



P0154

ViraQ HBV Trend 50



REF P0154



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

P0154 ViraQ HBV Trend 50 is intended to be used as external trend control for hepatitis B virus (HBV)-DNA 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 HBV 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:



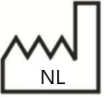




- acceptance (transport integrity) testing of TMA reagent lots
- installation qualification of instruments
- training of technicians.

Table 1. Assays and platforms covered by P0154 ViraQ HBV Trend control

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

P0154 ViraQ HBV Trend 50 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

P0154 ViraQ HBV Trend 50 control has been formulated to mimic natural plasma specimens with a low HBV-DNA 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 50 copies/mL of HBV-DNA (equivalent to 9.4 International Units (IU)/mL) and has been designed to ensure sufficient analytical sensitivity of transcription mediated amplification (TMA) tests in blood screening laboratories. The HBV-DNA 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. P0154 ViraQ HBV Trend 50 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 S0043 HBV-RNA genotype A2 standard, prepared by heat-inactivation of a pool of HBsAg plasma units from the same

donor⁶⁻⁸. 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 S0043 HBV standard has been calibrated in copies/mL and IU/mL against the Viral Quality Control (VQC)-Sanquin, Eurohep and World Health Organization (WHO) International Standards (figure 1). The low concentration of HBV genotype A in the run control is representative for HBV Genotypes A to H that are prevalent in different geographical regions of the world (and that are detected with similar analytical sensitivity by the above mentioned TMA assays)^{4,9}. 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 HBV standard dilution panels in Procleix Ultrio assay versions

standard	panel	NAT method	n	50% LOD (CI) cp/mL	95% LOD (CI) cp/mL
S0043 BioQ HBV-DNA genotype A inact.	P0031	Ultrio Plus	24	6.6 (2.7-17.4)	64 .2 (22.4-1099)
	P0031	Ultrio Elite	25	5.7 (4.0-8.2)	40.8 (24.3-91.7)
	P0031	Ultrio Plus/Elite	49	7.6 (5.9-9.5)^	33.3 (23.8-56.4)^
S0011 VQC-Sanquin HBV-DNA genotype A	P0007	Ultrio Plus	48	4.8 (3.7-6.2)	38.8 (25.6-68.5)
	P0007	Ultrio Elite	74	3.4 (2.3-4.8)	43.2 (24.8-98.0)
	P0007	Ultrio Plus/Elite	122	4.3 (2,9-6,1)^	35.4 (20,6-87,8)^
S0010 Eurohep HBV- DNA genotype A	P0001	Ultrio Plus	96	3.6 (2.9-4.4)	40.4 (29.2-60.2)
	P0001	Ultrio Elite	24	7.9 (5.5-11.2)	49.1 (29.4-116)
WHO HBV-DNA 97/750 [#]	P0023	Ultrio Plus	303	4.4 (3.3-5.9)	28.4 (18.0-57.7)
	P0023	Ultrio Elite	252	4.4 (3.6-5.4)	30.9 (22.4-47.4)

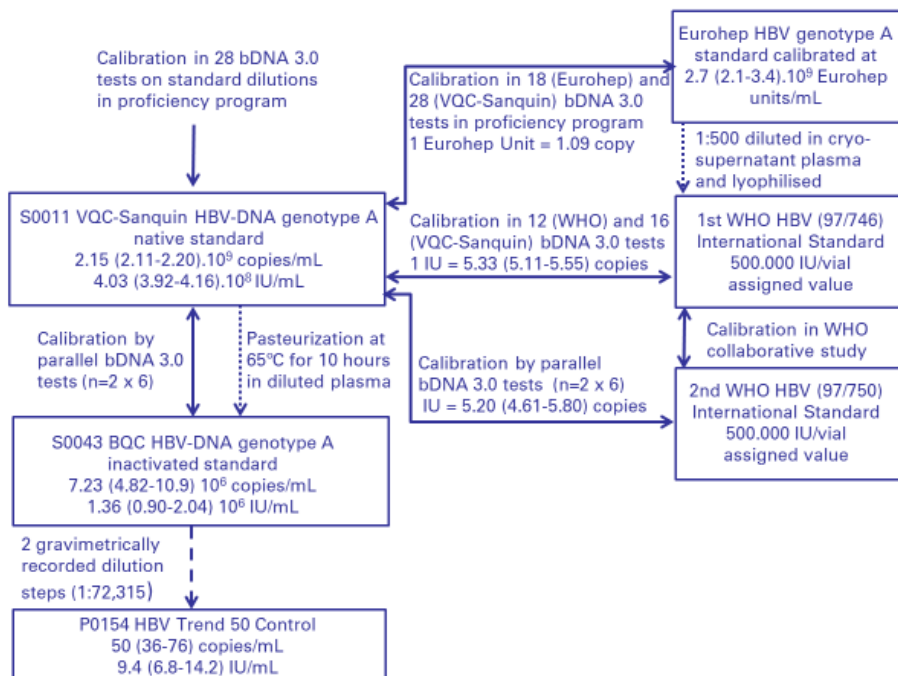
^ probit analysis without two lowest concentrations in dilution panel. # 1 IU = 5.33 copies

Traceability to HBV-DNA copies and International Units

Figure 1 shows the traceability chain between the ViraQ run control, the Bio Quality Control (BQC) standard, VQC-Sanquin standard, the Eurohep standard and the 1st and 2nd WHO 97/746 and 96/750 International Standards for HBV-DNA. The inactivated S0043 HBV-DNA standard (used for preparation of the P0154 ViraQ Trend control) has been calibrated in copies/mL by replicate testing in the Siemens Versant bDNA 3.0 assay¹⁰ against the historically established S0011 VQC-Sanquin HBV-DNA genotype A standard¹¹. The VQC-Sanquin HBV-DNA genotype A standard has been calibrated at 5.33 (5.11-5.55) and 5.20 (4.61-5.80) copies per IU against the first and second WHO HBV-DNA (97/746 and 97/750)

standards respectively in two experiments¹². It must be emphasized that this conversion factor from copies to IU values has not been confirmed for the later 3rd WHO 10/264 replacement standard. The copy number assigned to the VQC-Sanquin standard was found to be comparable to that of the Eurohep standard¹³ used for preparation of the WHO standards¹⁴. The accurate calibration of the VQC-Sanquin and the inactivated BQC standard against the WHO and Eurohep standards in IU/mL and in copies/mL has been confirmed in analytical sensitivity studies of the Grifols Procleix TMA and Roche cobas MPX assays^{4,12}. The BQC manufacturing and quality control procedures guarantee consistent virus concentrations in consecutive ViraQ HBV Trend 50 batches¹⁵. The inactivated BQC HBV genotype A 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 trend control, BQC and VQC-Sanquin standards and WHO International Standards



Stability of HBV standards and run control

The long term stability of the liquid frozen S0043 HBV standard stored at $\leq 65^{\circ}\text{C}$ has been firmly established¹⁶; 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 no degradation of HBV-DNA in P0065 ViraQ HBV Check 125 control and P0069 HBV Trend 25 control when stored at -30°C ¹⁶. Hence, it can be guaranteed that also the P0154 trend control is still functional and should generate a reactivity rate above 95% when stored at -30°C and used before the expiration date (two years after preparation of the run control batch)^{15,16}.

Kit contents (materials provided)

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

P0154/01 and P0154/02 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 HBV. 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
P0154/01	8718719831540	60 x 1.5 mL	10 mL	60 vials in rack/box
P0154/02	8718719832110	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 years¹⁶. 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 P0154 ViraQ HBV Trend 50 contains inactivated HBV particles⁶⁻⁸ the plasma may still be potentially bio-hazardous. The matrix is prepared from human blood plasma that tested negative for blood borne viruses (HBV-DNA, HCV-RNA, HIV-RNA, HBsAg, anti-HBc, anti-HBs, anti-HIV, anti-HCV and anti-Treponema *pallidum*). No test method can offer complete assurance that products derived from human blood cannot transmit (unknown) infectious agents. The run control should only be used by trained laboratory workers who are aware of the potential risk of infectious agents in human plasma samples and take the necessary precautions. Observe the universal precautions for prevention of transmission of infectious agents when handling these materials^{17,18}.

- 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 P0154 ViraQ HBV Trend 50. The statistical evaluation methods were developed by BioQControl and not reviewed nor approved by the manufacturer of the Ultrio assay versions.

Qualitative detection of HBV-DNA in Procleix Ultrio versions

The results of the Procleix Ultrio Plus and Ultrio Elite assays are expressed as a sample to cut-off ratio (S/CO). P0154 ViraQ HBV Trend 50 Control should react positive in approximately 95 to 99 % of TMA test runs. Approximately 93-95% 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 12.0. Approximately 3-5% of test results are expected in the dynamic range of the TMA assay with S/CO ratios below 12.0 (see interpretation of test results below)¹⁵. 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 HBV Trend 50 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 rules¹⁹ 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 P0154 ViraQ HBV Trend 50 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 12.0 and 17.0 (figure 2). A minority of 3-5% of TMA reactions on the trend control are not yet complete and have S/CO values in the lower dynamic range of the assay (between 1.0 and 12.0).

When one batch of P0154 HBV Trend 50 control was tested in parallel with one batch of P0069 HBV Trend 25 control (which contains 25 instead of 50 copies/mL) in two Ultrio Elite reagent lots the overall proportions of reactive results were 98.3% and 92.6% respectively (table 5a)¹⁶.

In a four year observation period of 2410 Ultrio (Plus and Elite) test runs the overall proportion of reactive results was 98.8%, but the reactivity rate varied between TMA reagent lot and trend control batch combinations (table 5b)¹⁶. The data on P0154 ViraQ Trend 50 control showed a small but significant difference in the overall reactivity rates between Ultrio Plus and Ultrio Elite reagent lots (99.4% versus 98.1%).

Table 4. Interpretation of a single TMA test result on P0154 ViraQ HBV Trend 50 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	>12.0	930 – 950	The test signal on the trend control reaches maximum values in the (near) saturated range of the TMA assay. This is an expected result.
Reactive lower dynamic	1.0–12.0	30 –50	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	20-30	The test signal on the run control is below the cut-off. This is an expected result

Table 5a. Comparison of reactivity rate on HBV Trend Control (TC) batches of 50 and 25 copies/mL in two Ultrio Elite (UE) reagent lots.

Ultrio Elite lot	P0154 ViraQ HBV 50			P0069 ViraQ HBV 25		
	Trend control batch	reactive/n	%	Trend control batch	reactive/n	%
UE1	TC4	427/434	98.5%	TC1	54/58	93.1%
UE2	TC4	138/141	97.9%	TC1	122/132	92.4%
UE all	TC4	565/575	98.3%	TC1	176/190	92.6%

Table 5a. Proportion of reactive results in daily test runs on P0154 ViraQ HBV Trend 50 Control batches in consecutive, Ultrio Plus (UP) and Ultrio Elite (UE) reagent lots.

TMA lot	Trend Control batch	reactive/n	% reactive	delta (95%CI) % to overall %
UP1	TC1	102/103	99.0%	0.3 (0.1,0.5)%
UP2	TC1	297/299	99.3%	0.6 (0.5,0.7)%
	TC1 All	399/402	99.3%	0.5 (0.4,0.6)%
UP2	TC2	66/67	98.5%	-0.2 (-0.6,0.1)%
UP2 All		363/366	99.2%	0.4 (0.3,0.5)%
UP3	TC2	179/179	100.0%	1.2 (1.2,1.3)%
UP4	TC2	203/204	99.5%	0.8 (0.7,0.8)%
UP5	TC2	227/228	99.6%	0.8 (0.7,0.9)%
UP6	TC2	90/90	100.0%	1.2 (1.2,1.3)%
UP7	TC2	89/91	97.8%	-1.0 (-1.4,-0.5)%
	TC2 All	854/859	99.4%	0.7 (0.6,0.7)%
UP All		1253/1261	99.4%	0.6 (0.5,0.7)%
UE1	TC3	132/132	100.0%	1.2 (1.2,1.3)%
UE2	TC3	345/355	97.2%	-1.6 (-1.9,-1.3)%
UE3	TC3	85/87	97.7%	-1.1(-1.5,-0.6)%
	TC3 All	562/574	97.9%	-0.8(-1.0,-0.7)%
UE3	TC4	427/434	98.4%	-0.4(-0.5,-0.2)%
UE3 All		512/521	98.3%	-0.5(-0.6,-0.3)%
UE4	TC4	138/141	97.9%	-0.9(-1.2,-0.5)%
	TC4 All	565/575	98.3%	-0.5(-0.6,-0.3)%
UE All		1127/1149	98.1%	-0.7(-0.8,-0.5)%
UP, UE All		2380/2410	98.8%	reference

Monitoring performance of Procleix Ultrio assay versions on trend control

Figure 2 shows Ultrio Elite performance data on P0154 ViraQ HBV Trend 50 obtained during six months of testing by one national blood service in a Levey-Jennings QC Chart.

Figure 2. Levey-Jennings chart of P0154 ViraQ HBV Trend 50 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.

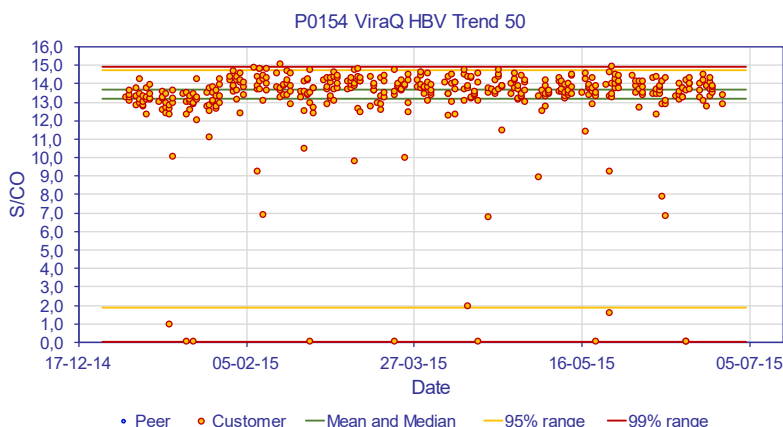


Table 6 presents the same Ultrio Elite data as presented in Figure 2 as well as a larger set of earlier obtained Ultrio Plus and Elite data presented in table 5.

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 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 0.60 the system is properly functioning¹⁵. 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. 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 Elite S/CO values on P0154 ViraQ HBV Trend 50 control

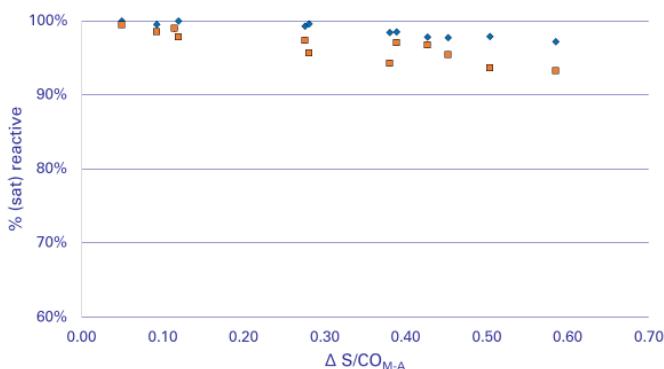
n test runs	Median S/CO	Average S/CO	$\Delta(S/CO_{M-A})$	S/CO Predictive interval	
				95%	99%
425#	13.68	13.21	0.47	1.86 – 14.75	0.05 – 14.93
1149^	13.56	13.03	0.53	2.26 – 14.80	0.06 – 15.30

#Ultrio Elite data if figure 2 ^Ultrio Elite data of table 5b

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 lots¹⁵. The result shows that the values of $\Delta(S/CO_{M-A})$ for TMA reagent lot/trend control batch combinations 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 4. Correlation between $\Delta(S/CO_{M-A})$ and proportion reactive (diamonds, $S/CO \geq 1.0$) and (near) saturated (squares, $S/CO \geq 12.0$) response levels observed with different Ultrio Plus and Ultrio Elite reagent lots on P0154 ViraQ HCV Trend 50 control. Each point represents a TMA reagent lot/trend control batch combination.



Acceptance testing of NAT system component using trend control

P0154 ViraQ HBV Trend 50 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. Since a small difference was found between the analytical sensitivity of the Ultrio Plus and Ultrio Elite assays the acceptance criteria are assumed to be different for the two assay versions (table 7). For the Ultrio Elite assay the reagent lot, instrument or operator performance is approved when at least 18/20 (90%) of tests are reactive and the median S/CO value is above 13.0. 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 recommended. These acceptance criteria were established by a simulation study with sliding sets of 20 sequential results out of a data base of only 1139 Ultrio Elite test runs¹⁵. This preliminary 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 P0154 ViraQ HBV Trend 50 control in one Procleix Ultrio (Plus or Elite) assay run

Acceptance criteria		Expected frequency	Decision
Ultrio Plus reactivity rate $\geq 19/20$ (95%)	Ultrio Plus Median S/CO ≥ 13.9		
Ultrio Elite reactivity rate $\geq 18/20$ (90%)	Ultrio Elite Median S/CO ≥ 13.0		
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

- P0154 ViraQ HBV Trend 50 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).
- P0154 ViraQ HBV Check 50 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 P0154 ViraQ HBV Trend 50 Control cannot be used to invalidate a test run. The Poisson distribution in samples with low HBV 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 P0154 ViraQ HBV Trend 50 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 0.60 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 P0154 HBV trend control in multiple replicates.

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