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 hepatitis C virus (HCV)-RNA detection by the multiplex transcription mediated amplification (TMA) assays on the automated nucleic acid amplification technology (NAT) platforms defined in Table 1. The trend control helps laboratories to ensure that HCV is detected with sufficient analytical sensitivity by consecutive reagent lots of the Procleix Ultrio assay versions and by each of the Tigris or Panther instruments in use. 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
- installation qualification of instruments
- training of technicians.

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

Assays (manufacturer)	Platform	Test environment
Procleix Ultrio® (Grifols)	Procleix Tigris®	Blood screening
Procleix Ultrio Plus® (Grifols)		
Procleix Ultrio Elite® (Grifols)	Procleix Panther®	

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 run control should not be used to reject the run or delay the release of test results on donor 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

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 platforms. The trend control contains 25 copies/mL of HCV-RNA (equivalent to 9 International Units (IU)/mL) and has been designed to ensure sufficient analytical sensitivity of transcription mediated amplification (TMA) tests in blood screening laboratories. The HCV-RNA concentration in the run control has been set near the 95% lower limit of detection (LOD) of the Ultrio (Plus and Elite) assays (table 2)[1-5]. P0067 ViraQ HCV Trend 25 Control enables laboratories to be alerted in case of a reduction of analytical sensitivity of NAT instruments or reagent lots and to identify changes in TMA performance 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 TMA assays)[4,10]. 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 run 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 of time allows for comparison of analytical performance of NAT reagent lots and laboratory instruments. The trend control can also be used in multiple replicates in the same test run to ensure that TMA reagents or instruments fulfil the minimum requirements for analytical sensitivity before they are accepted for routine blood screening.

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)

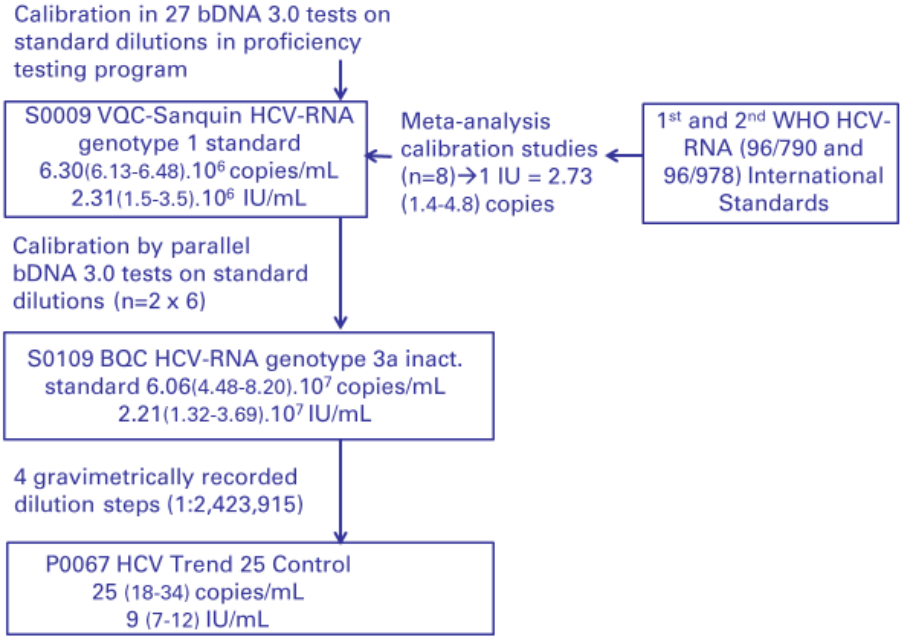
#1 IU = 2.73 copies

Traceability to HCV-RNA copies and International Units

Figure 1 shows the traceability chain between the ViraQ trend 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 P0067 ViraQ trend control) has been calibrated in copies/mL by replicate testing in the Siemens Versant bDNA 3.0 assay[11] against the historically established S0009 VQC-Sanquin HCV-RNA genotype 1 standard[12]. The VQC-Sanquin HCV-RNA genotype 1 standard has been calibrated at 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[13-15]. 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[4,13]. The BioQControl manufacturing and quality control procedures guarantee consistent virus concentrations in consecutive ViraQ HCV Trend 25 batches[16]. 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 trend control

The long term stability of the liquid frozen S0109 HCV standard stored below -65˚C has been firmly established[17]; hence the stock solution from which the run control is prepared has 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 per year in P0067 ViraQ HCV Trend 25 control (and in standard dilutions of higher concentration) when stored at -30˚C[17]. Hence, it can be guaranteed that the trend control is still functional and should generate a reactivity rate near 95% when stored at -30˚C and used before the expiration date (two years after preparation of the run control batch)[16,17].

Kit contents (materials provided)

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

P0067/01 and P0067/02 are intended to accommodate blood screening 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. The barcode can be read by the automated NAT systems.

Table 3. Description of kit formats and contents

Cat. Code	UDI code	Quantity run control	Size vials	packing
P0067/01	8718719830673	60 x 1.5 mL	10 mL	60 vials in rack/box
P0067/02	8718719830287	10 x 1.5 mL	10 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 trend controls should be stored at or below -30°C for a maximum of two years[17]. 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[17]. 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[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[18,19].

- 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 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.

The following sections in this package insert provide guidance on interpretation and analysis of test results on P0067 ViraQ HCV Trend 25. The statistical evaluation methods were developed by BioQControl 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). P0067 ViraQ HCV Trend 25 Control should react positive in approximately 90% to 95% of TMA test runs. Approximately 70% of test results on the trend control are expected in the saturated range of the TMA assay with S/CO values equal to or above 7.0. Approximately 20% to 25% of test results are expected in the lower dynamic range of the TMA assay with S/CO rations below 7.0 (see interpretation of test results below)[16]. 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 Trend 25 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% predictive interval, and the 2.5% and 97.5% percentiles for the 95% predictive 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 is 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[20] to identify deviations in the Levey Jennings trend analysis.

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

The expected frequency of S/CO values on P0067 ViraQ HCV Trend 25 control in the below cut-off, the lower dynamic and (near) saturated range of the TMA assay as well as the interpretation of these categories of test result are shown in table 4. The majority of S/CO values on the run control reach (near) saturated TMA response levels and are found between 7.0 and 11.0 (figure 2). A fifth to a quarter of TMA reactions on the trend control are not yet complete and have S/CO values in the dynamic range of the assay (between 1.0 and 7.0). In a four year observation period of 2700 Ultrio (Plus and Elite) test runs the overall proportion of reactive results was 92.4%, but the reactivity rate varied between TMA reagent lot and trend control batch combinations (table 5)[16].

Table 4. Interpretation of a single TMA test result on P0067 ViraQ HCV Trend 25 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	>7.0	662 – 727	The test signal on the trend control reaches values in the (near) saturated range of the TMA assay. This is an expected result.
Reactive lower dynamic	1.0–7.0	215 –253	The test signal on the run control is in the lower dynamic range of the assay because the TMA reaction is not yet complete. This is an expected result.
Non-reactive	<1.0	67-89	The test signal on the run control is below the cut-off. This is an expected result

[#]95% confidence limits found in 2700 Ultrio (Plus and Elite) test runs

Table 5. Proportion of reactive results observed in daily test runs on P0067 ViraQ HCV Trend 25 Control (TC) batches in consecutive Ultrio (U), Ultrio Plus (UP) and Ultrio Elite (UE) reagent lots.

TMA reagent lot	Trend Control batch	reactive/n	% reactive	delta (95%CI) % to overall %
U1	TC1	184/192	95.8%	3.4 (2.8-4.1)%
UP1	TC1	58/74	78.4%	-14.0 (-19.0,-9.1)%
	TC1 All	242/266	91.0%	-1.4 (-2.6,-0.3)%
UP1	TC2	88/99	88.9%	-3.5 (-5.7,-1.3)%
UP1 All		146/173	84.4%	-8.0 (-10.4,-5.7)%
UP2	TC2	252/286	88.1%	-4.3 (-5.7,-2.9)%
	TC2 All	340/385	88.3%	-4.1 (-5.3,-2.9)%
UP2	TC3	80/80	100.0%	7.6 (7.3,7.9)%
UP2 All		332/366	90.7%	-1.7 (-2.7,-0.7)
UP3	TC3	168/179	93.9%	1.4 (0.5,2.4)%
UP4	TC3	195/203	96.1%	3.7 (3.0,4.3)%
UP5	TC3	210/228	92.1%	-0.3 (-1.4,0.8)%
UP6	TC3	82/90	91.1%	-1.3 (-3.2,0.6)%
UP7	TC3	86/91	94.5%	2.1 (0.9,3.3)%
	TC3 All	821/871	94.3%	1.9 (1.4,2.3)%
UP All		1219/1330	91.7%	-0.8 (1.3,-0.2)%
UE1	TC4	31/35	88.6%	-3.8 (-7.7-0.0)%
UE2	TC4	158/177	89.3%	-3.1 (-4.8,-1.5)%
UE3	TC4	330/354	93.2%	0.8 (0.0,1.6)%
	TC4 All	519/566	91.7%	-0.7 (-1/5,0.0)%
UE4	TC5	439/472	93.0%	0.6 (-0.1,1.3)%
UE5	TC5	134/140	95.7%	3.3 (2.5,4.1)%
	TC5 All	573/612	93.6%	1.2 (0.6,1.8)%
UE All		1092/1178	92.7%	0.3 (-0.2,0.8)%
U, UP, UE All		2495/2700	92.4%	reference

Monitoring performance of Procleix Ultrio assay versions on trend control

Figure 2 shows Ultrio Elite performance data on P0067 ViraQ HCV Trend 25 obtained during six months of testing by one national blood service in a Levey-Jennings QC Chart.

Figure 2. Levey-Jennings chart of P0068 ViraQ HIV-1 Trend 25 Control results in Grifols Ultrio Elite assay reported by one national blood organisation using four Panther instruments. The average and median (green lines) and 95% and 99% predictive intervals (orange and red lines) are calculated as described in the text.

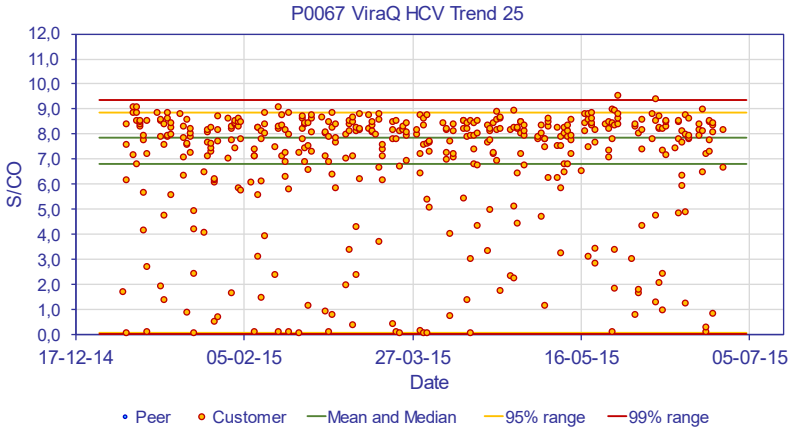


Table 6 presents the same Ultrio Elite data as presented in Figure 2 as well as a larger set of earlier obtained Ultrio Plus and Elite data presented in table 5.

Table 6. Reproducibility of Ultrio (Plus and Elite) S/CO values on P0067 ViraQ HCV Trend 25 control

n test runs	Median S/CO	Average S/CO	$\Delta(S/CO_{M-A})$	S/CO Predictive interval	
				95%	99%
429#	7.88	6.80	1.08	0.07 – 8.87	0.04 – 9.34
2700^	8.20	7.03	1.17	0.09 – 9.94	0.04 – 10.2

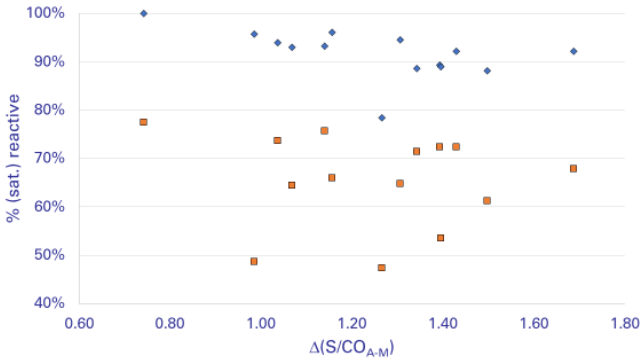
#Ultrio Elite data if figure 2 ^Ultrio Plus and Elite data of table 5

The difference between the median and the average of S/CO values can be used as an indicator of the skewness of the distribution curve and the analytical sensitivity of the NAT system (table 6). Based on the available results one may conclude that if $\Delta(S/CO_{M-A})$ is below 1.60 the system is properly functioning[16]. The presence of a higher proportion of non-reactive results coincides with higher values of $\Delta(S/CO_{M-A})$, thereby confirming its ability to be a trend indicator for analytical performance of the TMA assay (figure 3). An alert threshold value for this parameter that is indicative for poor NAT performance cannot be given with the available data.

The parameter $\Delta(S/CO_{M-A})$ can also be applied to compare other experimental conditions such as the TMA reagent lot, the ViraQ trend control batch or the testing robot (Tigris or Panther). An example using $\Delta(S/CO_{M-A})$ as performance indicator is shown in figure 3

comparing different TMA reagent lot/trend control batch combinations[16]. The result shows that the values of $\Delta(S/CO_{M-A})$ for TMA reagent lot/trend control batch combinations roughly correlate with the reactivity rates. Hence, if the reagent lot performance indicator $\Delta(S/CO_{M-A})$ has an outlier value it could be used as an alert signal for checking technical performance of that particular TMA reagent lot or trend control batch.

Figure 3. Correlation between $\Delta(S/CO_{M-A})$ and proportion reactive (diamonds, S/CO≥1.0) and (near) saturated (squares, S/CO≥7.0) response levels observed with different Ultrio, Ultrio Plus and Ultrio Elite reagent lots on P0067 ViraQ HCV Trend 25 control. Each point represents a TMA reagent lot/trend control batch combination.



Acceptance testing of NAT system component using trend control

P0067 ViraQ HCV Trend 25 can also be used for acceptance testing of a new TMA reagent lot, a new trend control batch, a reagent transport integrity check, a (re)-installation qualification of a Panther or Tigris instrument or training of an operator. For these applications it is recommended to test 20 vials of the trend control in one Ultrio (Plus or Elite) test run. The reagent lot, instrument or operator performance is approved when at least 16/20 (80%) of tests are reactive and the median S/CO value is above 6.5. If either one of these criteria is not fulfilled it is recommended to repeat the acceptance test procedure in another test run. If in the repeat test either one of these criteria is again not fulfilled further investigation of the performance of the reagent batch or instrument is required. These acceptance criteria were established by a simulation study with sliding sets of 20 sequential results out of a data base of 2700 Ultrio Plus and Elite test runs[16]. The decision algorithm for accepting the NAT system component is summarized in table 7.

Table 7. Decision algorithm and criteria for acceptance of reagents, instruments or operators by replicate testing of 20 vials of P0067 ViraQ HCV Trend 25 control in one Procleix Ultrio (Plus or Elite) assay run

Acceptance criteria		Expected frequency	Decision
reactivity rate ≥16/20 (80%)	Median S/CO ≥6.5		
OK	OK	>95%	Accept
either one of criteria not fulfilled on initial test		<5%	Repeat acceptance test protocol
either one of criteria not fulfilled on repeat test		<0.25%	Initiate root cause analysis

Limitations

- P0067 ViraQ HCV Trend 25 Control cannot be used to determine the analytical or diagnostic sensitivity of NAT blood screening assays (although changes in analytical sensitivity of the NAT system can become apparent with the trend control).
- 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 nonreactive 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 distributions of assay response values on P0067 ViraQ HCV Trend 25 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 $\Delta(S/CO_{M-A})$ as performance indicator of Ultrio (Plus and Elite) assays and the proposed threshold value of 1.60 above which a deterioration of the test system is possible needs to be further evaluated and confirmed in post-market performance follow up studies.
- The decision algorithm for acceptance testing of NAT system components was based on testing of a limited number of Ultrio Plus and Elite reagent lots. The validity of the acceptance criteria need to be confirmed by testing more Ultrio Plus and Elite reagent lots on the P0067 HCV trend control in multiple replicates

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