0.34-0.44) copies and 0.58 (0.51-0.66) and per IU against the first and second WHO HIV-1 97/656 and second HIV-1 RNA 97/650 standards respectively in multiple replicate bDNA 3.0 assays[21,25,26].

It must be emphasized that these conversion factor from copies to IU values have not been determined or confirmed for the 3rd WHO HBV 10/264, 3rd WHO HCV 06/100, 4th WHO HCV 06/102, 5th WHO HCV 14/150, 3rd WHO HIV-1 10/152 and 4th WHO HIV-1 16/194 replacement standards[14].

The copies assigned to the VQC-Sanquin HBV standard were found to be equivalent to those in the Eurohep standard[27] which was used for preparation of the WHO standards. The accurate calibration of the native VQC-Sanquin and inactivated BioQControl standards against the WHO and Eurohep standards in IU/mL and in copies/mL has been confirmed in analytical sensitivity studies of the Grifols Procleix TMA and Roche cobas MPX assays[21]. The BioQControl manufacturing and quality control procedures guarantee consistent virus concentrations in consecutive ViraQ Check Control batches[28]. The inactivated BioQControl standards are available in sufficient supply to ensure batch to batch consistency of ViraQ run controls for a prolonged period of time.

Stability of standards and run control

The long term stability of the liquid frozen S0043 HBV-DNA, S0109 HCV-RNA and S0041 HIV-1 RNA standards stored at ≤65˚C has been firmly established[29]; hence the stock solutions from which the run control is prepared have shown to be stable in the BioQControl storage facilities. Real time stability experiments using quantitative NAT assays showed less than 10% degradation of HCV-RNA and HIV-1 RNA (and no degradation of HBV-DNA) in ViraQ Check Controls (and in standard dilutions of higher concentrations) when stored at -30˚C[29]. Hence, it can be guaranteed that the run control is still functional and should generate a reactivity rate greater than 99.5% when stored at -30˚C and used before the expiration date (two years after preparation of the run control batch)[28,29].

Figure 1. Traceability chain between P0273 Multi-Marker Check 75 control, BioQControl (BQC), VQC-Sanquin, Eurohep and WHO International Standards for HBV-DNA

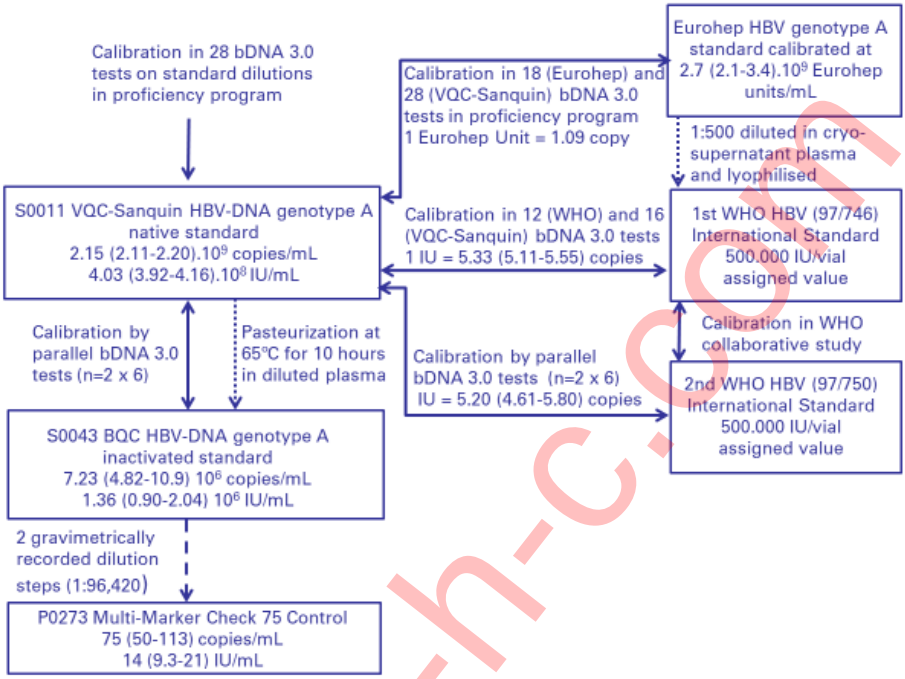


Figure 2. Traceability chain between P0273 Multi-Marker Check 75 control, BioQControl (BQC), VQC-Sanquin and WHO International Standards for HCV-RNA

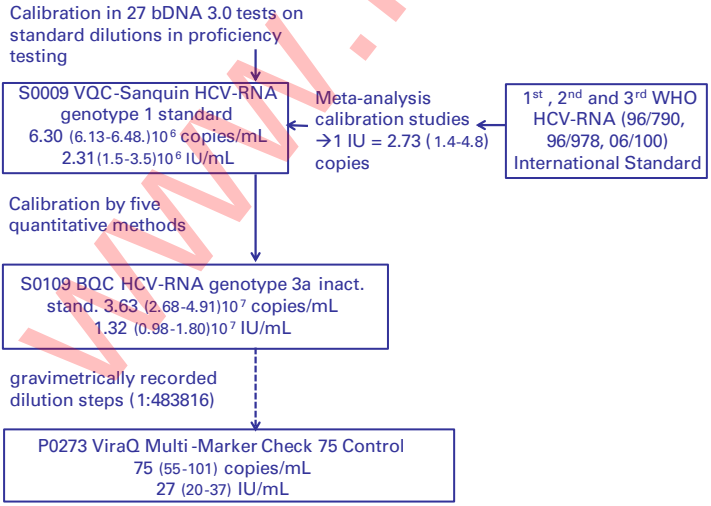
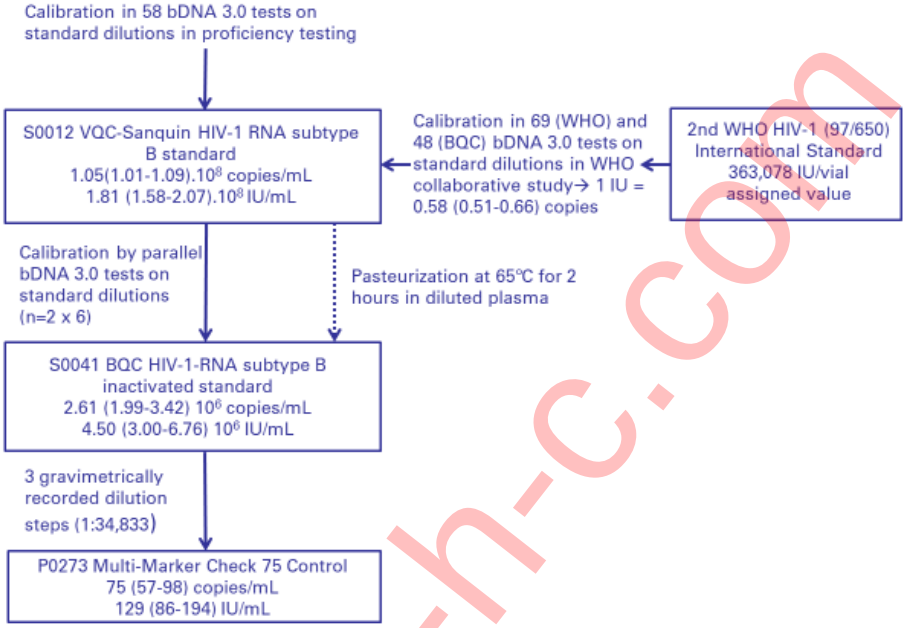


Figure 3. Traceability chain between P0273 Multi-Marker Check 75 control, BioQControl (BQC), VQC-Sanquin and WHO International Standards for HIV-1 RNA



Kit Contents (materials provided)

The run control contains human plasma without preservatives and is provided in two formats as detailed in Table 2.

Table 2. Description of kit formats and contents.

Cat. Code	UDI code	Quantity run control	Size vials	packing
P0273/01	8718719830109	60 x 1.5 mL	10 mL	60 vials in rack/box
P0273/02	8718719831831	10 x 1.5 mL	10 mL	Plastic zip bag

To facilitate automation the run control is presented in a polypropylene tube with screw cap comparable in size to Vacutainer tubes used for donor sample collection. In addition, the label includes a barcode identifying the product, sequential batch number and multi-marker: MM. The barcode of each run control tube is unique and can be read by the Roche cobas 6800/8800 instrument.

Materials required but not supplied

The test kits and liquid handling devices provided by the NAT manufacturer as specified in Table 1.

Storage instructions

The run controls should be stored at or below -30°C for a maximum of two years[29]. Once thawed the run control samples should be used within 8 hours. During this period, when

not in use, store sample at 2-8°C[29]. Do not refreeze the controls after thawing to prevent formation of cryoprecipitates. Any control sample that appears cloudy or contains precipitates after thawing and mixing should be discarded.

Warning and precautions

Although P0273 ViraQ Multi-Marker Check 75 control contains inactivated viral particles[2-8] the plasma may still be potentially bio-hazardous. The matrix is prepared from human blood plasma that tested negative for blood borne viruses (HBV-DNA, HCV-RNA, HIV-RNA, HBsAg, anti-HBc, anti-HBs, anti-HIV, anti-HCV and anti-Treponema *pallidum*). No test method can offer complete assurance that products derived from human blood cannot transmit (unknown) infectious agents. The run control should only be used by trained laboratory workers who are aware of the potential risk of infectious agents in human plasma samples and take the necessary precautions. Observe the universal precautions for prevention of transmission of infectious agents when handling these materials[30,31].

- Do not pipette by mouth.
- Use personal protective equipment, including lab coats, gloves and safety glasses.
- Do not eat, drink or smoke in areas where the run controls is handled.
- Disinfect spills using a 0.5% hypochlorite solution (1:10 v/v household bleach) or equivalent disinfectant.
- Dispose unused or spilled materials according to the normal practices for biological waste disposal in your institution.
- If precipitates are visible, mix the run controls for 2 minutes thoroughly.
- Once thawed, do not re-freeze and thaw the run control samples to avoid formation of cryoprecipitates that could alter reactivity or cause pipetting errors in the automated sampling systems.
- Store run controls in an upright position

Reagent preparation

- Thaw the run control quickly in a water bath at 37°C.
- Mix gently during thawing until contents are just thawed.
- Immediately after thawing remove the run control tube from the water bath.
- Vortex the run control.
- Give a short spin in a centrifuge to remove liquid before releasing screw cap from vial.
- Minimise the time period from thawing until usage of the control samples.
- Use within 8 hours after thawing
- After thawing when not in use: store at 2-8°C

Test procedure and calculations

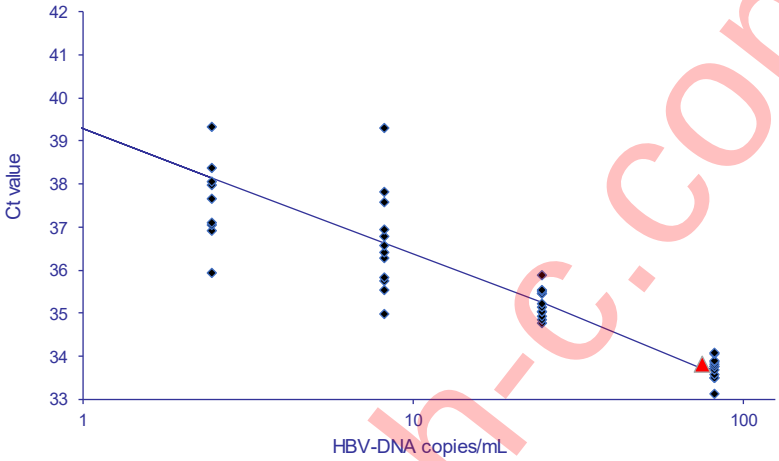
The run control should be tested in a manner identical to that of clinical specimens and the result be calculated according to the instructions for use of the NAT procedure.

The cobas MPX assay gives qualitative results (reactive, nonreactive or invalid) and if reactive a Ct value is generated. P00273 ViraQ Multi-Marker 75 Control should react positive for all three markers in more than 99.9% of cobas MPX test runs.

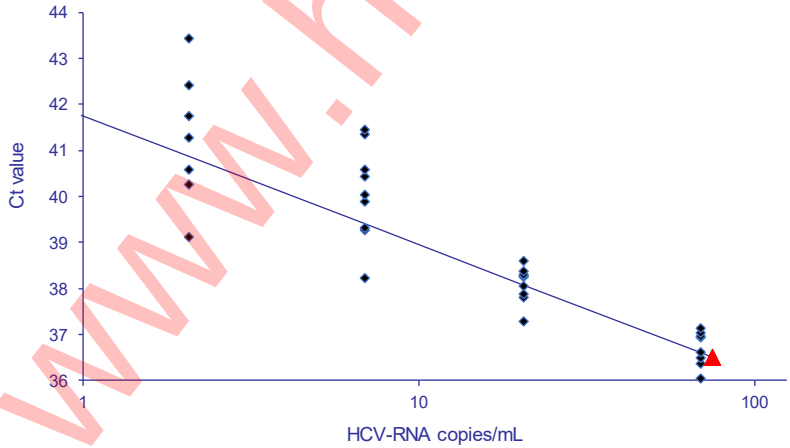
The positioning of P0273 ViraQ Multi-Marker Check 75 control is near the Poisson detection endpoint range of the cobas MPX assay but at enough distance to guarantee sufficient reproducibility of Ct values. This has been demonstrated by testing dilution panels of the inactivated viral standards (figure 4). At the concentration of 75 copies/mL a normal distribution of Ct values can be assumed for statistical analysis. Hence for monitoring the performance of the cobas MPX assay one can use untransformed Ct values in a Levey-Jennings QC chart for trend analysis.

Figure 4. Distributions of Ct values on inactivated BQC standard dilutions in cobas MPX assay. The red triangle is the run control level at 75 copies/mL

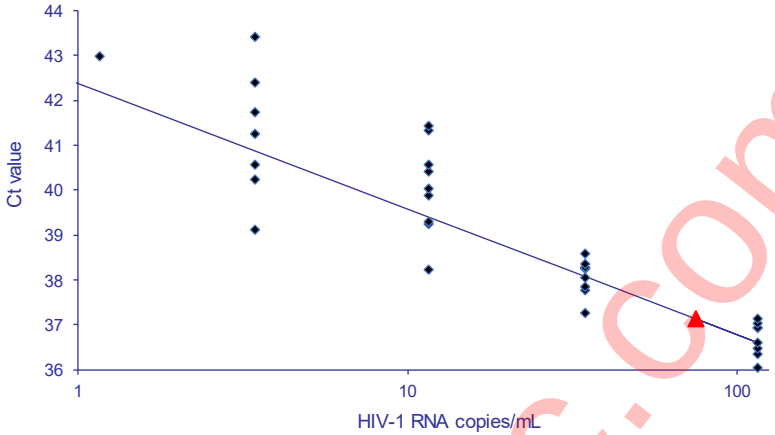
S0043 HBV-DNA genotype A standard (dilution panel P0031)



S0109 HCV-RNA genotype 3 standard (dilution panel P0020)



S0041 HIV-1 subtype B standard (dilution panel P0026)



Levey-Jennings QC chart.

Test the run control at least 10-20 times during the reference period, Since Ct values are used no log transformation is required and confidence intervals can be calculated from the arithmetic mean and standard deviation (SD). The Levey-Jennings chart (figure 5) is designed to identify individual aberrant values outside the 95% and 99% confidence intervals (CI). With collecting additional data the chart characteristics may be updated.

Use table 5 to obtain Student-t-values belonging to the 95% and 99% CI for different number of observations (n). Calculate the 95% and 99% confidence limits as follows:

- 99% Lower limit: Average – 99% Student-t-Value x SD
- 95% Lower limit: Average – 95% Student-t-Value x SD
- 99% Upper limit: Average + 99% Student-t-Value x SD
- 95% Upper limit: Average + 99% Student-t-Value x SD

Table 5. Relation of Student t value and numbers of runs (n) to calculate CI's.

Run (n)	t-value at 95% CI	t-value at 99% CI
10	2.306	3.355
20	2.101	2.878
30	2.048	2.763
infinite	1.960	2.576

Use the Westgard rules[32] to identify deviations in the Levey Jennings trend analysis.

Interpretation of test results on run control in cobas MPX assay

The cobas MPX test results on P0273 ViraQ Multi-Marker Check 75 control are expected to be reactive in 99.9-100% of cases according to probit analysis on the inactivated S0043 HBV, S0109 HCV and S0041 HIV-1 standard dilutions in the P0031, P0020 and P0026 reference panels. Repeatedly non-reactive results are indicative of a significantly reduced analytical sensitivity of the NAT system. A single event of a non-reactive result is however possible without deterioration of the test system and can be explained by Poisson distribution.

The expected Ct values on P0273 ViraQ Multi-Marker Check 75 Control are shown in figure 5 and table 7. The Levey-Jennings charts in figure 5 give the data reported by three laboratories over a period of 4 years in which nonreactive results were not found.

Since the concentration of the inactivated HCV-RNA standard was recently adjusted 1.67-fold based on calibration experiments in different quantitative NAT methods (rather than in one method) the distance of the HCV concentration in the P0273 ViraQ Multi-Marker Check 75 control to the 95% LOD in the Roche cobas MPX assay has shifted from 2-3 times to 4-5 times the 95% LOD, similar as for HBV-DNA (table 2 and 3). The HCV-RNA Ct values in figure 5 were projected from the actual data by adjusting each datapoint to a lower Ct value (by subtracting a delta Ct value of ^{2}Log 1.67 = 0.74). However this adjustment of Ct values ignores the impact of Poisson distribution on the Ct value distribution which was observed with previous batches of the run control. These actually contained 45 copies/mL instead of 75 copies/mL according to the recalibration of the S0109 HCV-RNA standard[21].

Figure 5. Levey-Jennings QC charts of cobas MPX assay Ct values for HBV-DNA, HCV-RNA and HIV-1 RNA on P0273 ViraQ Multi-Marker Check 75 Control, whereby HCV-RNA Ct values were adjusted for 1.67 fold recalibration of the HCV standard in current batches of the run control (by subtracting a delta Ct value of ^{2}Log 1.67 = 0.74 for each datapoint).

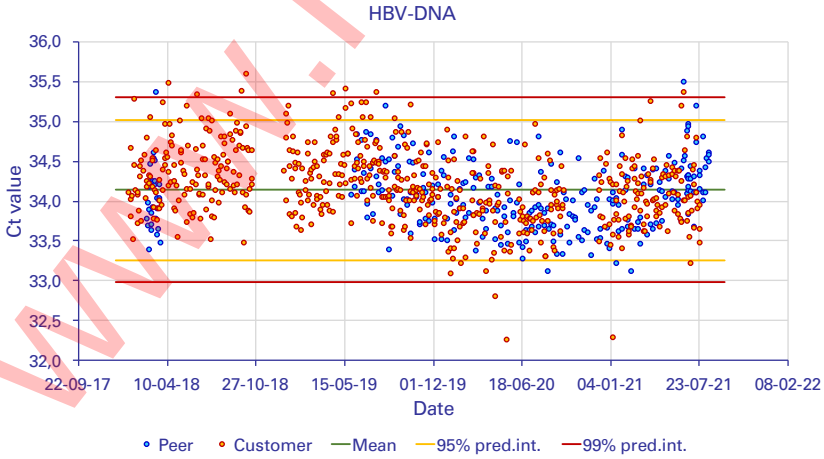
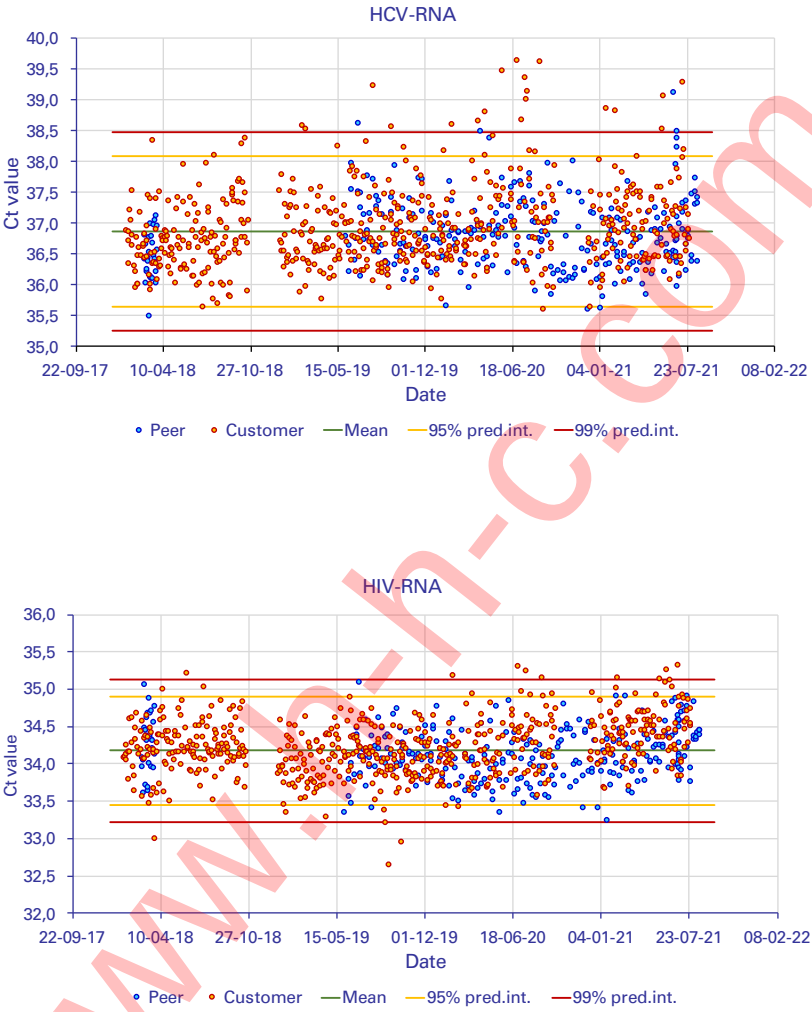
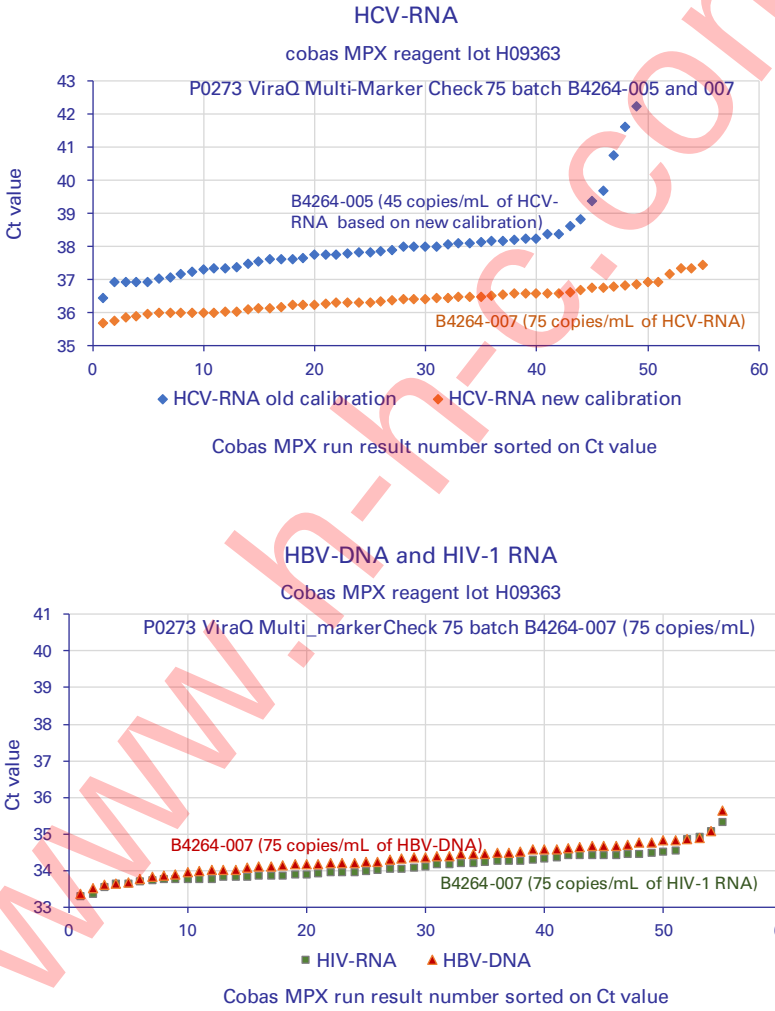


Figure 5 continued



The upper graph in figure 6 compares the HCV-RNA Ct value distribution on two P0273 ViraQ Multi-Marker Check 75 run control bathes before and after recalibration of the HCV standard in one cobas MPX reagent lot. The older run control batch B6264-005 containing 45 copies/mL of HCV-RNA generated a number of outlier Ct values (between 39.0 and 43.0) whereas the recently manufactured batch B4164-007 containing 75 copies/mL showed a normal distribution of HCV-RNA Ct values, similar as the Ct value distribution observed for HBV-DNA and HIV-1 RNA (lower graph in figure 6).

Figure 6. Performance evaluation data of P0273 ViraQ Multi-Marker Check 75 Control batch B4264-007 after 1.67-fold recalibration of the inactivated S0109 HCV standard in multiple quantitative methods[21]. A normal HCV-RNA Ct value distribution was found after recalibration on P0273 batch B4264- 007 (upper graph) comparable to the Ct value distribution for HBV-DNA and HIV-1 RNA on this batch (lower graph). Note that the Ct value distribution on 45 copies/mL of HCV-RNA in batch B4264 005 (upper graph), which was tested in parallel in the same cobas MPX reagent lot, was impacted by Poisson distribution so that outlier Ct values (between 39.0 and 43.0) were generated.



So far only limited performance evaluation data are available for P0273 ViraQ Multi-Marker Check 75 batch B4264-007 after recalibration of the HCV-RNA standard. The performance evaluation data of P0273 ViraQ Multi-Marker Check 75 batch B4264-007 are summarized in table 7 which compares the average Ct values and the 95% and 99% confidence interval for the different run control batches. As expected the HBV-DNA and HIV-1 RNA Ct values of the recent run control batch 007 were comparable to the ones found on the previous batches 002 to 004 but the average HCV-RNA Ct values were slightly lower than projected from the actual data.

Table 7. Expected Ct values on P0273 ViraQ Multi-Marker Check 75 Control in cobas MPX test runs as deduced from results found on different batches of the run control

P0273 batches	Marker	Copies/ mL	n	Average Ct	95 % confidence interval Ct	99 % confidence interval Ct
002-004	HBV-DNA	75	883	34.1	33.3-35.0	33.0-35.3
007	HBV-DNA	75	55	34.3	33.5-35.2	33.2-35.5
002-004	HCV-RNA	45$	884	37.7	36.4-38.9	36.0-39.3
002-004	*HCV-RNA*	*75#*	*884*	*36.9#*	*35.6-38.1*	*35.2-38.5*
005	HCV-RNA	45$	49	38.0	35.8-40.3	35.1-41.0
007	HCV-RNA	75^	55^	36.4	35.6-37.2	35.4-37.5
002-004	HIV-1-RNA	75	881	34.2	33.5-34.9	33.2-35.1
007	HIV-1-RNA	75	55	34.1	33.3-34.9	33.1-35.2

$ 45 copies/mL after recalibration of inactivated S0109 HCV-RNA standard

#Ct values were projected from actual data on 45 copies/mL of HCV-RNA (data presented in row above) by subtracting a delta Ct value of ^{2}Log 1.67 = 0.74 for each data point. (the projected data are presented in Figure 5)

^because of recent adjustment of the HCV concentration in the run control only limited performance evaluation data are available on an actual concentration of 75 copies/mL for HCV-RNA (data on batch 007 in Figure 6).

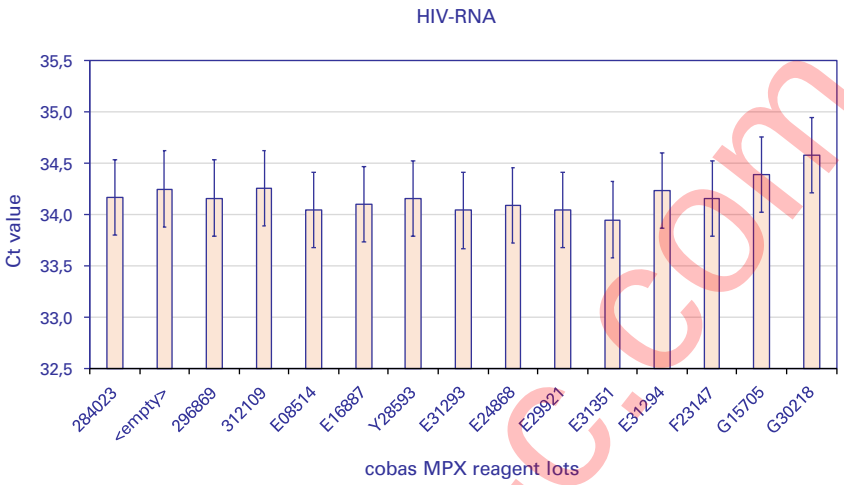
One can also use the Ct values obtained over a certain period of time on the run control for comparison of different experimental conditions, such as different run control batches, NAT reagent lots or cobas instruments. Examples are shown in table 8 and figure 7 comparing the average and standard deviation (SD) of the observed Ct values on different run control batches or cobas MPX reagent lots respectively.

Table 8. Comparison of Ct values on three batches of the P0273 ViraQ Multi-Marker Check 75 Control in the cobas MPX assay for two of the three markers^

P0273	Date			Ct HBV-DNA		Ct HIV-RNA	
Batch	Start	End	n	Mean	SD	Mean	SD
B4264-002	16-01-18	22-10-18	185	34,30	0,43	34,22	0,34
B4264-003	01-01-19	28-07-21	630	34,09	0,45	34,16	0,38
B4264-004	15-02-21	17-08-21	69	34,22	0,39	34,27	0,33

^no comparison data are available yet for 75 copies/mL of HCV-RNA in run control batches after recent 1.67-fold recalibration of the HCV standard

Figure 7. Comparison of HIV-RNA Ct values on P0273 ViraQ Multi-Marker Check 75 run control with different cobas MPX reagent lots (error bar = SD of total dataset, n=881)



Since the concentration of P0273 ViraQ Multi-Marker Check 75 is just above the Poisson detection endpoint range of the cobas MPX assay a shift towards higher Ct values on the run control (and/or a reduced analytical sensitivity of the NAT system) may coincide with an increased SD[17].

Limitations

- P0273 ViraQ Multi-Marker Check 75 Control cannot be used to evaluate the analytical or diagnostic sensitivity of the cobas MPX or other multi-dye real time PCR assays (although a significant reduction of analytical sensitivity of the NAT system can become apparent with repeated occurrence of non-reactive results or an upward shift in Ct values).
- P0273 ViraQ Multi-Marker Check 75 Control must not be substituted for the mandatory controls or calibrators provided with NAT test kits for calculating the cut-off and/or criteria for releasing test results.
- The Poisson distribution in samples with low virus concentrations cannot guarantee that 100% reactive results will always be found on P0273 ViraQ Multi-Marker Check 75 Control in NAT blood screening assays. Therefore the response values on the run controls should not be used for a decision to accept or reject the test run.
- The expected distributions of Ct values on P0273 ViraQ Multi-Marker Check 75 Control that are presented in this package insert were based on evaluation studies involving a limited number of run control batches and NAT reagent lots. It cannot be guaranteed that slightly different results will be found on other NAT reagent lots or instruments.

References

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