P0063
ViraQ HCV Check 125

CE
0483

IVD

REF P0063

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

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Intended use

P0063 ViraQ HCV Check 125 is intended to be used as external run control for hepatitis C virus (HCV)-RNA amplification tests in combination with the assays on the platforms defined in Table 1. The run control helps laboratories to ensure sufficient analytical sensitivity and consistent performance of:

- qualitative multiplex nucleic acid amplification tests (NAT) for blood screening
- quantitative NAT methods with a lower limit of quantification (LOQ) sufficiently below the run control concentration of 125 copies/mL (~ 46 International Units (IU)/mL)

Table 1. Assays and platforms covered by P0063 ViraQ HCV Check 125 run control

Assays (manufacturer)	Platform	Test environment
Procleix Ultrio® (Grifols)	Procleix Tigris®	Blood screening
Procleix Ultrio Plus® (Grifols)		
Procleix Ultrio Elite® (Grifols)	Procleix Panther®	
Aptima® HCV Quant Dx (Hologic)	Panther®	Viral load monitoring

P0063 ViraQ HCV Check 125 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

Manufacturer

Lot number

Catalogue number

In vitro diagnostic medical device

Country of origin

Contains human blood derivatives

Store below -30°C

Expiry date

Number of controls

Caution

CE mark with Notified Body number

Unique device identification

Read instructions for use

Biological substance Category B

Principle of method

P0063 ViraQ HCV Check 125 control has been formulated to mimic natural plasma specimens with a low HCV-RNA concentration. 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 125 copies/mL of HCV-RNA (equivalent to 46 IU/mL) and has been designed to ensure sufficient analytical sensitivity of transcription mediated amplification (TMA) tests in blood screening laboratories. The run control is also suitable for monitoring performance of quantitative HCV-RNA assays in diagnostic laboratories using real time TMA or polymerase chain reaction (PCR) methods. The HCV-RNA concentration in the run control has been set at 4 to 5 times the 95% lower limit of detection (LOD) of the Ultrio (Plus and Elite) assays (table 2)[1-5] and at 3-5 times the LOQ of the above mentioned quantitative NAT assays[5]. The positioning of P0063 ViraQ HCV Check 125 control ensures reactivity rates above 99.5% in the NAT systems listed in table 1. The run control enables laboratories to be alerted in case of a significant reduction of analytical sensitivity of NAT test systems and to identify changes in the (precision of) viral load tests over time. The run control is a dilution of the S0109 HCV-RNA genotype 3a

standard, prepared by inactivation of an anti-HCV non-reactive (window period) plasma unit with betapropiolactone[6-9]. 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 S0109 HCV standard has 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 HCV genotype 3a in the run control is representative for HCV Genotypes 1 to 6 that are prevalent in different geographical regions of the world (and that are detected with similar analytical sensitivity by the above mentioned commercial NAT assays)[4,10,11]. A positive (and quantifiable) result on the run control indicates that the NAT method has been performed with sufficient analytical sensitivity. A non-reactive result or a reactive result below the LOQ is indicative of reduced analytical sensitivity of the NAT system and should trigger investigation of the technical performance of the assay. The run control generates sample to cut-off (S/CO) ratios in the Procleix Ultrio assay versions and Ct values or viral loads (expressed in IU/mL) in quantitative TMA and real time PCR assays. Statistical analysis of these assay response values generated over a certain period of time allows for comparison of analytical performance of NAT reagent batches and laboratory instruments.

Table 2. Detection limits on native and inactivated HCV standard dilution panels in Procleix Ultrio assay versions

standard	BQC panel	NAT method	n	50% LOD (CI) copies/mL	95% LOD (CI) copies/mL
S0109 BQC HCV-RNA genotype 3a inact.	P0020	Ultrio	52	3.7 (2.8-4.7)	28.8 (19.5-48.8)
S0009 VQC-Sanquin HCV-RNA genotype 1	P0019	Ultrio	36	2.9 (2.1-3.9)	23.9 (15.0-46.7)
	P0019	Ultrio Plus	48	1.8 (1.3-2.3)	15.1 (9.9-26.6)
	P0019	Ultrio Elite	112	1.7 (1.5-2.0)	10.0 (7.7-13.8)
WHO HCV-RNA 06/100#	P0024	Ultrio	32	2.5 (1.8-3.4)	18.9 (11.7-39.0)
	P0024	Ultrio Plus	288	2.9 (2.0-4.2)	20.7 (12.2-50.3)
	P0024	Ultrio Elite	244	3.4 (2.0-5.4)	26.8 (14.2-89.4)

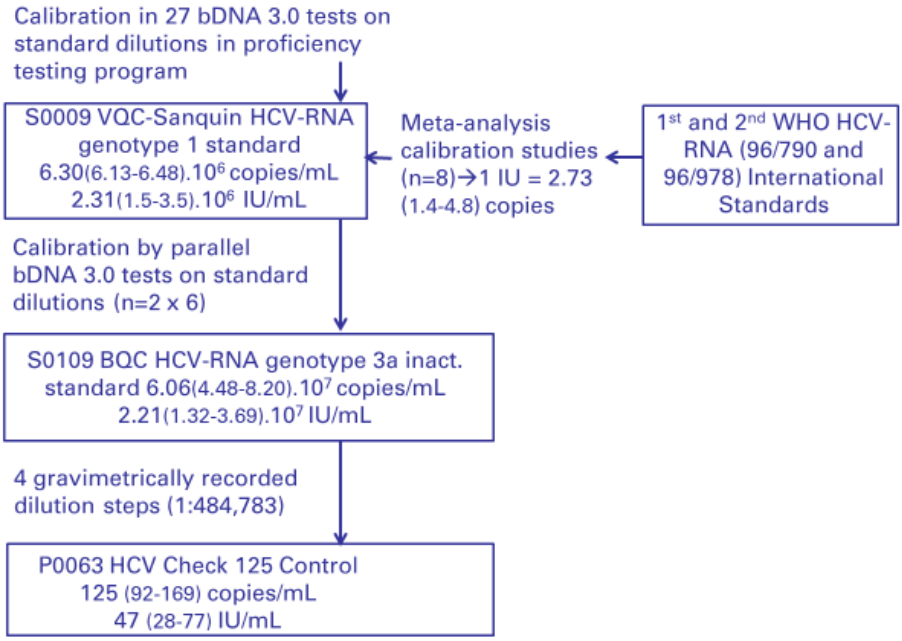
#1 IU = 2.73 copies

Traceability to HCV-RNA copies and International Units

Figure 1 shows the traceability chain between the ViraQ run control, the Bio Quality Control (BQC) standard, VQC-Sanquin standards and the 1st and 2nd (WHO 96/790 and 96/798) International Standards for HCV-RNA. The inactivated S0109 HCV-RNA standard (used for preparation of the P0063 ViraQ run control) has been calibrated in copies/mL by replicate testing in the Siemens Versant bDNA 3.0 assay[12] against the historically established S0009 VQC-Sanquin HCV-RNA genotype 1 standard[13]. The VQC-Sanquin HCV-RNA genotype 1 standard has been calibrated at 2.73 (1.4-4.8) copies per IU against the 1st and 2nd WHO HCV-RNA standards according to data from different studies[14-16]. It must be emphasized that this conversion factor from copies to IU values has not been confirmed for the later 3rd WHO 06/100, 4th WHO 06/102 and 5th WHO 14/150 replacement standards. The accurate calibration of the VQC-Sanquin HCV genotype 1 and the inactivated BQC genotype 3a standard in IU/mL and in copies/mL has been confirmed in analytical sensitivity studies of the Grifols Procleix TMA and Roche cobas MPX assays[4,14]. The BQC manufacturing and quality control procedures guarantee consistent virus concentrations in consecutive ViraQ HCV Check 125 batches[17]. The inactivated BQC HCV genotype 3a

standard is available in sufficient supply to ensure batch to batch consistency of ViraQ run controls for a prolonged period of time.

Figure 1. Traceability chain between run control, BQC and VQC-Sanquin standards and WHO International Standards



Stability of HCV standards and run control

The long term stability of the liquid frozen S0109 HCV standard stored below -65˚C has been firmly established[18]; hence the stock solution from which the run control is prepared has shown to be stable in the BQC storage facilities. Real time stability experiments using quantitative NAT assays showed less than 10% degradation of HCV-RNA per year in P0063 ViraQ HCV Check 125 control (and in standard dilutions of higher concentration) when stored at -30˚C[18]. 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)[17,18].

Kit contents (materials provided)

The run control contains human plasma without preservatives and is provided in three formats as detailed in Table 3.

P0063/01 and P0063/02 are intended to accommodate both blood screening and diagnostic laboratories. 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. The tube label has a barcode identifying the product, sequential batch number and marker HCV. The barcode can be read by the automated NAT systems.

P0063/03 is intended to accommodate molecular diagnostic laboratories using smaller vials in routine procedures. The vial label does *not* have a barcode; the control should be identified on the work list.

Table 3. Description of kit formats and contents

Cat. Code	UDI code	Quantity run control	Size vials	packing
P0063/01	8718719830639	60 x 1.5 mL	10 mL	60 vials in rack/box
P0063/02	8718719830281	10 x 1.5 mL	10 mL	Plastic zip bag
P0063/03	8718719830282	10 x 1.5 mL	2 mL	Plastic zip bag

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[18]. 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[18]. 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 P0063 ViraQ HCV Check 125 contains inactivated HCV particles[6-9] 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-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[19,20].

- 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 following sections in this package insert provide guidance on interpretation and analysis of test results on P0063 ViraQ HCV Check 125. The statistical evaluation methods were developed by BioQ Control and were not reviewed nor approved by the manufacturer of the Ultrio assay versions.

Qualitative detection of HCV RNA in Procleix Ultrio versions

The results of the Procleix Ultrio, Ultrio Plus and Ultrio Elite assays are expressed as a sample to cut-off ratio (S/CO). P0063 ViraQ HCV Check 125 Control should react positive in more than 99.5% of TMA test runs.

More than 99% of test results on the run control are expected in the (near) saturated range of the TMA assay with S/CO values equal to or above 5.0 (range 5.0-10.0). Less than 1% of results are expected in the lower dynamic range of the TMA assay with S/CO rations below 5.0 (see interpretation of test results below)[17]. A Levey-Jennings QC chart can be used to monitor the performance of the Ultrio assay versions on the run control.

Levey-Jennings QC chart.

The S/CO responses on ViraQ HCV Check 125 in the Ultrio Plus and Elite assay versions are not normally distributed, also not after transformation of the S/CO ratios. For developing a Levey-Jennings QC chart a distribution-free approach can be taken whereby the ranges containing 95% and 99% of the data are calculated. For this purpose the 0.5% and 99.5% percentiles are calculated for the 99% interval, and the 2.5% and 97.5% percentiles for the 95% interval. In case the total dataset does not contain sufficient data, values just outside the observed range can be presented in order to allow for a graphical presentation. For this non-defined distribution of S/CO ratios the median is a relevant measure, in addition to the mean. The difference between the median and the average of S/CO values may be an indicator of the skewness of the distribution curve. The value of this parameter $\Delta(S/CO_{M-A})$ is expected to become higher with lower analytical sensitivity of the NAT system or lower virus concentration in the run control. It is recommended to use the Nelson rules[21] to identify deviations in the Levey Jennings trend analysis.

Quantitative detection of HCV-RNA by viral load assays

For monitoring the accuracy and precision in viral load assays one can use a Levey-Jennings QC chart for trend analysis.

Levey-Jennings QC chart.

Test the run control at least 10 times during the reference period, apply log transformation on values expressed in IU/mL or copies/mL, estimate the geometric mean, standard deviation (SD) and its confidence interval (CI) as described below. [If Ct values are used no log transformation is required and confidence intervals can be calculated from the arithmetic mean and SD]. The Levey-Jennings chart is designed to identify individual aberrant values outside the 95% and 99% confidence intervals. With collecting additional data the chart characteristics may be updated.

The quantitative values for HCV-RNA viral load are 'log normal' distributed.

- Calculate from each measurement the log(concentration) in IU/mL or copies/mL.

- Calculate mean and SD on these log values
- Take anti-log of the mean of log values, i.e. the geometric mean of the measurements in IU/mL or copies/mL.

Use table 4 to obtain Student-t-values belonging to the 95% and 99% CI for different number of observations (n). Calculate the log(95% and 99% CI) as follows:

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

Table 4. Relation of Student t value and numbers of runs (n) to calculate CI's.

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

Use the Nelson rules[21] to identify deviations in the Levey Jennings trend analysis.

Interpretation of test results on run control in Procleix Ultrio assay versions

The expected frequency of S/CO values on P0063 ViraQ HCV Check 125 control in the TMA assay as well as the interpretation of three categories of test result are shown in table 5.

The vast majority of S/CO values on the run control reach TMA signals in the (near) saturated range of the assay (between 5.0 and 10.0). Only a small fraction of TMA reactions on the run control are not yet complete and have S/CO values in the lower dynamic range of the assay (between 1.0 and 5.0). Repeatedly non-reactive results and a significant higher proportion of lower dynamic responses are indicative of 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.

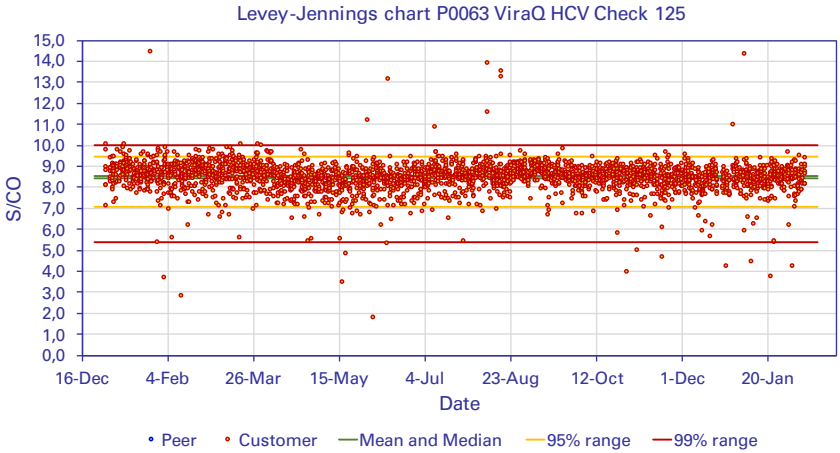
Table 5. Interpretation of a single TMA test result on P0063 ViraQ HCV Check 125 in Procleix Ultrio assay versions and expected frequency of S/CO values in three ranges

Result	S/CO	Expected frequency per 1000	Interpretation
Reactive near saturated	>5.0	>995	The test signal on the run control reaches values in the (near) saturated range of the TMA assay. This is an expected result.
Reactive lower dynamic	1.0–5.0	≤5	The test signal on the run control is in the dynamic range of the assay because the TMA reaction is not yet complete. This is an expected result.
Non-reactive	<1.0	0 – 1	The test signal on the run control is below the cut-off. This is an unexpected result that should trigger an investigation of the technical performance of the test system.

Monitoring performance of Ultrio Elite assay on run control

Figure 2 and table 6 show Ultrio Elite performance data on P0063 ViraQ HCV Check 125 obtained during 14 months of testing of the run control by one blood establishment using eight Panther instruments.

Figure 2. Levey-Jennings chart of P0063 ViraQ HCV Check 125 control results in Grifols Ultrio Elite assay reported by one national blood organisation using eight Panther instruments. The average and median (green lines) and 95% and 99% CI (orange and red lines) are calculated as described in the text.



In 2902 Ultrio Elite test runs 12 S/CO values (0.41%) on the run control were below 5.0, one of which was near the cut-off.

Table 6. Reproducibility of Ultrio Elite S/CO values on P0063 ViraQ HCV Check 125 control observed during a 14 month observation period by one national blood service

n test runs	Median S/CO	Mean S/CO	$\Delta(S/CO_{M-A})$	S/CO Predictive interval	
				95%	99%
2902	8.52	8.45	0.07	7.1-9.5	5.4-10.0

The performance evaluation data can also be used to compare ViraQ run control batches, Ultrio Elite reagent lots or Panther instruments (table 7).

Table 7. Comparison of test results on different P0063 ViraQ HCV Check 125 run control batches, Ultrio Elite reagent lots and Panther instruments during 14 months of testing by one national blood service

Item	Code	n	Median S/CO	St dev	Start date	End date
Run control product Batch	B4058-020	639	8,72	0,735	30-12-16	29-03-17
	B4058-021	1087	8,45	0,735	30-03-17	29-08-17
	B4058-022	1176	8,50	0,648	30-08-17	11-02-18
Ultrio Elite Test Reagent Lot	154471	734	8,70	0,717	30-12-16	11-04-17
	159260	599	8,32	0,736	12-04-17	06-07-17
	171962	630	8,63	0,626	07-07-17	01-10-17
	180939	669	8,47	0,611	02-10-17	05-01-18
	186731	270	8,44	0,821	06-01-18	11-02-18
Panther instrument	1237	372	8,59	0,705	30-12-16	11-02-18
	1427	367	8,46	0,748	30-12-16	11-02-18
	1428	369	8,29	0,808	30-12-16	11-02-18
	1429	363	8,70	0,576	30-12-16	11-02-18
	1430	377	8,71	0,647	30-12-16	11-02-18
	1433	358	7,98	0,720	30-12-16	11-02-18
	1434	335	8,54	0,536	30-12-16	11-02-18
	1438	361	8,55	0,572	02-01-17	11-02-18

Interpretation of test results on run control in quantitative NAT methods

P0063 ViraQ HCV Check 125 can be used as a quantitative run control in conjunction with the Hologic Aptima HCV Quant tests and other viral load assays with a LOQ sufficiently below 125 copies/mL. Table 8 gives the expected frequency of three categories of results on the run control in viral load assays.

Table 8. Interpretation of a single quantitative NAT test result on P0063 ViraQ HCV Check 125 control and expected frequency of viral load measurements above the lower limit of quantification (LOQ) of the current commercial real time PCR and TMA assays.

Result	HCV IU/mL	Expected frequency	Interpretation
Reactive quantifiable	≥LOQ	>99%	This is an expected result.
Reactive unquantifiable	<LOQ	<1%	This is an unexpected result but is possible. An investigation of technical performance of the NAT system is recommended
Non-reactive undetectable	<CO	0%	This is an unexpected result. An investigation of technical performance of the NAT system is required

Repeatedly non-reactive or unquantifiable results are indicative of a significantly reduced analytical sensitivity of the NAT system. A single event of a test result below the LOQ is however possible without deterioration of the test system and can be explained by Poisson distribution

The linear range of the quantitative NAT methods tests starts at enough distance below the run control concentration of 125 copies/mL to expect quantifiable results (above the LOQ) in more than 99% of test runs[5]. The quantitative HCV-RNA assays report values in IU/mL based on calibration against the WHO standard. The HCV-RNA concentration (95%CI) of P0063 ViraQ HCV Check control of 125 (92-169) copies/mL is equivalent to 46 (28-77) IU/mL (figure 1), more than three-fold higher than the LOQ's claimed by the manufacturers of the real time PCR and TMA assays (table 9).

Table 9. Distance of lower limit of quantification (LOQ) to concentration of P0063 ViraQ HCV Check 125 control as reported in the package inserts of HCV viral load assays of three manufacturers.

Manufacturer	NAT test	LOQ (IU/mL)	Factor (95%CI)#
Abbott	RealTime HCV	12	3.8 (2.6 - 5.2)
Roche Molecular systems	HCV Cobas 6800/8800	15	3.1 (2.3 - 4.1)
Hologic	Aptima HCV Quant	10	4.6 (3.4 - 6.2)

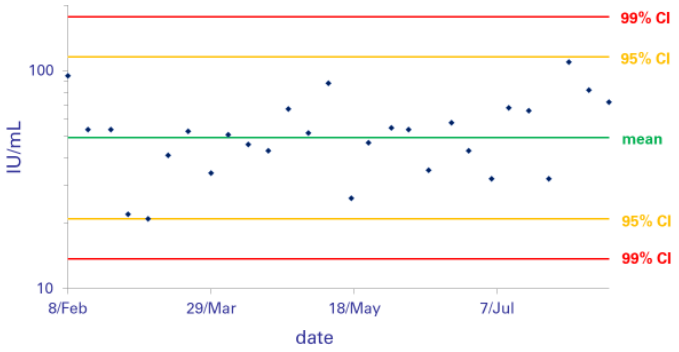
#Factor between Concentration of HCV-RNA in IU/ml of P0063 ViraQ HCV Check 125 and LOQ; 95% CI's derived from uncertainty in calibration of P0063 ViraQ P0063 Check 125 control.

One should be careful with comparing the IU/mL levels in table 10 because different methods and WHO replacement standards have been used for calibration of the run control and (calibrators of) the NAT systems.

Monitoring performance of quantitative NAT methods on run control

For the identification of aberrant quantitative results log (viral load) values should be recorded in a Levey-Jennings chart to visualise trends over time. The Neslon rules[21] provide guidance on the interpretation of results outside the 95% or 99% confidence intervals. An example is given in figure 4 showing data points of Aptima Quant test runs on P0063 ViraQ HCV Check 125 control in a Levey-Jennings scatter plot.

Figure 3. Reproducibility of Hologic Aptima HCV Quant test runs on P0063 ViraQ HCV Check 125 control presented in a Levey-Jennings chart.



Testing of P0063 ViraQ HCV Check 125 control in 28 test runs of the Aptima HCV Quant assay (figure 4) gave a geometric mean value (95% CI) of 49 (21-155) IU/mL comparable to the estimated concentration of 46 (28-77) IU/mL in the run control[17].

The distance from the geometric mean viral load (green line in graph) represents the deviation from the expected TMA response level on the run control. The orange lines represent the 95% CI and the red lines the 99% CI.

One can use the quantitative results on the run control for comparison of different experimental conditions, such as different laboratories, NAT reagent lots or instruments. Since the concentration of P0063 HCV Check 125 is just above the Poisson detection endpoint range of the quantitative NAT methods, lower reported IU/mL values on the run control (or reduced analytical sensitivity of the test system) may coincide with an increased standard deviation[17].

Limitations

- P0063 ViraQ HCV Check 125 Control cannot be used to evaluate the analytical or diagnostic sensitivity of NAT blood screening assays (although a significant reduction of analytical sensitivity of the NAT system can become apparent with repeated occurrence of non-reactive or unquantifiable results).
- P0063 ViraQ HCV Check 125 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 HCV concentrations cannot guarantee that 100% reactive results will be found on P0063 ViraQ HCV Check 125 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 assay response values on P0063 ViraQ HCV Check 125 Control that are presented in this package insert were based on evaluation studies involving a limited number of tests and NAT reagent lots. Therefore it cannot be guaranteed that different results will be found on other assay versions or NAT reagent lots.
- The parameter $\Delta(S/CO_{M-A})$ is an indicator of the skewness of the distribution curve of S/CO values and may be a performance indicator for the analytical sensitivity of Ultrio assay versions and reagent lots. However a threshold value above which a deterioration of the test system is predicted cannot be given.
- P0063 ViraQ HCV Check 125 should not be used for establishing accuracy of quantitative NAT results expressed in IU/mL. For this purpose only a dilution of the current WHO International Standard can be used.
- More quantitative data need to be collected in the viral load assays to confirm the suitability of P0063 HCV Check 125 control for these methods and to ensure that the proportion of unquantifiable results is less than 1%.

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