Bio QControl

P0065
ViraQ HBV Check 125

CE 0088

IVD

REF P0065

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

Table of contents

Intended Use

P0065 ViraQ HBV Check 125 is intended to be used as external run control for hepatitis B virus (HBV)-DNA amplification assays in combination with the test kits on the plat-forms defined in Table 1. The run control helps laboratories to ensure sufficient analytical sensitivity and consistent performance of:

- qualitative multiplex nucleic acid amplification tests (NAT) for blood screening
- quantitative NAT methods with a lower limit of quantification (LOQ) sufficiently below the run control concentration of 125 copies/mL (~ 23 International Units (IU)/mL)

Table 1. Test kits and platforms covered by P0065 ViraQ HBV Check 125 run control

Platform	Test kits	Test environment
Grifols Procleix Tigris®	Procleix ULTRIO Plus®	Blood screening
Grifols Procleix Panther®	Procleix ULTRIO Elite®	
Hologic Panther	Aptima HBV Quant Dx	Viral load monitoring

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

P0065 ViraQ HBV Check 125 control has been formulated to mimic natural plasma specimens with a low HBV-DNA concentration. After thawing the run control tubes are ready for use and can be placed at random positions in sample racks on the NAT platforms. The run control contains 125 copies/mL of HBV-DNA (equivalent to 23 IU/mL) and has been designed to ensure sufficient analytical sensitivity of transcription mediated amplification (TMA) tests in blood screening laboratories. The run control is also suitable for monitoring performance of quantitative HBV-DNA assays in diagnostic laboratories using real time TMA or polymerase chain reaction (PCR) methods. The HBV-DNA concentration in the run control has been set at ~4 times the 95% lower limit of detection (LOD) of the Ultrio (Plus and Elite) assays (table 2)[1-5] and at 2.4-4.3 times the LOQ of the above mentioned quantitative NAT assays[5]. The positioning of P0065 ViraQ HBV Check 125 control ensures reactivity rates above 99.5% in the NAT systems listed in table 1. The run control enables laboratories to be alerted in case of a significant reduction of analytical sensitivity of NAT test systems and to identify changes in the (precision of) viral

load tests over time. The run control is a dilution of the S0043 HBV-RNA genotype A2 standard, prepared by heat-inactivation of a pool of HBV positive plasma units from the same donor[6-8]. 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 commercial NAT assays)[4,9]. A positive (and quantifiable) result on the run control indicates that the NAT method has been performed with sufficient analytical sensitivity. A non-reactive result or a weakly reactive result (below the LOQ) is indicative of reduced analytical sensitivity of the NAT system and should trigger investigation of the technical performance of the assay. The run control generates sample to cut-off (S/CO) ratios in the Procleix Ultrio assay versions and Ct values or viral loads (expressed in IU/mL) in quantitative TMA and real time PCR assays. Statistical analysis of these assay response values generated over a certain period of time allows for comparison of analytical performance of NAT reagent batches and laboratory instruments.

Table 2. Detection limits on native and inactivated 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)

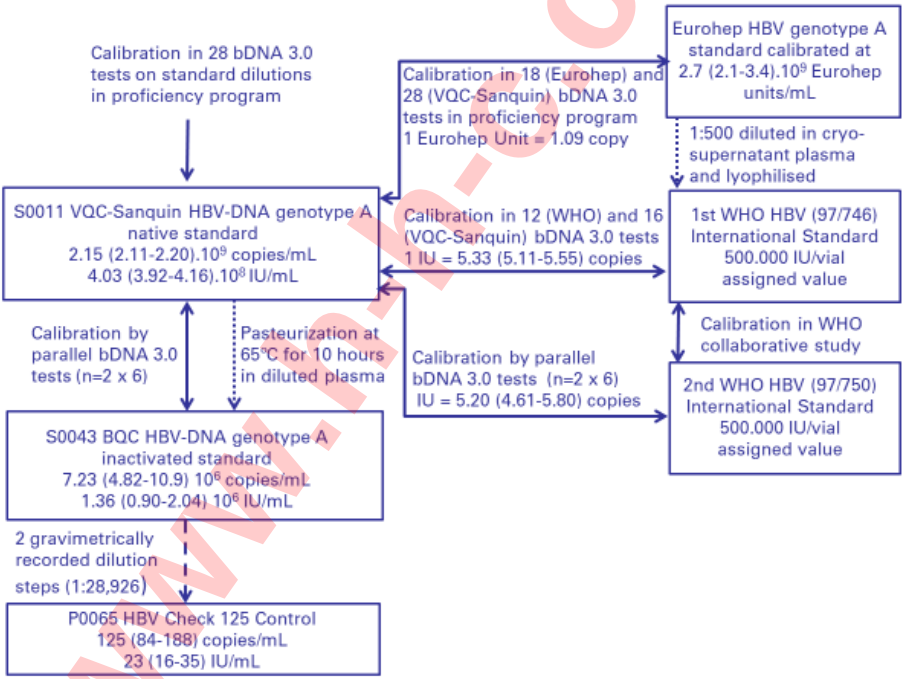
^ probit analysis without two lowest concentrations in panel P0031 # 1 IU = 5.33 copies

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 P0065 ViraQ run control) has been calibrated in copies/mL by replicate testing in the Siemens Versant bDNA 3.0 assay[10] against the historically established S0011 VQC-Sanquin HBV-DNA genotype A standard[11]. 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 experiments[12]. 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 standard[13] used for preparation of the WHO standards[14]. 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 Check 125 batches[15]. The inactivated BQC HBV genotype A 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 HBV standards and run control

The long term stability of the liquid frozen S0043 HBV standard stored at ≤65˚C has been firmly established[16]; hence the stock solution from which the run control is prepared has shown to be stable in the BQC storage facilities. Real time stability experiments using quantitative NAT assays showed no degradation of HBV-DNA in P0065 ViraQ HBV Check 125 control when stored at -30˚C[16]. Hence, it can be guaranteed that the run control is still functional and should generate a reactivity rate greater than 99.5% when stored at -30˚C and used before the expiration date (two years after preparation of the run control batch)[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.

P0065/01 and P0065/02 are intended to accommodate both blood screening and diagnostic laboratories. To facilitate automation the run control is presented in a polypropylene tube with screw cap comparable in size to vacutainer tubes used for donor sample collection. The tube label has a barcode identifying the product, sequential batch number and marker HBV. The barcode can be read by the automated NAT systems.

P0065/03 is intended to accommodate molecular diagnostic laboratories using smaller vials in routine procedures. The vial label does *not* have a barcode; the control should be identified on the work list.

Table 3. Description of kit formats and contents

Cat. Code	Description of contents	Primary packing	Secondary packing
P0065/01	60 x 1.5 mL run control	10 mL vial	60 vial rack in box
P0065/02	10 x 1.5 mL run control	10 mL vial	Plastic zip bag
P0065/03	10 x 1.5 mL run control	2 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 run controls should be stored at or below -30°C for a maximum of two years[16]. 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[16]. 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 P0065 ViraQ HBV Check 125 contains inactivated HBV particles[6-8] 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. 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 run control should be tested in a manner identical to that of clinical specimens and the result be calculated according to the instructions for use of the NAT procedure.

The following sections in this package insert provide guidance on interpretation and analysis of test results on P0065 ViraQ HBV Check 125. The statistical evaluation methods were developed by BioQ Control 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, Ultrio Plus and Ultrio Elite assays are expressed as a sample to cut-off ratio (S/CO). P0065 ViraQ HBV Check 125 Control should react positive in more than 99.5% of TMA test runs. More than 98% of test results on the run control are expected in the saturated range of the TMA assay with S/CO values equal to or above 12.0 (range 11.0-13.0). Less than 2% of results are expected in the dynamic range of the TMA assay with S/CO rations below 12.0 (range 11.0-13.0) (see interpretation of test results below)[15].

The S/CO responses on ViraQ HBV Check 125 in the Ultrio Plus and Elite assay versions are not normally distributed. 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)[15].

Quantitative detection of HBV-DNA by viral load assays

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

Levey-Jennings QC chart.

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

The quantitative values for [HBV-DNA] are 'log normal' distributed.

- Calculate from each measurement the log(concentration) in IU/mL or copies/mL.
- Calculate mean and SD on these log values

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

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

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

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

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

Use the Westgard rules[19] to identify deviations in the Levey Jennings trend analysis.

Comparison of variation in quantitative values between result sets

For this analysis result sets could represent e.g. laboratory, reagent batch, instrument, operator, etcetera.

The cumulative Chi-square distribution is used to calculate the probability that the SD of the test population (s) is different from the SD of reference population (σ):

- n is number of measurements over the evaluated period
- Within the set evaluated: calculate SD on the log(concentration): s
- Within the reference set: calculate SD on the log(concentration): σ.
- Calculate $X^2 = (n-1)\frac{s^2}{\sigma^2}$

Use table 5 to determine if the precision of the quantitative NAT method has significantly changed.

Table 5. Chi-square (X^2) values for p=0.05

n-1 (df)	X^2	n-1 (df)	X^2	n-1 (df)	X^2
11	19.69	21	32.67	40	55.76
12	21.04	22	33.92	50	67.51
13	22.36	23	35.17	60	79.08
14	23.69	24	36.42	70	90.53
15	25.00	25	37.65	80	101.88
16	26.30	26	38.89	90	113.15
17	27.59	27	40.11	100	124.34
18	28.87	28	41.34		
19	30.14	29	42.56		
20	31.41	30	43.77		

Interpretation:
Chi-square: $X^2_{(Calculated)} < X^2_{(P=0.05)}$: precision is not significantly changed.
Chi-square: $X^2_{(Calculated)} \geq X^2_{(P=0.05)}$: precision has changed significantly.

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

The expected frequency of S/CO values on P0065 ViraQ HBV Check 125 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 6. The vast majority of S/CO values on the run control reach maximum TMA response levels and are found between 11.0 and 16.0 (figure 2). Only a small fraction of TMA reactions on the run control are not yet complete and have S/CO values in the dynamic range of the assay (between 1.0 and 12.0). The threshold S/CO value between dynamic and saturated response levels varies over time and is dependent on the Ultrio (Plus and Elite) reagent batch[15]. This affects the frequency of S/CO response values above and below the arbitrarily chosen threshold value of 12.0. In a two month observation period of 338 Ultrio Plus test runs the proportion of S/CO values below 12.0 was 1.5% (figure 2)[15]. Although the reactivity rate on the run control was 100% it cannot be excluded that in rare cases a non-reactive result will be found[15].

Table 6. Interpretation of a single TMA test result on P0065 ViraQ HBV Check 125 in Procleix Ultrio assay versions and expected frequency of S/CO values in three ranges

Result	S/CO	Expected frequency per 1000[#]	Interpretation
Reactive saturated	>12.0	893 - 1000	The test signal on the run control reaches maximum values in the saturated range of the TMA assay. This is an expected result.
Reactive dynamic	1.0–12.0	12 – 17	The test signal on the run control is in the dynamic range of the assay because the TMA reaction is not yet complete. This is an expected result.
Non-reactive	<1.0	0^	The test signal on the run control is below the cut-off. This is an unexpected result that should trigger an investigation of the technical performance of the test system.

[#]95% confidence limits found in 338 Ultrio Plus test runs ^data set too small to determine

Repeatedly non-reactive results (or a higher proportion of dynamic responses than 10%) are indicative of a significantly reduced analytical sensitivity of the NAT system. A single event of a non-reactive result is however possible without deterioration of the test system and can be explained by Poisson distribution

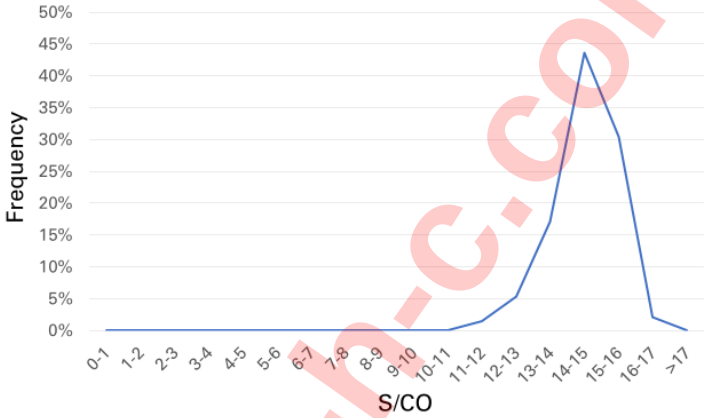
Monitoring performance of Procleix Ultrio assay versions on run control

The difference between the median and the average of S/CO values can be used as an indicator of the reproducibility and analytical sensitivity of the NAT system (table 7). One can plot the mean and median at each time point of testing of the run control for 50 earlier and 50 later S/CO measurements and compare this with the proportion reactive and proportion of saturated reactive responses over the same observation period. It is expected that the highest values of Δ (median S/CO – average S/CO) coincide with the lowest proportions of saturated responses. From this longitudinal analysis one can determine a value of $\Delta(S/CO_{M-A})$ above which the system may no longer be properly functioning[15]. An alert threshold value for this parameter could not yet be established with the available data.

Table 7. Reproducibility of Ultrio Plus S/CO values on P0065 ViraQ HBV Check 125 control

n test runs	Median S/CO	Average S/CO	$\Delta(S/CO_{M-A})$	S/CO Percentile	
				95%	99%
338	14.7	14.5	0.2	12.2-15.8	11.3-16.3

Figure 2. Distribution of S/CO values in Ultrio Plus test runs on P0065 ViraQ HBV Check 125 control



The parameter $\Delta(S/CO_{M-A})$ can also be applied to compare other experimental conditions such as the TMA reagent batch, the ViraQ run control batch or the testing robot (Tigris or Panther). An example using $\Delta(S/CO_{M-A})$ as performance indicator is shown in table 8 comparing six Tigris instruments[17]. The result shows that the values of $\Delta(S/CO_{M-A})$ differ by instrument. Hence, if the instrument 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 instrument.

Table 8. Example of using $\Delta(S/CO_{M-A})$ for performance evaluation of six Tigris instruments used during 2 months

Instrument #	n	Average S/CO	Median S/CO	$\Delta(S/CO_{M-A})$
1	57	15.19	15.29	0.10
2	60	14.16	14.22	0.06
3	55	14.56	14.57	0.01
4	52	13.29	13.27	-0.03
5	60	14.66	14.67	0.01
6	55	15.32	15.21	-0.11

Interpretation of test results on run control in quantitative NAT methods

P0065 ViraQ HBV Check 125 can be used as a quantitative run control in conjunction with the Hologic Aptima HBV Quant tests and other viral load assays with a LOQ sufficiently below 125 copies/mL. Table 9 gives the expected frequency of three categories of results on the run control in viral load assays.

Table 9. Interpretation of a single quantitative NAT test result on P0065 ViraQ HBV Check 125 control and expected frequency of viral load measurements above the lower limit of quantification (LOQ) of the current commercial real time PCR and TMA assays.

Result	HBV IU/mL	Expected frequency	Interpretation
Reactive quantifiable	≥LOQ	>99%	This is an expected result.
Reactive unquantifiable	<LOQ	<1%	This is an unexpected result but is possible. An investigation of technical performance of the NAT system is recommended
Non-reactive undetectable	<CO	<0.5%	This is an unexpected result. An investigation of technical performance of the NAT system is required

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

The linear range of the quantitative NAT methods tests starts at enough distance below the run control concentration of 125 copies/mL to expect quantifiable results (above the LOQ) in more than 99% of test runs[5]. The quantitative HBV-DNA assays report values in IU/mL based on calibration against the WHO standard. The HBV-DNA concentration (95%CI) of P0065 ViraQ HBV Check control of 125 (84-188) copies/mL is equivalent to 23 (16-35) IU/mL (figure 1), 2.4- to 4.3-fold higher than the LOQ's claimed by the manufacturers of the real time PCR and TMA assays (table 10).

Table 10. Distance of lower limit of quantification (LOQ) to concentration of P0065 ViraQ HBV Check 125 control as reported in package inserts of HBV viral load assays of three manufacturers.

Manufacturer	NAT test	LOQ (IU/mL)	Factor (95%CI)#
Abbott	RealTime HBV	10	2.4 (1.6 – 3.9)
Roche Molecular systems	HBV Cobas 6800/8800	10	2.4 (1.6 – 3.9)
Hologic	Aptima HBV Quant	5.6	4.3 (2.9 – 6.5)

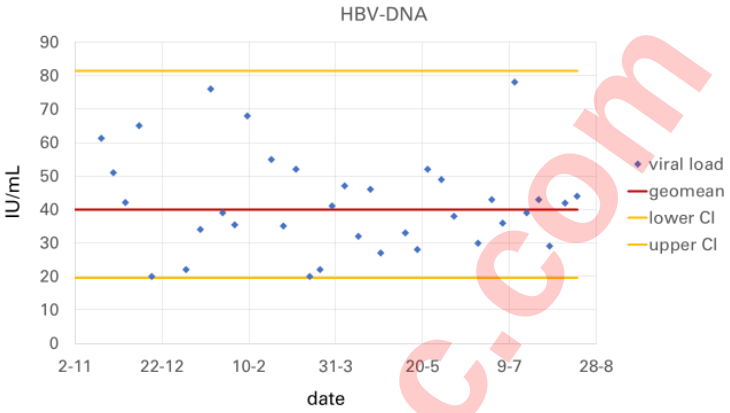
#Factor between Concentration of HBV-DNA in IU/ml of P0065 ViraQ HBV Check 125 and LOQ; 95% CI's derived from uncertainty in calibration of P0065 ViraQ Check 125 control.

One should be careful with comparing the IU/mL levels in table 10 because different methods and WHO replacement standards have been used for calibration of the run control and (calibrators of) the NAT systems. Testing of another HBV run control containing 250 copies/mL of HBV-DNA (P0155 ViraQ HBV Check 250) in 36 test runs of the Aptima HBV Quant assay (figure 3) gave a geometric mean value (95% CI) of 40 (20-81) IU/mL comparable to the estimated concentration of 47 (30-70) IU/mL in that run control[15].

Monitoring performance of quantitative NAT methods on run control

For the identification of aberrant quantitative results log (viral load) values should be recorded in a Levey-Jennings chart to visualise trends over time. The Westgard rules[19] provide guidance on the interpretation of results outside the 95% or 99% confidence intervals. An example is given in figure 3 showing data points of Aptima Quant test runs on another HBV run control containing 250 copies/mL (P0155 ViraQ HBV Check 250) in a Levey-Jennings scatter plot.

Figure 3. Reproducibility of Hologic Aptima HBV Quant test runs on P0155 ViraQ HBV Check 250 control presented in a Levey-Jennings chart.



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

One can use the quantitative results on the run control for comparison of different experimental conditions, such as different laboratories, NAT reagent batches or instruments. Since the concentration of P0065 HBV Check 125 is just above the Poisson detection endpoint range of the quantitative NAT methods, lower reported IU/mL values on the run control or reduced analytical sensitivity of the test system may coincide with an increased standard deviation (SD)[15].

Limitations

- P0065 ViraQ HBV Check 125 Control cannot be used to evaluate the analytical or diagnostic sensitivity of NAT blood screening assays (although a significant reduction of analytical sensitivity of the NAT system can become apparent with repeated occurrence of non-reactive or unquantifiable results).
- P0065 ViraQ HBV Check 125 Control must not be substituted for the mandatory controls or calibrators provided with NAT test kits for calculating the cut-off and/or criteria for releasing test results.
- The Poisson distribution in samples with low HBV concentrations cannot guarantee that 100% reactive results will be found on P0065 ViraQ HBV Check 125 Control in NAT blood screening assays. Therefore the response values on the run controls should not be used for a decision to accept or reject the test run.
- The expected distributions of assay response values on P0065 ViraQ HBV Check 125 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 a threshold value above which a deterioration of the test system is predicted) needs to be evaluated and confirmed in post-market surveillance studies.
- P0065 ViraQ HBV Check 125 should not be used for establishing accuracy of quantitative NAT results expressed in IU/mL. For this purpose only a dilution of the current WHO International Standard can be used.
- More quantitative data need to be collected in the Abbott HBV real time and Roche cobas assays to confirm the suitability of P0065 HBV Check 125 control for these methods and to ensure that the proportion of unquantifiable results is less than 1%.

References

1. Grabarczyk P, van Drimmelen H, Kopacz A, Gdowska J, Liszewski G, Piotrowski D, Górska J, Kuśmierczyk J, Candotti D, Lętowska M, Lelie N, Brojer E. Head-to-head comparison of two transcription-mediated amplification assay versions for detection of hepatitis B virus, hepatitis C virus, and human immunodeficiency virus Type 1 in blood donors. Transfusion. 2013; 53:2512-2524.
2. Assal A, Barlet V, Deschaseaux M, Dupont I, Gallian P, Guitton C, Morel P, David B, and De Micco P. Comparison of the analytical and operational performance of two viral nucleic acid test blood screening systems: Procleix Tigris and cobas s 201. Transfusion 2009; 49:289-300.
3. Koppelman M, Assal A, Chudy M, Torres P, de Villaescusa RG, Reesink HW, Lelie PN, Cuypers HT. Multi-center performance evaluation of a transcription-mediated amplification assay for screening of human immunodeficiency virus-1 RNA, hepatitis C virus RNA, and hepatitis B virus DNA in blood donations. Transfusion 2005; 45:1258-66.
4. Grabarczyk P, Koppelman M, Boland F, Sauleda S, Fabra C, Cambie G, O'Riordan K, Van Drimmelen H, Vermeulen M, O'Riordan J, Lelie N. Inclusion of human immunodeficiency virus Type 2 (HIV-2) in a multiplex transcription-mediated amplification assay does not affect detection of HIV-1 and hepatitis B and C virus genotypes: a multicenter performance evaluation study. Transfusion 2015; 55:2246-55.
5. Lelie PN, Van Drimmelen AAJ. Positioning of ViraQ Check and Trend Controls compatible with analytical sensitivity of NAT assays. VR4059. www.bioqcontrol.com
6. Lelie PN. Van Drimmelen AAJ. Preparation of inactivated secondary viral standards: Safety assessment of quality control samples for viral serology and NAT assays in blood screening laboratories.CE4006. www.bioqcontrol.com
7. Lelie PN, Reesink HW, Niessen J, Brotman B, Prince AM. Inactivation of 10^{15} chimpanzee-infectious doses of hepatitis B virus during preparation of a heat-inactivated hepatitis B vaccine. J Med Virol. 1987 Nov;23(3):289-95
8. Lelie PN, Reesink HW, Lucas CJ. Inactivation of 12 viruses by heating steps applied during manufacture of a hepatitis B vaccine. J Med Virol. 1987;23:297-301.
9. Chudy M, Hanschmann KM, Kress J, Nick S, Campos R, Wend U, Gerlich W, Nübling CM.First WHO International Reference Panel containing hepatitis B virus genotypes A-G for assays of the viral DNA. J Clin Virol. 2012;55:303-9
10. Collins ML, Zayati C, Detmer JJ, Daly B, Kolberg JA, Cha TA, Irvine BD, Tucker J, Urdea MS. Preparation and characterization of RNA standards for use in quantitative branched DNA hybridization assays. Anal Biochem. 1995 20; 226:120-9.

11. Lelie PN, Van Drimmelen AAJ, Cuypers HTM, Best SJ, Stramer Hyland SL C, J.-Allain P, Moncharmont P, Defer C, Nubling CM, Glauser A, da Silva Cardoso M, -F. Viret J, Lankinen M, Grillner L, Wirthmuller U, Coste J, Schottstedt V, Masecar B. and E.M. Dax. Sensitivity of HCV-RNA and HIV-RNA blood screening assays. Transfusion. 2002,42:527-36.
12. Lelie PN, Van Drimmelen AAJ. Calibration of native and inactivated viral standards and traceability to viral nucleic acid copies and International Units. VR4060, www.bioqcontrol.com
13. Heermann KH, Gerlich WH, Chudy M, Schaefer S, Thomssen R.J. Quantitative detection of hepatitis B virus DNA in two international reference plasma preparations. Eurohep Pathobiology Group. Clin Microbiol. 1999;37:68-73.
14. Saldanha J, Gerlich W, Lelie N, Dawson P, Heermann K, Heath A; WHO Collaborative Study Group. An international collaborative study to establish a World Health Organization international standard for hepatitis B virus DNA nucleic acid amplification techniques. Vox Sang. 2001;80:63-71.
15. Van Drimmelen AAJ, Lelie PN. Performance evaluation of ViraQ run controls for HBV, HCV and HIV-1 detection in different NAT assays. VR4061. www.bioqcontrol.com
16. Van Drimmelen AAJ, Lelie PN. Stability of ViraQ run controls for NAT. VR4058. www.bioqcontrol.com
17. Centers for Disease Control (CDC). Update: Universal precautions for prevention of transmission of human immunodeficiency virus, hepatitis B virus, and other blood borne pathogens in health-care settings. MMWR 1988; 37:377-388.
18. Centers for Disease Control (CDC). Guidelines for prevention of transmission of human immunodeficiency virus and hepatitis B virus to health-care and public-safety workers. MMWR 1989; 38(S-6): 1-36.
19. Westgard rules. www.westgard.com.

BioQControl B.V.
Droogmakerij 31h
1851 LX, Heiloo
The Netherlands

Telephone : +31-72-2020730
Telefax : +31-72-2020731
E-mail : info@bioQControl.com
Internet: www.bioQControl.com

KI4061
v5.0 October 2018