P0067
ViraQ HCV Trend 25

CE
0483

IVD

REF P0067

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

P0067 ViraQ HCV Trend 25 is intended to be used as external trend control for detection of hepatitis C virus (HCV)-RNA by the nucleic acid amplification technology (NAT) assays on the platform defined in Table 1. P0067 ViraQ HCV Trend 25 is an inactivated HCV-RNA standard in plasma quantified at a concentration of 25 copies/mL giving approximately 95% to 99% reactive results in the Procleix Ultrio assay versions. The trend control is intended to be used by trained laboratory workers. The trend control helps laboratories to ensure sufficient analytical sensitivity and consistent performance of the multiplex HBV/HCV/HIV transcription mediated amplification (TMA) assays. The trend control can be used in daily test runs to continuously monitor NAT performance over time or tested occasionally in multiple replicates in one test run for acceptance (transport integrity) testing of TMA reagent lots.

P0067 ViraQ HCV Trend 25 should not be used to replace the internal controls or calibrators in the test kits. The test result on the trend control should not be used to reject the run or delay the release of test results on donor samples.

Table 1. Assays and platform covered by P0067 ViraQ HCV Trend 25 control.

Assay (manufacturer)	Platform	Test environment
Procleix® Ultrio Elite (Grifols)	Procleix® Panther®	Blood screening
Procleix® UltrioPlex E (Grifols)		

Key to symbols used

Manufacturer

Lot number

Catalogue number

In vitro diagnostic medical device

Country of origin

Contains human blood derivatives

Store below -65°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

P0067 ViraQ HCV Trend 25 control has been formulated to mimic natural plasma specimens with a low HCV-RNA concentration. After thawing the trend control tubes are ready for use and can be placed at random positions in sample racks on the NAT platform. P0067 ViraQ HCV Trend 25 contains 25 copies/mL of inactivated HCV-RNA (equivalent to 9 IU/mL). The trend control has been designed to ensure sufficient analytical sensitivity of TMA tests in blood screening laboratories. The HCV-RNA concentration in the trend control has been set near the 95% lower limit of detection (LOD) of the Ultrio, Ultrio Plus, Ultrio Elite and UltrioPlex E assays (Table 2)[1-6]. The trend control enables laboratories to be alerted in case of a significant reduction of the analytical sensitivity of NAT test systems and to identify changes in TMA performance over time. The trend 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[7-10]. The plasma matrix in which the trend 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 trend 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)[1,4,11,12]. A positive result on the trend control indicates that the NAT method has been performed with sufficient analytical sensitivity. A higher-than-expected proportion of non-reactive or weakly reactive results is indicative of reduced analytical sensitivity of the NAT system and should trigger investigation of the technical performance of the assay. The trend control generates sample to cut-off (S/CO) ratios in the Procleix Ultrio assay versions. Statistical analysis of these assay response values generated over a certain period allows for comparison of the analytical performance of NAT reagent lots and laboratory instruments. For this purpose, users of the Procleix assays in combination with the P0067 ViraQ HCV Trend 25 Control can generate a statistical report for post-market performance follow-up[13] using the DataQ Analytics system accessible via the website www.bioqcontrol.com. The trend control can also be used in multiple replicates in the same test run to ensure that TMA reagents fulfil the minimum requirements for analytical sensitivity before they are accepted for routine blood screening. A summary of the safety and performance of the P0067 ViraQ HCV Trend 25 control will be made available at the EUDAMED website of the European Union, and is currently available upon request[14].

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

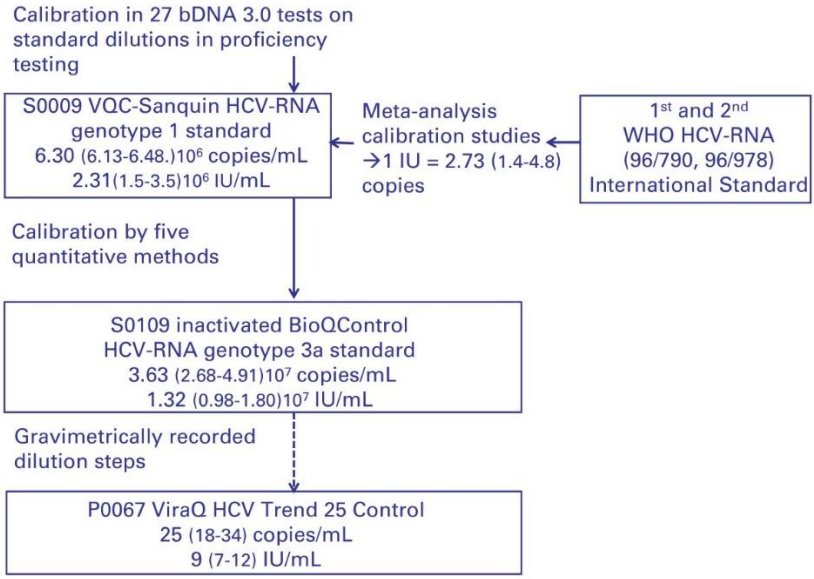
standard	panel	NAT method	n	50% LOD (CI) copies/mL	95% LOD (CI) copies/mL
S0109 BQC HCV-RNA genotype 3a inactivated	P0020	Ultrio	52	2.2 (1.7-2.8)	17.2 (11.7-29.2)
S0009 VQC-Sanquin HCV-RNA genotype 1 native	P0019	Ultrio	36	2.9 (2.1-3.9)	23.9 (15.0-46.7)
	P0019	Ultrio Plus	48	1.8 (1.3-2.3)	15.1 (9.9-26.6)
	P0019	Ultrio Elite	112	1.7 (1.5-2.0)	10.0 (7.7-13.8)
	P0288	Ultrio Elite	24	2.5 (1.7-3.7)	20.3 (11.7-47.5)
	P0288	UltrioPlex E	72	2.2 (1.5-3.2)	14.1 (8.2-35.1)
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 trend control, the inactivated BioQControl standard, the native VQC-Sanquin standards and the 1st and 2nd (WHO 96/790 and 96/798) International Standards for HCV-RNA. The inactivated S0109 HCV-RNA genotype 3a standard (used for preparation of the P0067 ViraQ trend control) has originally been calibrated in copies/mL by replicate testing in the Siemens Versant bDNA 3.0 assay[15] against the historically established S0009 VQC-Sanquin HCV-RNA genotype 1 standard[16]. Later the S0109 HCV genotype 3 standard was recalibrated against the primary S0009 HCV genotype 1 standard based on five quantitative NAT methods and the composition of the trend control was adjusted accordingly to a concentration of 25 copies/mL (Figure 1)[17]. The primary 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[16-19]. 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 BioQControl 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[1-5,11,16-19]. The manufacturing and quality control procedures of BioQControl guarantee consistent virus concentrations in consecutive ViraQ HCV Trend 25 batches[13,20]. The inactivated BioQControl S0109 HCV genotype 3a standard is available in sufficient supply to ensure batch-to-batch consistency of ViraQ run controls for a prolonged period.

Figure 1. Traceability chain between ViraQ trend control, inactivated BioQControl, native VQC-Sanquin and WHO International Standards.



Stability of HCV standards and trend control

P0067 ViraQ HCV Trend 25 control can be stored at ≤–65°C for five years and if stored at –30 °C for no longer than 6 months. The long-term stability of the liquid frozen S0109 HCV standard stored below -65˚C has been firmly established[21]; hence the stock solution from which the trend control is prepared has shown to be stable in the BioQControl's storage facilities. Realtime stability experiments using quantitative NAT assays showed less than 10% degradation of HCV-RNA per year in standard dilutions of higher concentration than in P0067 HCV Trend 25 control when stored at –30˚C[21]. Since the relative degradation is independent of concentration the degradation estimate can be extrapolated to P0067 HCV Trend 25 control. Hence, it can be guaranteed that the trend control is still functional and should generate a reactivity rate of 94-99% when stored at ≤–65°C or less than 6 months at ≤–30°C[13,20].

Kit contents (materials provided)

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

Table 3. Description of P0067 ViraQ HCV Trend 25# kit formats and contents.

Cat. Code	GTIN/UDI-DI code^	Quantity	Tube size	Sample volume	Secondary packing
P0067/01	8718719830673	60 tubes	10 mL	1.4 mL (+overfill)	Rack in box
P0067/02	8718719832042	10 tubes	10 mL	1.4 mL (+overfill)	Plastic zip bag

^ Global Trade Item Number = Unique Device Identification - Device Identifier (UDI-DI) code,
# Global Model Number (GMN) = Basic UDI code for P0067 is 871871983P0067ET

P0067/01 and P0067/02 are intended to accommodate blood screening laboratories. To facilitate automation the trend 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 marker: HCV. The barcode of each trend control tube can be read by the automated NAT systems.

Materials required but not supplied

The test kits and liquid handling devices by the NAT manufacturer as specified in Table 1, a water bath of 37°C for quickly thawing of trend control and a vortex instrument for thorough mixing of samples are not provided.

Storage instructions

The trend controls should be stored at or below –65°C for a maximum of five years after preparation of the trend control batch and not be used for more than six months after storage at –30°C[21]. Once thawed, the trend control samples should be used within 8 hours. During this period, when the trend control is not in use, store sample at 2-8°C[21]. 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 P0067 ViraQ HCV Trend 25 contains inactivated HCV particles[7-10] 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 trend 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[22,23].

- 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 trend control 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 trend controls for 2 minutes thoroughly.
- Once thawed, do not re-freeze and thaw the trend control samples to avoid formation of cryoprecipitates that could alter reactivity or cause pipetting errors in the automated sampling systems.
- Store trend controls in an upright position.

Reagent preparation

- Thaw the trend control quickly in a water bath at 37°C.
- Mix gently during thawing until contents are just thawed.
- Immediately after the ice clot has disappeared remove the trend control tube from the water bath.
- Before testing allow the trend control tube to adapt to room temperature.
- Mix the trend control tube thoroughly prior to use with a vortex instrument.
- Give a short spin in a centrifuge to remove liquid before releasing screw cap from vial.
- Minimise the time from thawing until testing of the control samples.
- Test trend control sample within 8 hours after thawing.
- After thawing when not in use, store trend control tube at 2-8°C.

Analytical Performance Characteristics

The results of the Procleix Ultrio assays are expressed as a sample to cut-off ratio (S/CO). P0067 ViraQ HCV Trend 25 Control should be reactive in approximately 95% to 99% of TMA test runs.

The positioning of P0067 ViraQ HCV Trend 25 control is near the 95% lower limit of detection (LOD) of the Procleix Ultrio assays. This has been demonstrated by testing dilution panels of the native S0009 HCV genotype 1 standard (Figure 2) and of the inactivated S0109 HCV genotype 3a standard used for preparation of the trend control (Figure 3). At the concentration of 25 copies/mL S/CO ratios follow a non-parametric distribution.

Figure 2. Distributions of S/CO ratios on dilutions of the native S0009 HCV standard dilutions in reference panel P0288 tested in 24 replicates by the UltrioPlex E assay with a 95% LOD (CI) of 13.5 (7.4-41.7) copies/mL.

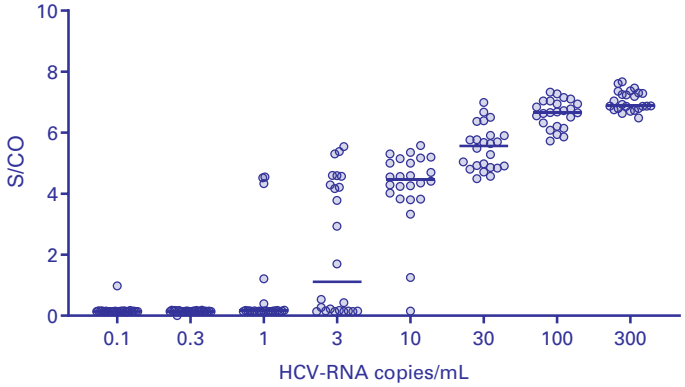
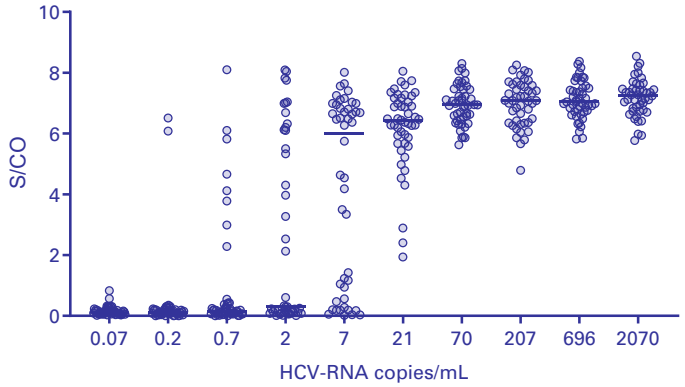


Figure 3. Distributions of S/CO ratios on dilutions of the inactivated S0109 HCV standard dilutions in the P0020 reference panel tested in 52 replicates by the Ultrio assay with a 95% LOD (CI) of 17.2 (11.7-29.2) copies/mL being near the the trend control concentration of 25 (18-34) copies/mL.



Expected assay response values on trend control

The expected results for the P0067 ViraQ HCV Trend 25 Control are as follows:

Procleix Ultrio Elite assay
HCV-RNA S/CO ratios range: 0.0 – 9.4

Procleix UltrioPlex E assay
HCV-RNA S/CO ratios range: 0.0 – 5.5

Approximately 95% to 99% of results in these assays are expected to be reactive, with approximately 85 to 90% of results in the saturation range of the assays. 5% to 10% of results are expected to be in the dynamic range of the assay, indicating incomplete TMA

reactions. Each TMA assay and reagent lot has its own distribution of response values on HCV standard dilutions and on P0067 ViraQ HCV Trend 25 Control. This depends on the design of the assay and the analytical sensitivity of the reagent lots that are in use. Thus, it cannot be guaranteed that the assay response values will always fall within these ranges.

Interpretation of results

The trend 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. Subsequent test runs can be analysed by appropriate statistical approaches on the response values obtained on the external control samples. A software system (DataQ Analytics) is available via the website www.bioqcontrol.com for entering response values and generating a statistical report with assay-specific calculations for preparing a Levey-Jennings Chart.

Calculations

Since the Procleix Ultrio Elite and UltrioPlex E assays return non-parametrically distributed S/CO ratios, predictive ranges are based on the percentiles of the data range. Calculate the 95% and 99% predictive limits as follows:

- 99% Lower limit: (interpolated) 0.005th percentile
- 95% Lower limit: (interpolated) 0.025th percentile
- 99% Upper limit: (interpolated) 0.995th percentile
- 95% Upper limit: (interpolated) 0.975th percentile

Test the trend control at least 30 times during the reference period. The Levey-Jennings chart (Figures 5 and 6) is designed to identify individual aberrant values outside the 95% and 99% ranges. By collecting additional data, the chart characteristics may be updated. Use Nelson rules[23] to identify deviations in the Levey-Jennings trend analysis.

The Procleix Ultrio Elite and UltrioPlex E test results on P0067 ViraQ HCV Trend 25 control are expected to be reactive in 95-99% of cases according to probit analysis on the inactivated S0109 HCV genotype 3a standard dilutions in the P0020 reference panel. A decrease in the proportion of reactive results or results in the saturated range of the assay is indicative of reduced analytical sensitivity of the NAT system.

Levey-Jennings Chart

The S/CO ratios obtained in consecutive Procleix Ultrio Elite and UlrioPlex E test runs for HCV-RNA can be plotted in a Levey-Jennings chart using the statistical report function of the DataQ Analytics system available on www.bioqcontrol.com as shown in the charts of Figure 5 and Figure 6.

Table 8 summarizes the Levey-Jennings chart parameters in Figure 5, which were deduced from the Ultrio Elite S/CO ratios reported on two P0067 ViraQ HCV Check Control batches by one laboratory over a period of 15 months.

Table 8. Median S/CO ratios with 95% and 99% ranges as found on two batches of P0067 ViraQ HCV Trend 25 Control in 1090 Ultrio Elite test runs in the period from 8-11-2022 to 9-02-2024 (data in Figure 5).

Assay	n	Median S/CO	95% range S/CO	99% range S/CO
Ultrio Elite	1090	8.42	5.06 – 9.22	0.49 – 9.44

Table 9 summarizes the Levey-Jennings chart parameters in Figure 6, which were calculated from the UltrioPlex E S/CO ratios reported on one P0067 ViraQ HCV Check Control batches by one laboratory over a period of 1 month.

Table 9. Median S/CO ratios with 95% and 100% ranges as found on one batch of P0067 ViraQ HCV Trend 25 Control in 90 UltrioPlex E test runs in the period from 22-08-2024 to 4-09-2024 (data in Figure 6).

Assay	n	Median S/CO	95% range S/CO	100% range S/CO
UltrioPlex E	90	4.93	4.36 – 5.47	3.92 – 5.53

Figure 5. Levey-Jennings QC chart of Ultrio Elite assay S/CO ratios for HCV-RNA on two batches of P0067 ViraQ HCV Trend Control.

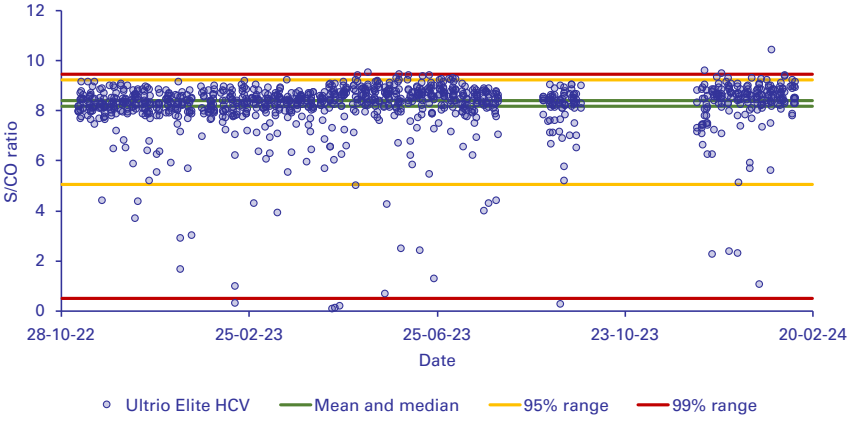
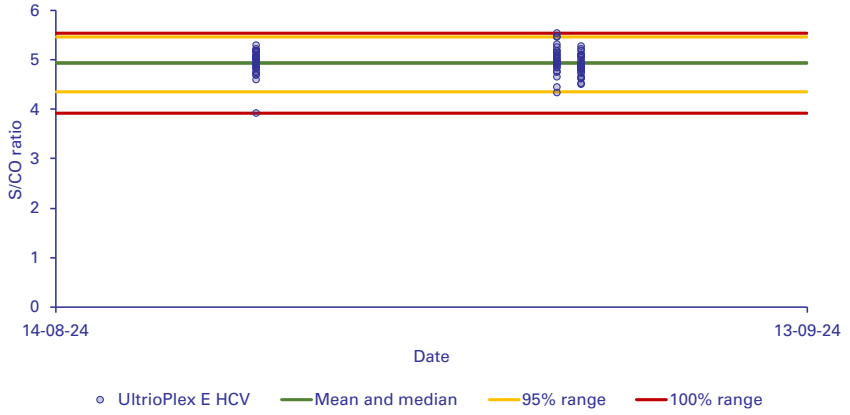


Figure 6. Levey-Jennings QC chart of UltrioPlex E assay S/CO ratios for HCV-RNA on one batch of P0067 ViraQ HCV Trend Control.



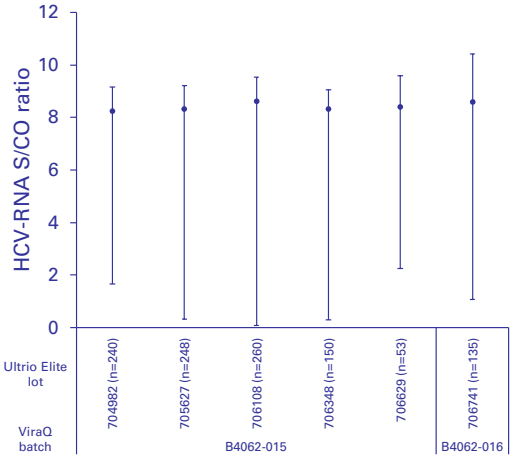
Post-market performance follow-up of trend control batches

One can use P0067 ViraQ HCV Trend 25 in combination with the DataQ Analytics system on www.bioqcontrol.com to compare the S/CO ratios on different trend control batches, Procleix Ultrio reagent lots or Procleix Panther instruments. Table 10 and Figure 7 compare the median S/CO ratios in the Ultrio Elite assay on P0067 ViraQ HCV batches and Procleix Ultrio reagent lots for HCV-RNA, showing no indications for changes in analytical sensitivity. The preliminary data of the UltrioPlex E assay is based on test runs with only one P0067 ViraQ batch (B4062-016) and one test reagent lot (707270). Therefore, no comparisons can be made for the UltrioPlex E assay. However, the reactivity rate of 100% in this limited data set indicates sufficient analytical sensitivity in the UltrioPlex E assay for HCV-RNA.

Table 10. Comparison of Ultrio Elite S/CO on P0067 ViraQ HCV Trend 25 Control batches and between consecutive Procleix Ultrio Elite reagent lots.

P0067 ViraQ batch	Ultrio Elite reagent lot	n	Median S/CO (range)	Avg. S/CO	$\Delta S/CO_{M-A}$	S/CO values ≥ 1
B4062-015	704982	240	8.26 (1.67 - 9.16)	8.08	0.19	240 (100.00%)
	705627	248	8.32 (0.33 - 9.23)	8.11	0.21	247 (99.60%)
	706108	260	8.63 (0.09 - 9.54)	8.29	0.34	256 (98.46%)
	706348	150	8.33 (0.29 - 9.06)	8.09	0.24	149 (99.33%)
	706629	53	8.41 (2.26 - 9.60)	8.06	0.35	53 (100.00%)
	All	**951**	**8.39 (0.09 - 9.60)**	**8.15**	**0.24**	**945 (99.37%)**
B4062-016	*706629*	*4*	*9.10 (8.85 - 9.51)*	*9.14*	*-0.04*	*4 (100.00%)*
	706741	135	8.60 (1.08 - 10.43)	8.37	0.23	135 (100.00%)
	All	**139**	**8.61 (1.08 - 10.43)**	**8.39**	**0.22**	**139 (100.00%)**
All	**All**	**1090**	**8.42 (0.09 - 10.43)**	**8.18**	**0.24**	**1084 (99.45%)**

Figure 7. Median S/CO (and min – max range) ratios for HCV-RNA in Procleix Ultrio Elite assay reagent lots on P0067 ViraQ HCV Trend 25 control batches (data in Table 10).



The S/CO responses on P0067 ViraQ HCV Trend 25 in the Procleix Ultrio Elite and UltrioPlex E assays are not normally distributed, since >85% of S/CO ratios are in the saturation range of the assays. Therefore, an increase in the number of S/CO ratios below the saturation range will increase the difference between the median and the average of S/CO values ($\Delta S/CO_{M-A}$). Hence, $\Delta S/CO_{M-A}$ is expected to become higher with lower analytical sensitivity of the NAT system and may be used for trend analysis[13,20].

Acceptance testing of reagent lots

To estimate the analytical sensitivity of a new reagent lot, test the trend control in 20 replicates in a single test run and follow the guidelines in Table 11. The expected frequencies are based on the lowest observed reactivity rate on P0067 ViraQ HCV Trend 25 control (98%, see Table 10).

Table 11. Decision algorithm and criteria for acceptance of reagent lots by replicate testing of 20 vials of P0067 ViraQ HCV Trend 25 control in one Procleix Ultrio Elite or UltrioPlex E assay test run.

Phase	Number of reactives	Expected frequency	Decision
Initial test	≥19	>94%	Accept
	≤18	<6%	Repeat acceptance testing procedure
Repeat test	≤17	<0.7%	Initiate root cause analysis

Limitations

- P0067 ViraQ HCV Trend 25 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 results and a higher frequency of weak reactive results).
- P0067 ViraQ HCV Trend 25 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.
- A single non-reactive test result on P0067 ViraQ HCV Trend 25 Control cannot be used to invalidate a test run. The Poisson distribution in samples with low HCV concentrations cannot guarantee that the response values are reproducible. Therefore, the trend control cannot be used for a decision to accept or reject a test run.
- The expected ranges of results in the Procleix Ultrio Elite and UltrioPlex E assays on P0067 ViraQ HCV Trend 25 Control that are presented in this package insert were based on performance evaluation studies involving a limited number of trend control batches and NAT reagent lots. It cannot be guaranteed that slightly different results will be found on other trend control batches, assay reagent lots or laboratory instruments.
- The parameter $\Delta(S/CO_{M\text{-}A})$ 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 for $\Delta(S/CO_{M\text{-}A})$ above which a deterioration of the test system is predicted cannot be given.
- It is not guaranteed that reagent lots that pass the acceptance testing procedure always have sufficient analytical sensitivity. A small reduction in analytical sensitivity is less likely to be identified by the procedure than a large reduction in analytical sensitivity.
- It cannot be excluded that some variation exists between the performance of consecutive batches of the P0067 ViraQ HCV Trend 25 control due to matrix effects or other manufacturing variables.

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