

Bio

QCControl

P0068
ViraQ HIV-1 Trend 25

CE
0088

IVD

REF P0068



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

P0068 ViraQ HIV-1 Trend 25 is intended to be used as external trend control for human immunodeficiency virus type 1 (HIV-1) RNA detection by the multiplex transcription mediated amplification (TMA) assays on the automated nucleic acid amplification technology (NAT) plat-forms defined in Table 1. The trend control helps laboratories to ensure that HIV-1 is detected with sufficient analytical sensitivity by consecutive reagent batches 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 batches
- installation qualification of instruments
- training of technicians.

Table 1. Test kits and platforms covered by P0068 ViraQ HIV-1 Trend 25 control

Platform	Test kits	Test environment
Grifols Procleix Tigris®	Procleix Ultrio®	Blood screening
	Procleix Ultrio Plus®	
Grifols Procleix Panther®	Procleix Ultrio Elite®	

The run control should not be used to replace the internal controls or calibrators in the test kits.

Key to Symbols Used



Manufacturer



Lot number



Catalogue number



Store below -30°C



CE mark with Notified Body number



Caution



In vitro diagnostic medical device



Expiry date



Contents



Biological substance Category B



Read instructions for use

Principle of method

P0068 ViraQ HIV-1 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 HIV-1 RNA (equivalent to 43 International Units (IU)/mL) and has been designed to ensure sufficient analytical sensitivity of transcription mediated amplification (TMA) tests in blood screening laboratories. The HIV-1 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. P0068 ViraQ HIV-1 Trend 25 Control enables laboratories to be alerted in case of a reduction of analytical sensitivity of NAT instruments or reagent batches and to identify changes in

TMA performance over time. The run control is a dilution of the S0041 HIV-1-RNA subtype B standard, prepared by heat-inactivation of tissue culture derived virus spiked in plasma⁶⁻⁸. 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 S0041 HIV-1 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 HIV-1 subtype B in the run control is meant to be representative for HIV-1 genotypes A-K and circulating recombinant forms that are prevalent in different geographical regions of the world (although not all genetic variants are detected with comparable analytical sensitivity by the commercial NAT assays)^{4,9-11}. 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 samples 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 batches 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 HIV-1 standard dilution panels in Procleix Ultrio assay versions

standard	panel	NAT method	n	50% LOD (CI) cp/mL	95% LOD (CI) cp/mL
S0041 BioQ HIV-1 RNA subtype B inact.	P0026	Ultrio	52	3.1 (2.4-3.9)	20.2 (13.9-33.3)
S0012 VQC-Sanquin HIV-1 RNA subtype B	P0025	Ultrio	60	1.5 (1.0-2.2)	11.2 (6.3-29.8)
	P0025	Ultrio Plus	48	1.7 (1.3-2.2)	15.1 (9.9-26.9)
	P0025	Ultrio Elite	24	2.1 (1.5-2.9)	9.0 (5.8-19.5)
WHO HIV-1 RNA 97/650 [#]	P0022	Ultrio	40	2.6 (2.1-3.3)	11.8 (8.2-20.7)
	P0022	Ultrio Plus	288	2.4 (2.2-2.6)	13.4 (11.4-16.3)
	P0022	Ultrio Elite	229	2.2 (1.4-3.2)	17.2 (10.3-40.1)

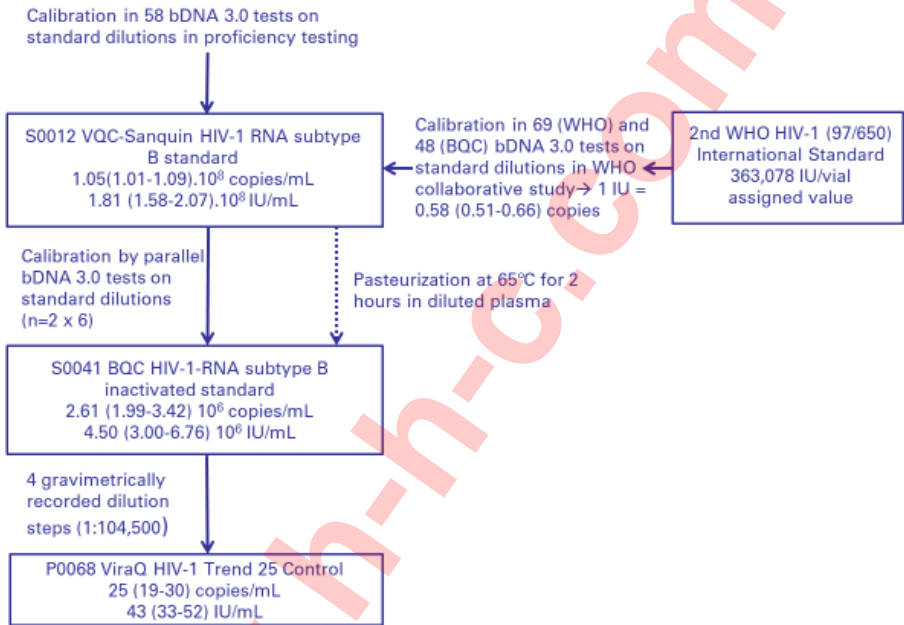
1 IU = 0.58 copy

Traceability to HIV-1 RNA copies and International Units

Figure 1 shows the traceability chain between the ViraQ trend control, the Bio Quality Control (BQC) standard, VQC-Sanquin standard and the 2nd WHO 97/650 International Standard for HIV-1 RNA. The inactivated S0041 HIV-1 RNA standard (used for preparation of the P0068 ViraQ trend control) has been calibrated in copies/mL by replicate testing in the Siemens Versant bDNA 3.0 assay¹² against the historically established S0012 VQC-Sanquin HIV-1 RNA subtype B standard¹³. The VQC-Sanquin HIV-1 RNA subtype B standard has been calibrated at 0.58 (0.51-0.66) copies per IU against the second WHO HIV-1 RNA 97/650 standard in multiple replicate bDNA 3.0 assays¹⁴⁻¹⁶. It must be emphasized that this conversion factor from copies to IU values was 0.39 (0.34-0.44) for the 1st WHO HIV-1 97/656 standard and has not been determined for the 3rd WHO 10/152 replacement standard¹⁴. The accurate calibration of the native VQC-Sanquin and inactivated BQC HIV-1 subtype B standards in copies/mL and IU/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 HIV-1 Trend 25 batches¹⁷. The inactivated BQC HIV-1 subtype B standard is available in sufficient supply to ensure batch to batch consistency of ViraQ trend controls for a prolonged period of time.

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



Stability of HIV-1 standards and run control

The long term stability of the liquid frozen S0041 HIV-1 standard stored below -65°C has been firmly established¹⁸; hence the stock solution from which the trend 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 HIV-1 RNA per year in P0064 ViraQ HIV-1 Check 125 control (and in standard dilutions of higher concentration) when stored at -30°C¹⁸. 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)^{17,18}.

Kit contents (materials provided)

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

P0068/01 and P0068/02 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	Description of contents	Primary packing	Secondary packing
P0068/01	60 x 1.5 mL run control	10 mL vial	60 vial rack in box
P0068/02	10 x 1.5 mL run control	10 mL vial	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 years¹⁷. Once thawed the run control samples should be used within 8 hours. During this period, when not in use, store sample at 2-8°C¹⁷. 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 P0068 ViraQ HIV-1 Trend 25 contains inactivated HIV-1 particles⁶⁻⁹ 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. 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 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 P0068 ViraQ HIV-1 Trend 25. The statistical evaluation methods were developed by BioQ Control and not reviewed nor approved by the manufacturer of the Ultrio assay versions.

The results of the Procleix Ultrio, Ultrio Plus and Ultrio Elite assays are expressed as a sample to cut-off ratio (S/CO). P0068 ViraQ HIV-1 Trend 25 Control should react positive in approximately 95% of TMA test runs. Approximately 80% 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 8.0 (range 7.0-9.0). Approximately 15% of test results are expected in the dynamic range of the TMA assay with S/CO ratios below 8.0 (see interpretation of test results below)¹⁷.

The S/CO responses on ViraQ HIV-1 Trend 25 in the Ultrio Plus and Elite assay versions are not normally distributed (figure 2). A Gumbel distribution is more suitable to describe the data. From this type of extreme value distribution it follows that the difference between the median and the average of S/CO values is an indicator of the skewness of the distribution curve. Hence, the value of this parameter $\Delta(S/CO_{M-A})$ becomes higher with lower analytical sensitivity of the NAT system and can be used for trend analysis or comparison of experimental conditions (see interpretation of test results below)¹⁷.

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

The expected frequency of S/CO values on P0068 ViraQ HIV Trend 25 control in the dynamic and saturated range of the TMA assay as well as the interpretation of three categories of test result are shown in table 4. The majority of S/CO values on the run control reach maximum TMA response levels and are found between 8.0 and 11.0 (figure 2). Approximately 15-17% 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 8.0). The threshold S/CO value between dynamic and saturated response levels varies over time (between 7.0 and 9.0) and is dependent on the Ultrio (Plus and Elite) reagent batch¹⁷. This affects the frequency of S/CO response values above and below the arbitrarily chosen threshold value of 8.0. In a four year observation period of 2689 Ultrio (Plus and Elite) test runs the overall proportion of reactive results was 96.0%, but the reactivity rate varied between TMA and trend control reagent batch combinations (table 5)¹⁷.

Table 4. Interpretation of a single TMA test result on P0068 ViraQ HIV-1 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 saturated	>8.0	795 – 867	The test signal on the trend control reaches maximum values in the saturated range of the TMA assay. This is an expected result.
Reactive dynamic	1.0–8.0	120 – 149	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	28-42	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 P0068 ViraQ HIV-1 Trend 25 Control (TC) batches in consecutive Ultrio (U), Ultrio Plus (UP) and Ultrio Elite (UE) reagent batches.

TMA batch	Trend Control batch	reactive/n	% reactive	delta (95%CI) % to overall %
U	TC1	180/200	90.0%	-5.5 (-6.9,-4.1)%
UP1	TC1	70/73	95.9%	0.4 (-0.6, 1.3)%
	TC1 All	250/273	91.6%	-4.0 (-2.9, -5.0)%
UP1	TC2	99/100	99.0%	3.5 (3.2,3.7)%
UP1 All		169/173	97.7%	2.2 (1.8, 2.5) %
UP2	TC3	67/67	100.0%	4,5 (4.3,4.6)%
UP3	TC3	172/179	96.1%	0.6 (0.0,1.2)%
UP4	TC3	202/204	99.0%	3.5 (3.3,3.7)%
UP5	TC3	219/228	96.1%	0.5 (0.0,1,1)%
UP6	TC3	89/89	100.0%	4.5 (4.3,4.6)%
UP7	TC3	90/91	98.9%	3.4 (3.1,3.7)%
	TC3 All	839/858	97.8%	2.3 (2.0,2.5)%
UP All		1293/1330	97.2%	1.7 (1.5,1.9)%
UE1	TC4	120/139	86.3%	-9.2 (-6.9, -11.5)%
UE2	TC4	338/355	95.2%	-0.3 (-0.8,0.2)%
UE3	TC4	67/73	91.8%	-3.8 (-5.7,-1.8)%
	TC4 All	525/567	92.6%	-2.9 (-2.6, -2.6)%
UE3	TC5	445/452	98.5%	2.9 (2.7,3.1)%
UE4	TC5	139/140	99.3%	3.8 (3.5,4.0)%
	TC5 All	584/592	98.6%	3.1 (2.9,3.3)%
UE All		1109/1159	95.7%	0.2(-0.1, 0.5)%
U, UP, UE All		2582/2689	96.0%	reference

Monitoring performance of Procleix Ultrio assay versions on trend control

The difference between the median and the average of S/CO values can be used as an indicator of the analytical sensitivity of the NAT system (table 6). To illustrate this the mean and median at each time point of testing of the run control was calculated for 50 earlier and 50 later S/CO measurements and the same was done for the proportion reactive and proportion of saturated reactive responses (figure 3). From the sliding values it can be seen that the highest values of Δ (median S/CO – average S/CO) coincided with the lowest proportions of saturated responses. Based on the available results one may conclude that $\Delta(S/CO_{M-A})$ should be below 0.80 when the system is properly functioning¹⁷. The presence of non-reactive results also coincides with high values of $\Delta(S/CO_{M-A})$, thereby confirming its ability to be a trend indicator for analytical performance of the TMA assay. An alert threshold value for this parameter that is indicative for poor NAT performance cannot be given with the available data.

Table 6. Reproducibility of Ultrio (Plus and Elite) S/CO values on P0068 ViraQ HIV-1 Trend 25 control

n test runs	Median S/CO	Average S/CO	$\Delta(S/CO_{M-A})$	S/CO Percentile	
				95%	99%
2689	8.79	8.32	0.47	0.69 – 10.59	0.11 – 12.58

The parameter $\Delta(S/CO_{M-A})$ can also be applied to compare other experimental conditions such as the TMA reagent batch, 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 4 comparing different TMA/trend control batch combinations¹⁷. [Note that in this case, all data per experimental condition are used without ‘sliding’]. The result shows that the values of $\Delta(S/CO_{M-A})$ for TMA/trend control reagent batch combinations correlate with the reactivity rates. Hence, if the reagent batch 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 (or trend control) batch.

Figure 2. Distribution of S/CO values in Ultrio Plus and Elite test runs on P0068 ViraQ HIV-1 Trend 25 control

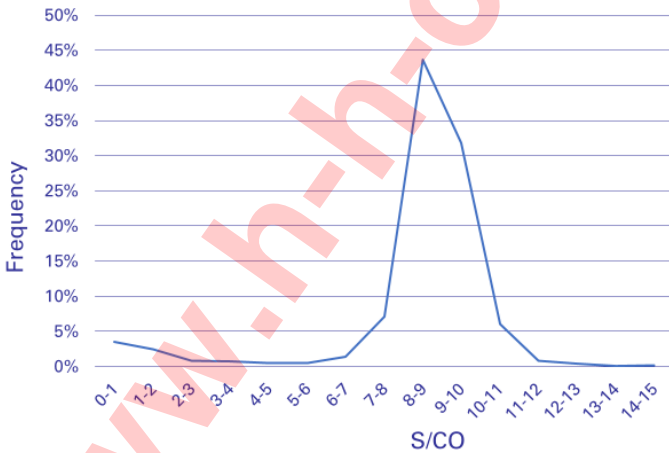


Figure 3. Sliding course of $\Delta(S/CO_{M-A})$ over time in relation to proportions reactive and saturated reactive on P0068 ViraQ HIV-1 Trend 25 Control. [Each data point represents a value derived from 50 S/CO measurements before and 50 S/CO measurements after the retrospective monitoring date].

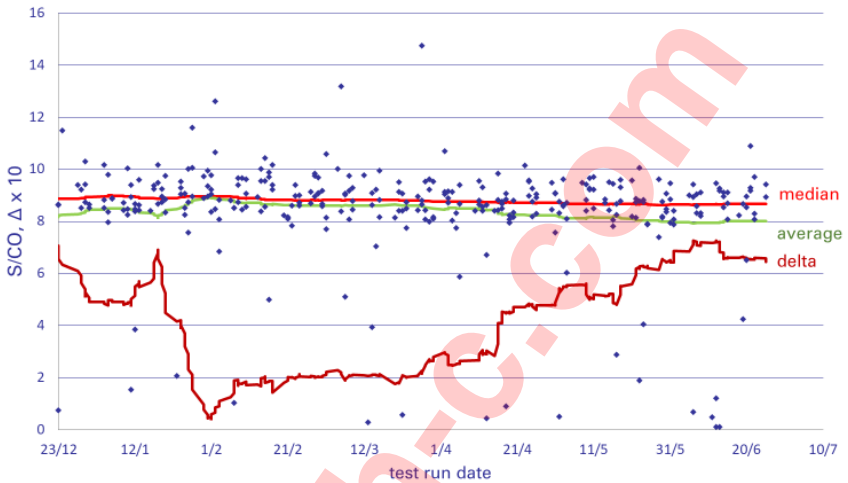
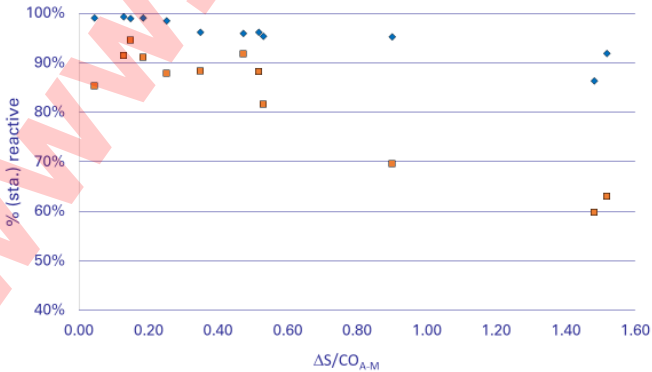


Figure 4. Correlation between $\Delta(S/CO_{M-A})$ and proportion reactive (diamonds, $S/CO \geq 1.0$) and saturated (squares, $S/CO \geq 8.0$) response levels observed with different Ultrio, Ultrio Plus and Ultrio Elite reagent batches on P0068 ViraQ HIV-1 Trend 25 control. Each point represents a TMA/trend control batch combination.



Acceptance testing of NAT system component using trend control

P0068 ViraQ HIV-1 Trend 25 can also be used for acceptance testing of a new TMA reagent batch, 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 batch, instrument or operator performance is approved when at least 17/20 (85%) of tests are reactive and the median S/CO value is above 8.1. 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 2689 Ultrio Plus and Elite test runs¹⁷. The decision algorithm for accepting the NAT system component is summarized in table 7.

Table 4. Decision algorithm and criteria for acceptance of reagents, instruments or operators by replicate testing of 20 vials of P0068 ViraQ HIV-1 Trend 25 control in one Procleix Ultrio (Plus or Elite) assay run

Acceptance criteria		Expected frequency	Decision
reactivity rate ≥17/20 (85%)	Median S/CO ≥8.1		
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

- P0068 ViraQ HIV-1 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).
- P0068 ViraQ HIV-1 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 P0068 ViraQ HIV-1 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 P0068 ViraQ HIV-1 Trend 25 Control that are presented in this package insert were based on evaluation studies involving a limited number of tests and NAT reagent batches. Therefore it cannot be guaranteed that slightly different results will be found on other assay versions or NAT reagent batches.
- The parameter $\Delta(S/CO_{M-A})$ as performance indicator of Ultrio (Plus and Elite) assays and the proposed threshold value of 0.80 above which a deterioration of the test system is possible needs to be further evaluated and confirmed in post-market surveillance studies.

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