Bio QControl

HBV-DNA reference panels

RUO

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

The HBV-DNA reference panels provide a consistent standard across nucleic acid amplification technology (NAT) methods, enabling blood screening laboratories and *in* vitro Diagnostics (IVD) manufacturers to assess the analytical sensitivity and quantification limits of molecular diagnostic test methods for the qualitative and quantitative detection of Hepatitis B virus (HBV)- DNA in blood samples. This product can be used with amplification methods, including (real time) polymerase chain reaction (PCR) and transcription mediated amplification (TMA) assays. The HBV-DNA reference panels are useful for establishing the lower limit of detection (LOD), limit of quantification (LOQ), NAT reagent batch acceptance, NAT system validation and training. The products are for research use only and not for diagnostic use.

Key to Symbols Used

Manufacturer

Lot number

Catalogue number

Store below -30°C

Research use only

Biological substance category B

Date of manufacturing

Contents

Caution

Read instructions for use

Summary and explanation

Over the last two decades a series of HBV-DNA standards and reference panels of different genotypes have been established for comparison of the analytical sensitivity of NAT methods. These analytical sensitivity panels help ensure that NAT methods for detection of HBV-DNA are properly validated and that test results are consistent across IVD manufacturers, laboratories, operators, NAT platforms and assay versions.

In the early 1990s the Eurohep and VQC-Sanquin HBV genotype A standards were the first reference materials used for evaluation of NAT methods[1-4]. Thereafter the Eurohep standard was used for preparation of the 1st and 2nd WHO (97/746 and 97/750) standards[5]. The Eurohep and VQC-Sanquin HBV genotype A standards were independently quantified in equivalent nucleic acid copies. The VQC-Sanquin standard has also been extensively calibrated against the 1st and 2nd lyophilised WHO (97/746 and 97/750) standards and the conversion factors (95% CI) were established at 5.33 (5-11-5.55) and 5.20 (4.61-5.80) copies per IU respectively. The VQC-Sanquin HBV genotype A standard was also calibrated against a chimpanzee plasma of known infectivity and according to this experiment the 50% chimpanzee minimum infectious dose (range) was determined at 4.0 (1.3-12.6) HBV-DNA copies or virions. The VQC-Sanquin standard has been used for preparation of a pasteurized standard from which the ViraQ Check and Trend Controls are prepared[6,7]. A series of Bio Quality Control (BQC) standards of different genotypes have been cross calibrated in copies/mL against the VQC-Sanquin standard by multiple replicate bDNA 3.0 assays as the reference method for quantification. A lyophilised WHO HBV genotype reference panel has been made available by the Paul Ehrlich Institute (Langen, Germany)[8] and again the panel members were cross calibrated in copies/mL against the VQC-Sanquin standard in multiple replicate bDNA 3.0 assays. The results were comparable to

the bDNA 3.0 calibration data in the WHO HBV genotype panel evaluation report[8].

Of all these HBV-DNA standards reference panels of (approximately) 3000, 1000, 300, 100, 30, 10, 3, 1, 0.3 and 0.1 copies/mL were tested in multiple replicate tests in different NAT blood screening assays in order to determine the 95% and 50% LOD by probit analysis[9-13]. More recently 8 member dilution panels of the same HBV genotype standards are manufactured starting at 300 copies/mL. The available replicate test data on the series of HBV-DNA reference panels (a total of 15,578 test results) are presented in this package insert. The proportion of reactive results and the 95% and 50% LODs estimated by probit analysis can be used for comparison.

Traceability to HBV-DNA copies and International Units

Figure 1 shows the traceability chain between the HBV-DNA reference panels, the Bio Quality Control (BQC) genotype A, B, C, D, E, F and G standards, the VQC-Sanquin genotype A standard, the Eurohep genotype A standard and the 1st and 2nd WHO 97/746 and 96/750 genotype A International Standards.

The viral concentration in the S0011 VQC-Sanquin HBV-DNA genotype A standard was established by laboratories testing dilutions of these standards in the VQC proficiency program organized between 1996 and 2004. Table 1 compares the geometric mean values in copies/mL as reported by five quantitative NAT methods. It was decided to use the Siemens bDNA 3.0 assay as the reference method for quantification and assign the value of 2.15 x 10^9 copies/mL to the undiluted S0011 VQC-Sanquin standard.

Table 1: Quantification of S0011 VQC-Sanquin HBV-DNA standard in proficiency studies performed between 1996 and 2004. The quantification in the Siemens bDNA 3.0 assay was chosen as the reference method for calibration in copies/mL

Assay	n	copies/mL (95% CI)
Chiron bDNA 1.0	17	3.22 (3.13-3.32) x 10^9
Siemens bDNA 3.0	**28**	**2.15 (2.11-2.20) x 10^9**
Roche Amplicor Monitor	198	2.11 (2.05-2.17) x 10^9
Roche Taqman	8	2.38 (1.01-5.61) x 10^9
Digene HCS	42	1.63 (1.57-1.69) x 10^9

Dr. T. Cuijpers and Dr. M. Koppelman (Sanquin, Amsterdam, the Netherlands) tested dilutions of 1:100, 1:1000, 1:10,000 and 1:30,000 of the S0011 VQC-Sanquin genotype A standard in 4 replicates against dilutions of 1:10 and 1:100 of the WHO 97/746 standard in 6 replicates in the same bDNA 3.0 test run and found a conversion factor (95%CI) of 5.33 (5.11-5.55) copies per IU. Later a 1:66667 dilution of the VQC standard was tested against a 1:543.2 dilution of the WHO 97/750 standard in 6 replicates in the same bDNA 3.0 test run and a conversion factor of 5.20 (4.61-5.80) copies per IU was found. It must be emphasized that this conversion factor from copies to IU values has not yet been established for the 3rd WHO 10/264 replacement standard.

Dilutions of the S0011 VQC-Sanquin HBV genotype A standard were calibrated against those of the Eurohep genotype A standard in the VQC proficiency studies. One copy assigned to the Eurohep standard by Heerman et al[1] was found to be equivalent to 1.09 bDNA copy assigned to the VQC-Sanquin standard.

The BQC standards of different genotypes have been have been calibrated in copies/mL by replicate testing in the Siemens Versant bDNA 3.0 assay[14] against the S0011 VQC-Sanquin HBV-DNA genotype A standard[9] (table 2). For all these standards of different genotypes

the same conversion factor of 5.33 copies per IU was assumed although they have not been directly calibrated against the WHO 97/746 and 97/750 standards.

Table 2. Calibration of HBV-DNA standards of different genotypes against the primary VQC-Sanquin HBV genotype A standard containing $2.15.10^9$ copies/mL according to quantification in bDNA 3.0 assay (table 1)

HBV-DNA standard	genotype	n	copies/mL (95% CI)#	(95% CI)%
S0011 VQC-Sanquin#	A2	28	$2.15\ (2.11\text{-}2.20).10^9$	(98-102)%
S0010 Eurohep	A2	6	$2.97\ (1.78\text{-}4.95).10^9$	(60-167)%
S0110 Chimp C-246 P-57	A2	6	$1.26\ (0.73\text{-}2.16).10^6$	(58-172)%
S0043 BQC inactivated	A2	6	$7.23\ (4.82\text{-}10.9).10^6$	(67-151)%
S0075 WHO 5086/08-3	A2	6	$3.30\ (2.75\text{-}3.96).10^6$	(83-120)%
S0073 WHO 5086/08-1	A1	6	$6.97\ (4.41\text{-}11.0).10^6$	63-158)%
S0074 WHO 5086/08-2	A1	6	$4.44\ (2.36\text{-}8.37).10^6$	(53-188)%
S0098 BQC	B	9	$1.94\ (1.62\text{-}2.33).10^9$	(83-120)%
S0076 WHO 5086/08-4	B1	6	$8.04\ (5.16\text{-}12.5).10^6$	(64-156)%
S0077 WHO 5086/08-5	B2	6	$5.22\ (3.51\text{-}7.75).10^6$	(67-149)%
S0078 WHO 5086/08-6	B4	6	$6.17\ (4.25\text{-}8.94).10^6$	69-145)%
S0057 BQC	C	9	$2.21\ (1.87\text{-}2.61).10^9$	(85-118)%
S0111 Chimp C272 P29	C	6	$1.85\ (1.28\text{-}2.67).10^6$	(69-144)%
S0094 WHO 5086/08-7	C2	6	$5.50\ (4.04\text{-}7.49).10^6$	(73-136)%
S0086 WHO 5086/08-8	C2	6	$6.81\ (4.68\text{-}9.90).10^6$	(69-145)%
S0087 WHO 5086/08-9	C2	6	$4.74\ (3.45\text{-}6.51).10^6$	(73-137)%
S0107 Eurohep	D	12	$2.53\ (2.03\text{-}3.17).10^9$	(80-125)%
S0058 BQC	D	9	$3.46\ (2.95\text{-}4.06).10^9$	(85-117)%
S0088 WHO 5086/08-10	D1	6	$4.12\ (2.61\text{-}6.48).10^6$	(63-158)%
S0089 WHO 5086/08-11	D3	6	$4.39\ (3.52\text{-}5.74).10^6$	(80-125)%
S0090 WHO 5086/08-12	D1	6	$3.96\ (2.60\text{-}6.03).10^6$	(66-152)%
S0059 BQC	E	9	$1.57\ (1.42\text{-}1.74).10^9$	(90-111)%
S0091 WHO 5086/08-13	E	6	$3.25\ (2.58\text{-}4.09).10^9$	(79-126)%
S0060 BQC	F	9	$1.43\ (0.92\text{-}2.23.10^9$	(64-156)%
S0092 WHO 5086/08-14	F3	6	$3.65\ (2.28\text{-}5.85).10^5$	(62-160)%
S0061 BQC	G	9	$8.29\ (6.89\text{-}9.97).10^6$	(83-120)%
S0093 WHO 5086/08-15	G	6	$5.79\ (3.3510.0).10^4$	(58-173)%

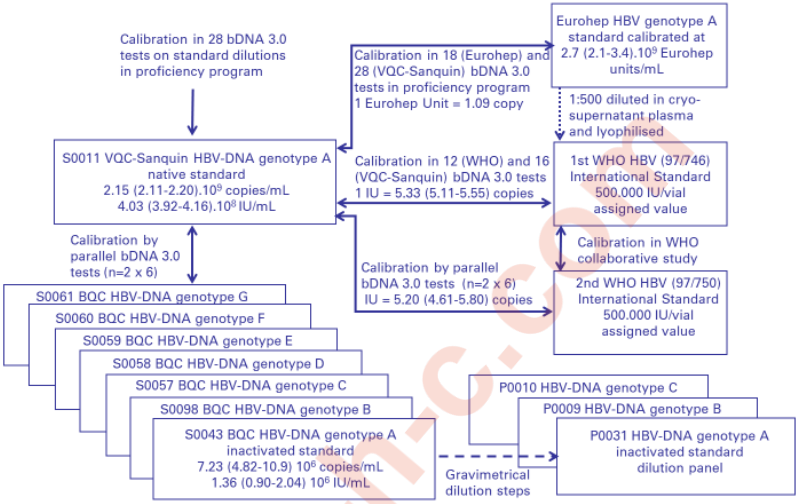
1 IU = 5.33 copies against 1st WHO 97/746 standard

Calibration of chimpanzee plasmas of known infectivity in copies/mL

Two HBV infected chimpanzee plasmas taken in the early ramp up phase of viremia were kindly obtained from prof Yoshizawa and Tanaka (Hiroshima University, Japan). According to interpretation of the chimpanzee infectivity data reported by Komiya et al[16] the 50% chimpanzee minimum infectious dose or CID_{50} (and 0% to 100% infectivity range) is 8.2 (2.6-26) copies for the genotype A plasma [C246-P57] and 9.5 (3.0-30) copies for a genotype C plasma [C272-P29]. These estimates were based on quantification in the Roche TaqMan assay. Recalibration of a 1:100 dilution of these ramp up phase plasma samples P57 and P29 of chimpanzees C-446 and C-272 in 6 replicate bDNA tests against the VQC-Sanquin genotype A standard (data in table 2) showed conversion factors of 2.06 and 1.62 from bDNA to TaqMan copies for genotype A and C respectively. As a consequence one CID_{50} (0% to 100% infectivity range) of the HBV genotype A and C strain contain 4.0 (1.3-12.6) copies and 5.9 (1.8-18.5) copies respectively when calibrated against the S0011 Sanquin-VQC genotype A standard. The Japanese chimpanzee infectivity standards are not commercially available and were only used for estimating the 50% minimum

infectious dose (MID_{50})[17,18]. Usually a MID_{50} of 3.16 virions (geometric mean value between 1 and 10 virions)[17,18] is used for estimating the length of the infectious window period and for calculating HBV transmission risk based on the 95% and 50% LODs that are found on the HBV-DNA reference panels listed in this package insert (table 3).

Figure 1. Traceability chain between HBV-DNA reference panels, BQC and VQC-Sanquin standards and WHO International Standards



Stability of HBV standards and reference panels

The long term stability of the liquid frozen HBV standard stored at ≤65°C has been firmly established[19]; hence the stock solutions from which the reference panels are prepared have shown to be stable for more than two decades in the BQC storage facilities. Real time stability experiments using quantitative NAT assays showed no degradation of HBV-DNA reference panels and controls when stored at -30°C[19]. Hence, it can be guaranteed that the reference panels are stable when stored at -30°C.[19]

Overview of HBV-DNA genotype reference panels

Table 3 gives an overview of the HBV-DNA reference panels that are available for establishing the analytical sensitivity or validation of NAT methods.

For preparation of the HBV-DNA reference panels, the HBV-DNA standards were diluted in a pool of plasma units that tested negative for viral markers by NAT and serology testing. Lot-to-lot consistency of the viral concentrations in the reference panel is ensured during manufacturing by gravimetrically recorded dilutions from calibrated viral stock solutions, stored below –65°C. 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[15]. The BQC manufacturing and quality control procedures guarantee consistent virus concentrations in consecutive batches of the HBV-DNA reference panels.

Table 3. Overview of HBV-DNA genotype reference panels for evaluation of analytical sensitivity of NAT methods

HBV-DNA genotype reference panels	Source/Standard	Quantity	range copies/mL$
P0001 HBV-DNA genotype A	Eurohep	10 x 4 mL^	0.11 - 3300
P0277 HBV-DNA genotype A	Eurohep	8 x 4 mL	0.1 - 300
P0272 Multi-Marker HBV/HCV/HIV-1	Eurohep	8 x 1.5 mL	0.78 - 50
P0004 HBV-DNA genotype A	2nd WHO 97/750	10 x 4 mL^	0.05 - 1471
P0279 HBV-DNA genotype A	2nd WHO 97/750	8 x 4 mL	0.11 - 320
P0023 HBV-DNA genotype A	2nd WHO 97/750	8 x 5.6 mL	0 - 266
P0007 HBV-DNA genotype A	VQC-Sanquin §	10 x 4 mL^	0.11 - 3225
P0280 HBV-DNA genotype A	VQC-Sanquin §	8 x 4 mL	0.1 - 300
P0031 HBV-DNA genotype A inact.	BQC inactivated	10 x 4 mL^	0.12 - 3538
P0295 HBV-DNA genotype A inact	BQC inactivated	8 x 4 mL	0.1 - 300
P0106 HBV-DNA genotype A1 (1)	WHO 5086/08-1	8 x 4 mL	0.1 - 299
P0107 HBV-DNA genotype A1 (2)	WHO 5086/08-2	8 x 4 mL	0.1 - 300
P0108 HBV-DNA genotype A2	WHO 5086/08-3	8 x 4 mL	0.1 - 310
P0009 HBV-DNA genotype B	BQC	10 x 4 mL^	0.1 - 3035
P0281 HBV-DNA genotype B	BQC	8 x 4 mL	0.1 - 300
P0109 HBV-DNA genotype B1	WHO 5086/08-4	8 x 4 mL	0.09 - 280
P0110 HBV-DNA genotype B2	WHO 5086/08-5	8 x 4 mL	0.1 - 297
P0111 HBV-DNA genotype B4	WHO 5086/08-6	8 x 4 mL	0.1 - 289
P0010 HBV-DNA genotype C	BQC	10 x 4 mL	0.1 - 2821
P0282 HBV-DNA genotype C	BQC	8 x 4 mL	0.1 - 300
P0112 HBV-DNA genotype C2	WHO 5086/08-7	8 x 4 mL	0.1 - 298
P0113 HBV-DNA genotype C2	WHO 5086/08-8	8 x 4 mL	0.1 - 286
P0114 HBV-DNA genotype C2	WHO 5086/08-9	8 x 4 mL	0.1 - 307
P0002 HBV-DNA genotype D	Eurohep	10 x 4 mL^	0.1 - 2924
P0278 HBV-DNA genotype D	Eurohep	8 x 4 mL	0.1 - 300
P0011 HBV-DNA genotype D	BQC	10 x 4 mL^	0.10 - 3134
P0283 HBV-DNA genotype D	BQC	8 x 4 mL	0.1 - 300
P0115 HBV-DNA genotype D1	WHO 5086/08-10	8 x 4 mL	0.1 - 283
P0116 HBV-DNA genotype D3	WHO 5086/08-11	8 x 4 mL	0.1 - 308
P0117 HBV-DNA genotype D1	WHO 5086/08-12	8 x 4 mL	0.1 - 318
P0012 HBV-DNA genotype E	BQC	10 x 4 mL^	0.11 - 3213
P0284 HBV-DNA genotype E	BQC	8 x 4 mL	0.1 - 300
P0118 HBV-DNA genotype E1	WHO 5086/08-13	8 x 4 mL	0.1 - 304
P0013 HBV-DNA genotype F	BQC	10 x 4 mL^	0.12 - 3607
P0285 HBV-DNA genotype F	BQC	8 x 4 mL	0.1 - 300
P0119 HBV-DNA genotype F3	WHO 5086/08-14	8 x 4 mL	0.1 - 310
P0014 HBV-DNA genotype G	BQC	10 x 4 mL^	0.11 -3188
P0286 HBV-DNA genotype G	BQC	8 x 4 mL	0.1 - 300
P0120 HBV-DNA genotype G	WHO 5086/08-15	8 x 4 mL	0.1 - 300

$ 1 IU = 5.33 copies ^10 x 4 mL format will be phased out and replaced by 8 x 4 mL format

Materials Provided

Table 4.1 to table 4.39 gives the composition of the HBV-DNA reference panels and the quantification of the panel members, listed in table 3. Either ten or eight member panels are filled off in 4.0 mL volumes in polypropylene tubes (10 mL) with screw caps. The quantification in copies/mL and the uncertainty expressed by the 95% confidence interval (CI) was based on calibration experiments in the bDNA 3.0 assay (table 2). The quantification in IU/mL is obtained using the same conversion factor of 5.33 copies per IU for all genotyped standards. A confidence interval was not given since the uncertainty for calibration of WHO replacement standards in IUs ignored.
The tube identification is Byyyy-xxx-number, where yyyy is product specific and xxx the sequential batch number. The identification is present on the bar-code and further explained on the tube label.

Materials not provided

Test kit and pipettes or pipetting devices for use in IVD test systems.

Storage Instructions

It is recommended that the panels are stored at –30°C or lower to ensure highest quality. At this temperature the panel is stable. Discard any unused material after the first use. Any panel members that appear cloudy or contain precipitates after thawing should be discarded.

Warning and precautions

Warning: The HBV-DNA reference panel members contain infectious HBV and are potentially bio-hazardous (except for P0031 that is prepared from a heat inactivated standard). Apply the universal precautions for prevention of transmission of infectious agents when handling these materials[20]. Although the normal human plasma used in the production of this panel was negative for blood borne infectious disease markers the reference panel members should be handled as if capable of transmitting (unknown) infectious agents.

- 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 reference panel is handled.
- Disinfect liquids, materials or spills with a 0.5% sodium hypochlorite solution or equivalent.
- Dispose of all materials and liquids used in the procedure as if they contained pathogenic agents.

Test procedure

- Thaw the panel members quickly in a water bath at 37°C.
- Mix gently during thawing until contents are just thawed.
- Immediately after thawing remove the panel member tube from the water bath.
- Mix the panel member(s).
- Give a short spin in a centrifuge before releasing screw cap from vial.
- Minimise the time period from thawing until usage of the members.
- The panel member should be handled and tested in a manner identical to that of clinical specimens in the test procedure being evaluated.
- Do not refreeze panel members after thawing. When a panel member is tested multiple times it should be organized within 8 hours. When not placed in the robot store at 2-8°C.

Interpretation of Results

Expected proportion of reactive test results in NAT assays

The historically observed proportion of reactive results in replicate tests on the HBV-DNA reference panels in Procleix Ultrio (Grifols) or cobas MPX (Roche) assay versions are presented in tables 4.1 to 4.39. These data can be used to select panel members to be tested in multiple replicates and for comparison of the proportion of reactive test results. It is recommended to test the panels in at least in 12 replicates (and preferably 24 to 48 times) for estimating the 50% and 95% LODs by probit analysis[21]. If HBV-DNA reference panels are used for NAT reagent batch acceptance testing the panel members could be tested in 4-6 replicates.

Table 4. Composition HBV-DNA standard dilution panels of different genotypes and proportion of NAT reactive results in Ultrio and cobas MPX assay versions

Table 4.1. P0001 HBV-DNA genotype A2 (Eurohep standard)

Sample-id	cp/mL (95% CI)	IU/mL	Tigris Ultrio	Tigris Ultrio Plus	Panther Ultrio Elite	cobas S201 MPX 1.0
B4022-xxx-11	3300 (1978-5500)	619	24/24 (100%)	72/72 (100%)		
B4022-xxx-12	1100 (659-1833)	206	48/48 (100%)	72/72 (100%)		
B4022-xxx-01	330 (198-550)	61.9	48/48 (100%)	96/96 (100%)		
B4022-xxx-02	110 (65.9-183)	20.6	48/48 (100%)	96/96 (100%)	24/24 (100%)	12/12 (100%)
B4022-xxx-03	33.0 (19.8-55.0)	6.19	38/48 (79%)	92/96 (96%)	22/24 (92%)	12/12 (100%)
B4022-xxx-04	11.0 (6.59-18.3)	2.06	27/48 (56%)	72/96 (75%)	13/24 (54%)	11/12 (92%)
B4022-xxx-05	3.30 (1.98-5.50)	0.62	3/48 (6%)	43/96 (45%)	6/24 (25%)	8/12 (67%)
B4022-xxx-06	1.10 (0.66-1.83)	0.21	5/48 (10%)	14/96 (15%)	1/24 (4%)	2/12 (17%)
B4022-xxx-07	0.33 (0.20-0.55)	0.06	2/24 (8%)	10/95 (11%)		1/12 (8%)
B4022-xxx-08	0.11 (0.07-0.18)	0.02	0/24 (0%)	1/72 (1%)		

Table 4.2. P0277 HBV-DNA genotype A2 (Eurohep standard)

Replacement of P0001 Eurohep standard dilution panel above (table 4.1)

Sample-id	cp/mL (95% CI)	IU/mL
B4268-xxx-01	300 (180-500)	56.2
B4268-xxx-02	100 (60.0-167)	18.7
B4268-xxx-03	30.0 (18.0-50.0)	5.62
B4268-xxx-04	10.0 (6.00-16.7)	1.87
B4268-xxx-05	3.00 (1.80-5.00)	0.56
B4268-xxx-06	1.00 (0.60-1.67)	0.19
B4268-xxx-07	0.30 (0.18-0.50)	0.06
B4268-xxx-08	0.10 (0.060-0.17)	0.02

Table 4.3. P0272 HBV-DNA genotype A2 (Eurohep standard)

Eurohep standard dilutions in HBV/HCV/HIV-1 Multimarker panel manufactured for Roche

Sample-id	cp/mL (95% CI)	IU/mL	cobas 6800 MPX
B4263-xxx-01	50 (30-83)	9.38	48/48 (100%)
B4263-xxx-02	25 (15-42)	4.69	48/48 (100%)
B4263-xxx-03	12.5 (7.5-21)	2.35	45/46 (98%)
B4263-xxx-04	6.25 (3.7-10.4)	1.17	44/48 (92%)
B4263-xxx-05	3.12 (1.87-5.21)	0.59	31/48 (65%)
B4263-xxx-06	1.56 (0.94-2.61)	0.29	17/48 (35%)
B4263-xxx-07	0.78 (0.47-1.30)	0.15	17/46 (37%)

Table 4.4. P0004 HBV-DNA genotype A2 (2nd WHO 97/750 standard)

Sample-id	cp/mL (95% CI)	IU/mL	Tigris Ultrio	Tigris Ultrio Plus
B4025-xxx-01	1471.08	276	33/33 (100%)	24/24 (100%)
B4025-xxx-02	490.36	92	33/33 (100%)	54/54 (100%)
B4025-xxx-03	147.11	27.6	32/33 (97%)	53/53 (100%)
B4025-xxx-04	49.04	9.2	25/33 (76%)	55/55 (100%)
B4025-xxx-05	14.71	2.76	15/33 (45%)	46/55 (84%)
B4025-xxx-06	4.90	0.92	9/33 (27%)	34/54 (63%)
B4025-xxx-07	1.44	0.27	3/33 (9%)	7/53 (13%)
B4025-xxx-08	0.49	0.092	2/33 (6%)	7/54 (13%)
B4025-xxx-09	0.16	0.03	2/33 (6%)	1/55 (2%)
B4025-xxx-10	0.05	0.01	0/33 (0%)	1/24 (4%)

Table 4.5. P0279 HBV-DNA genotype A2 (2nd WHO 97/750 standard)

Replacement of P0004 WHO standard dilution panel above (table 4.4)

Sample-id	cp/mL (95% CI)	IU/mL
B4270-xxx-01	319.80	60
B4270-xxx-02	106.60	20
B4270-xxx-03	31.98	6
B4270-xxx-04	10.66	2
B4270-xxx-05	3.20	0.6
B4270-xxx-06	1.07	0.2
B4270-xxx-07	0.32	0.06
B4270-xxx-08	0.11	0.02

Table 4.6. P0023 HBV-DNA genotype A2 (2nd WHO 97/750 standard)

WHO standard dilution panel previously manufactured for Grifols

Sample-id	cp/mL	IU/mL	Tigris Ultrio	Tigris Ultrio Plus	Panther Ultrio Elite	cobas 6800 MPX
B4090-xxx-01	266.50	50	32/32 (100%)	302/302 (100%)	251/251 (100%)	12/12 (100%)
B4090-xxx-02	79.95	15	32/32 (100%)	301/301 (100%)	253/253 (100%)	12/12 (100%)
B4090-xxx-03	26.65	5	23/32 (72%)	296/303 (98%)	237/250 (95%)	12/12 (100%)
B4090-xxx-04	8.00	1.5	7/32 (22%)	198/303 (65%)	167/252 (66%)	11/12 (92%)
B4090-xxx-05	2.67	0.5	5/32 (16%)	82/303 (27%)	77/249 (31%)	9/12 (75%)
B4090-xxx-06	0.80	0.15	3/32 (9%)	32/276 (12%)	13/136 (10%)	2/12 (17%)
B4090-xxx-07	0.27	0.05	0/32 (0%)	2/149 (1%)	3/108 (3%)	
B4090-xxx-08	0.00	0	0/8 (0%)	0/256 (0%)	0/213 (0%)	

Table 4.7. P0007 HBV-DNA genotype A2 (VQC-Sanquin standard)

Sample-id	cp/mL (95% CI)	IU/mL	Tigris Ultrio	Tigris Ultrio Plus	Panther Ultrio Elite	cobas 6800 MPX
B4028-xxx-01	3225 (3165-3300)	605			25/25 (100%)	
B4028-xxx-02	1078 (1058-1103)	202	24/24 (100%)		25/25 (100%)	
B4028-xxx-03	322 (316-330)	60.5	24/24 (100%)	24/24 (100%)	49/49(100%)	24/24 (100%)
B4028-xxx-04	108 (106-110)	20.2	22/24 (92%)	48/48 (100%)	74/74 (100%)	24/24 (100%)
B4028-xxx-05	32.2 (31.6-33.0)	6.05	12/24 (50%)	47/47 (100%)	73/74 (99%)	24/24 (100%)
B4028-xxx-06	10.8 (10.6-11.0)	2.02	10/24 (42%)	31/48 (65%)	51/73 (70%)	22/24 (92%)
B4028-xxx-07	3.22 (3.16-3.30)	0.61	7/24 (29%)	14/47 (30%)	29/74 (39%)	16/24 (67%)
B4028-xxx-08	1.08 (1.06-1.10)	0.2	0/24 (0%)	7/48 (15%)	18/73 (25%)	8/24 (33%)
B4028-xxx-09	0.32 (0.31-0.33)	0.06		2/48 (4%)	6/48 (13%)	2/24 (8%)
B4028-xxx-10	0.11	0.02			1/48 (2%)	0/24 (0%)

Table 4.8. P0280 HBV-DNA genotype A2 (VQC-Sanquin standard)

Replacement of P0007 VQC-Sanquin standard dilution panel above (table 4.7)

Sample-id	cp/mL (95% CI)	IU/mL
B4271-xxx-01	300 (294-307)	56.2
B4271-xxx-02	100 (98.0-102)	18.7
B4271-xxx-03	30.0 (29.4-30.7)	5.62
B4271-xxx-04	10.0 (9.80-10.2)	1.87
B4271-xxx-05	3.00 (2.94-3.07)	0.56
B4271-xxx-06	1.00 (0.98-1.02)	0.19
B4271-xxx-07	0.30 (0.29-0.31)	0.06
B4271-xxx-08	0.10 (0.098-0.10)	0.02

Table 4.9. P0031 HBV-DNA genotype A2 (heat inactivated VQC-Sanquin standard)

Sample-id	cp/mL (95% CI)	IU/mL	Tigris Ultrio	Tigris Ultrio Plus	Panther Ultrio Elite	cobas 6800 MPX
B4001-xxx-01	3538 (2358-5333)	664	58/58 (100%)			
B4001-xxx-02	1183 (788-1783)	222	57/57 (100%)			
B4001-xxx-03	354 (236-533)	66.4	53/58 (91%)	24/24 (100%)	25/25 (100%)	
B4001-xxx-04	118 (78.8-178)	22.2	39/58 (67%)	24/24 (100%)	25/25 (100%)	12/12 (100%)
B4001-xxx-05	35.4 (23.6-53.3)	6.64	14/58 (24%)	24/23 (96%)	24/25 (96%)	12/12 (100%)
B4001-xxx-06	11.8 (7.88-17.8)	2.22	10/58 (17%)	15/24 (63%)	18/25 (72%)	11/12 (92%)
B4001-xxx-07	3.54 (2.36-5.33)	0.66	1/58 (2%)	3/24 (13%)	7/25 (28%)	6/12 (50%)
B4001-xxx-08	1.18 (0.79-1.78)	0.22	3/58 (5%)	3/24 (13%)	2/25 (8%)	4/12 (33%)
B4001-xxx-09	0.35 (0.24-0.53)	0.07	0/58 (0%)	2/24 (8%)	1/25 (4%)	1/12 (8%)
B4001-xxx-10	0.12 (0.079-0.18)	0.02	0/58 (0%)			0/12 (0%)

Table 4.10. P0295 HBV-DNA genotype A2 (heat inactivated VQC-Sanquin standard)

Replacement of P0031 heat inactivated BQC standard dilution panel above (table 4.9)

Sample-id	cp/mL (95% CI)	IU/mL
B4286-xxx-01	300 (200-452)	56.2
B4286-xxx-02	100 (66.7-151)	18.7
B4286-xxx-03	30.0 (20.0-45)	5.62
B4286-xxx-04	10.0 (6.7-15)	1.87
B4286-xxx-05	3.00 (2.94-3.07)	0.56
B4286-xxx-06	1.00 (0.67-1.51)	0.19
B4286-xxx-07	0.30 (0.20-0.45)	0.06
B4286-xxx-08	0.10 (0.07-0.15)	0.02

Table 4.11. P0108 HBV-DNA genotype A2 (WHO reference panel member 5086/08-3)

Sample-id	cp/mL (95% CI)	IU/mL	Tigris Ultrio Plus	cobas S201 MPX 1.0
B4108-xxx-01	310 (258-373)	58.2		
B4108-xxx-02	103 (86.1-124)	19.4		
B4108-xxx-03	31.0 (25.8-37.3)	5.82	6/6 (100%)	4/4 (100%)
B4108-xxx-04	10.3 (8.61-12.4)	1.94	11/12 (92%)	11/11 (100%)
B4108-xxx-05	3.10 (2.58-3.73)	0.58	5/12 (42%)	7/12 (58%)
B4108-xxx-06	1.03 (0.86-1.24)	0.19	1/12 (8%)	3/10 (30%)
B4108-xxx-07	0.31 (0.26-0.37)	0.06	1/12 (8%)	1/11 (9%)
B4108-xxx-08	0.10 (0.086-0.12)	0.02		

Table 4.12. P0106 HBV-DNA genotype A1 (WHO reference panel member 5086/08-1)

Sample-id	cp/mL (95% CI)	IU/mL	Tigris Ultrio Plus	cobas S201 MPX 1.0
B4106-xxx-01	299 (189-473)	56.1		
B4106-xxx-02	99.7 (63.1-158)	18.7		
B4106-xxx-03	29.9 (18.9-47.3)	5.61	6/6 (100%)	6/6 (100%)
B4106-xxx-04	9.97 (6.31-15.8)	1.87	10/12 (83%)	11/12 (92%)
B4106-xxx-05	3.00 (1.89-4.73)	0.56	5/12 (42%)	8/12 (67%)
B4106-xxx-06	1.00 (0.63-1.58)	0.19	3/12 (25%)	3/10 (30%)
B4106-xxx-07	0.30 (0.19-0.47)	0.06	0/12 (0%)	1/12 (8%)
B4106-xxx-08	0.10 (0.063-0.16)	0.02		

Table 4.13. P0107 HBV-DNA genotype A1 (WHO reference panel member 5086/08-2)

Sample-id	cp/mL (95% CI)	IU/mL	Tigris Ultrio Plus	cobas S201 MPX 1.0
B4107-xxx-01	300 (159-566)	56.3		
B4107-xxx-02	100 (53.1-189)	18.8		
B4107-xxx-03	30.0 (15.9-56.6)	5.63	6/6 (100%)	6/6 (100%)
B4107-xxx-04	10.0 (5.31-18.9)	1.88	9/12 (75%)	9/12 (75%)
B4107-xxx-05	3.00 (1.59-5.66)	0.56	5/12 (42%)	
B4107-xxx-06	1.00 (0.53-1.89)	0.19	1/12 (8%)	1/10 (10%)
B4107-xxx-07	0.30 (0.16-0.57)	0.06	0/12 (0%)	0/11 (0%)
B4107-xxx-08	0.10 (0.053-0.19)	0.02		

Table 4.14. P0009 HBV-DNA genotype B (BQC standard)

Sample-id	cp/mL (95% CI)	IU/mL	Tigris Ultrio	Tigris Ultrio Plus	Panther Ultrio Elite
B4002-xxx-01	3035 (2534-3645)	569			
B4002-xxx-02	1017 (849-1221)	191	12/12 (100%)		
B4002-xxx-03	302 (253-363)	56.7	12/12 (100%)	11/11 (100%)	
B4002-xxx-04	101 (84.6-121)	19	12/12 (100%)	35/35 (100%)	
B4002-xxx-05	30.1 (25.2-36.2)	5.65	12/12 (100%)	36/36 (100%)	18/18 (100%)
B4002-xxx-06	10.1 (8.42-12.1)	1.89	9/12 (75%)	31/36 (86%)	16/18 (89%)
B4002-xxx-07	3.00 (2.51-3.61)	0.56	6/12 (50%)	18/36 (50%)	7/18 (39%)
B4002-xxx-08	1.00 (0.84-1.20)	0.19	2/12 (17%)	3/31 (10%)	3/18 (17%)
B4002-xxx-09	0.30 (0.25-0.36)	0.06		3/36 (8%)	2/18 (11%)
B4002-xxx-10	0.10 (0.08-0.12)	0.02			

Table 4.15. P0281 HBV-DNA genotype B (BQC standard)

Replacement of P0009 BQC standard dilution panel above (table 4.14)

Sample-id	cp/mL (95% CI)	IU/mL
B4272-xxx-01	300 (251-360)	56.2
B4272-xxx-02	100 (84.0-120)	18.7
B4272-xxx-03	30.0 (25.1-36.0)	5.62
B4272-xxx-04	10.0 (8.40-12.0)	1.87
B4272-xxx-05	3.00 (2.51-3.60)	0.56
B4272-xxx-06	1.00 (0.84-1.20)	0.19
B4272-xxx-07	0.30 (0.25-0.36)	0.06
B4272-xxx-08	0.10 (0.084-0.12)	0.02

Table 4.16. P0109 HBV-DNA genotype B1 (WHO reference panel member 5086/08-4)

Sample-id	cp/mL (95% CI)	IU/mL	Tigris Ultrio Plus	cobas S201 MPX 1.0
B4109-xxx-01	280 (180-436)	52.6		
B4109-xxx-02	93.4 (60.0-145)	17.5	6/6 (100%)	6/6 (100%)
B4109-xxx-03	28.0 (18.0-43.6)	5.26	9/12 (75%(	12/12 (100%)
B4109-xxx-04	9.34 (6.00-14.5)	1.75	9/12 (75%)	8/12 (67%)
B4109-xxx-05	2.80 (1.80-4.36)	0.53	4/12 (33%)	8/12 (67%)
B4109-xxx-06	0.93 (0.60-1.45)	0.18	3/12 (25%)	0/12 (0%)
B4109-xxx-07	0.28 (0.18-0.44)	0.05		
B4109-xxx-08	0.093 (0.060-0.15)	0.02		

Table 4.17. P0110 HBV-DNA genotype B2 (WHO reference panel member 5086/08-5)

Sample-id	cp/mL (95% CI)	IU/mL	Tigris Ultrio Plus	cobas S201 MPX 1.0
B4110-xxx-01	297 (199.9-441.2)	55.7		
B4110-xxx-02	99.0 (66.6-147)	18.6	6/6 (100%)	6/6 (100%)
B4110-xxx-03	29.7 (19.9-44.1)	5.57	11/12 (92%)	12/12 (100%)
B4110-xxx-04	9.90 (6.66-14.7)	1.86	11/12 (92%)	9/12 (75%)
B4110-xxx-05	2.97 (2.00-4.41)	0.56	4/12 (33%)	3/12 (25%)
B4110-xxx-06	0.99 (0.67-1.47)	0.19	2/12 (17%)	4/12 (33%)
B4110-xxx-07	0.30 (0.20-0.44)	0.06		
B4110-xxx-08	0.099 (0.067-0.15)	0.02		

Table 4.18. P0111 HBV-DNA genotype B3 (WHO reference panel member 5086/08-6)

Sample-id	cp/mL (95% CI)	IU/mL	Tigris Ultrio Plus	cobas S201 MPX 1.0
B4111-xxx-01	289 (199-419)	54.2		
B4111-xxx-02	96.3 (66.5-140)	18.1	6/6 (100%)	6/6 (100%)
B4111-xxx-03	28.9 (19.9-41.9)	5.42	11/12 (92%)	12/12 (100%)
B4111-xxx-04	9.63 (6.64-14.0)	1.81	8/12 (67%)	9/12 (75%)
B4111-xxx-05	2.89 (1.99-4.19)	0.54	4/12 (33%)	5/12 (42%)
B4111-xxx-06	0.96 (0.66-1.40)	0.18	3/12 (25%)	3/12 (25%)
B4111-xxx-07	0.29 (0.20-0.42)	0.05		
B4111-xxx-08	0.096 (0.066-0.14)	0.02		

Table 2.19. P0010 HBV-DNA genotype C (BQC standard)

Sample-id	cp/mL (95% CI)	IU/mL	Tigris Ultrio	Tigris Ultrio Plus	Panther Ultrio Elite
B4003-xxx-01	2821 (2387-3331)	529			
B4003-xxx-02	936 (792-1105)	176	12/12 (100%)		
B4003-xxx-03	282 (239-333)	52.9	12/12 (100%)	12/12 (100%)	
B4003-xxx-04	93.6 (79.2-111)	17.6	12/12 (100%)	36/36 (100%)	18/18 (100%)
B4003-xxx-05	28.2 (23.9-33.3)	5.29	6/12 (50%)	34/36 (94%)	18/18 (100%)
B4003-xxx-06	9.36 (7.92-11.1)	1.76	5/12 (42%)	23/36 (64%)	14/18 (78%)
B4003-xxx-07	2.82 (2.39-3.33)	0.53	2/12 (17%)	10/35 (29%)	3/18 (17%)
B4003-xxx-08	0.94 (0.79-1.11)	0.18	0/12 (0%)	4/36 (11%)	1/18 (6%)
B4003-xxx-09	0.28 (0.24-0.33)	0.05		1/35 (3%)	
B4003-xxx-10	0.094 (0.079-0.11)	0.02		1/24 (4%)	

Table 4.20. P0282 HBV-DNA genotype C (BQC standard)

Replacement of P0010 BQC standard dilution panel above (table 4.19)

Sample-id	cp/mL (95% CI)	IU/mL
B4273-xxx-01	300 (254-354)	56.2
B4273-xxx-02	100 (85.0-117)	18.7
B4273-xxx-03	30.0 (25.4-35.4)	5.62
B4273-xxx-04	10.0 (8.50-11.7)	1.87
B4273-xxx-05	3.00 (2.54-3.54)	0.56
B4273-xxx-06	1.00 (0.85-1.12)	0.19
B4273-xxx-07	0.30 (0.25-0.35)	0.06
B4273-xxx-08	0.10 (0.085-0.11)	0.02

Table 4.21. P0112 HBV-DNA genotype C2 (WHO reference panel member 5086/08-7)

Sample-id	cp/mL (95% CI)	IU/mL	Tigris Ultrio Plus	cobas S201 MPX 1.0
B4112-xxx-01	298 (219-406)	55.9		
B4112-xxx-02	99.3 (72.9-135.3)	18.6	6/6 (100%)	6/6 (100%)
B4112-xxx-03	29.8 (21.9-40.6)	5.59	12/12 (100%)	12/12 (100%)
B4112-xxx-04	9.93 (7.29-13.5)	1.86	6/12 (50%)	11/12 (92%)
B4112-xxx-05	2.98 (2.19-4.06)	0.56	3/12 (25%)	4/12 (33%)
B4112-xxx-06	0.99 (0.73-1.35)	0.19	0/12 (0%)	5/12 (42%)
B4112-xxx-07	0.30 (0.22-0.41)	0.06		
B4112-xxx-08	0.099 (0.073-0.14)	0.02		

Table 4.22. P0113 HBV-DNA genotype C2 (WHO reference panel member 5086/08-8)

Sample-id	cp/mL (95% CI)	IU/mL	Tigris Ultrio Plus	cobas S201 MPX 1.0
B4113-xxx-01	286 (196-415)	53.6		
B4113-xxx-02	95.2 (65.5-138)	17.9	6/6 (100%)	6/6 (100%)
B4113-xxx-03	28.6 (19.6-41.5)	5.36	12/12 (100%)	12/12 (100%)
B4113-xxx-04	9.52 (6.55-13.8)	1.79	9/12 (75%)	12/12 (100%)
B4113-xxx-05	2.86 (1.96-4.15)	0.54	5/12 (42%)	6/12 (50%)
B4113-xxx-06	0.95 (0.66-1.38)	0.18	1/12 (8%)	2/12 (17%)
B4113-xxx-07	0.29 (0.20-0.42)	0.05		
B4113-xxx-08	0.095 (0.065-0.14)	0.02		

Table 4.23. P0114 HBV-DNA genotype C2 (WHO reference panel member 5086/08-9)

Sample-id	cp/mL (95% CI)	IU/mL	Tigris Ultrio Plus	cobas S201 MPX 1.0
B4114-xxx-01	307 (223-421)	57.5		
B4114-xxx-02	102 (74.4-140)	19.2	6/6 (100%)	6/6 (100%)
B4114-xxx-03	30.7 (22.3-42.1)	5.75	12/12 (100%)	12/12 (100%)
B4114-xxx-04	10.2 (7.44-14.0)	1.92	10/12 (83%)	12/12 (100%)
B4114-xxx-05	3.07 (2.23-4.21)	0.58	3/12 (25%)	8/12 (67%)
B4114-xxx-06	1.02 (0.74-1.40)	0.19	3/12 (25%)	4/12 (33%)
B4114-xxx-07	0.31 (0.22-0.42)	0.06		
B4114-xxx-08	0.10 (0.074-0.14)	0.02		

Table 4.24. P0002 HBV-DNA genotype D (Eurohep standard)

Sample-id	cp/mL (95% CI)	IU/mL	Tigris Ultrio	Tigris Ultrio Plus
B4023-xxx-01	2924 (2346-3663)	548	24/24 (100%)	24/24 (100%)
B4023-xxx-02	974 (782-1221)	183	48/48 (100%)	24/24 (100%)
B4023-xxx-03	292 (235-366)	54.8	48/48 (100%)	48/48 (100%)
B4023-xxx-04	97.3 (78.1-122)	18.3	48/48 (100%)	48/48 (100%)
B4023-xxx-05	29.1 (23.4-36.5)	5.47	48/48 (100%)	47/47 (100%)
B4023-xxx-06	9.73 (7.81-12.2)	1.83	41/48 (85%)	43/48 (90%)
B4023-xxx-07	2.91 (2.34-3.65)	0.55	16/48 (33%)	19/48 (40%)
B4023-xxx-08	0.97 (0.78-1.22)	0.18	3/48 (6%)	10/48 (21%)
B4023-xxx-09	0.29 (0.23-0.37)	0.05	3.48 (6%)	10/48 (21%)
B4023-xxx-10	0.097 (0.078-0.12)	0.02		

Table 4.25. P0278 HBV-DNA genotype D (Eurohep standard).
Replacement of P0002 Eurohep standard dilution panel above (table 4.24)

Sample-id	cp/mL (95% CI)	IU/mL
B4269-xxx-01	300 (241-376)	56.2
B4269-xxx-02	100 (80.0-125)	18.7
B4269-xxx-03	30.0 (24.1-37.6)	5.62
B4269-xxx-04	10.0 (8.00-12.5)	1.87
B4269-xxx-05	3.00 (2.41-3.76)	0.56
B4269-xxx-06	1.00 (0.80-1.25)	0.19
B4269-xxx-07	0.30 (0.24-0.38)	0.06
B4269-xxx-08	0.10 (0.080-0.013)	0.02

Table 4.26. P0011 HBV-DNA genotype D (BQC standard)

Sample-id	cp/mL (95% CI)	IU/mL	Tigris Ultrio	Tigris Ultrio Plus	Panther Ultrio Elite
B4004-xxx-01	3134 (2672-3677)	588			
B4004-xxx-02	1041 (887-1222)	195	12/12 (100%)		
B4004-xxx-03	313 (267-368)	58.8	12/12 (100%)	12/12 (100%)	
B4004-xxx-04	104 (88.8-122)	19.5	11/12 (92%)	36/36 (100%)	18/18 (100%)
B4004-xxx-05	31.3 (26.7-36.8)	5.88	9/12 (75%)	34/35 (97%)	17/18 (94%)
B4004-xxx-06	10.4 (8.88-12.2)	1.95	4/12 (33%)	28/36 (78%)	9/18 (50%)
B4004-xxx-07	3.13 (2.67-3.68)	0.59	2/12 (17%)	9/36 (25%)	5/18 (28%)
B4004-xxx-08	1.04 (0.89-1.22)	0.2	0/12 (0%)	5/36 (14%)	5/18 (28%)
B4004-xxx-09	0.31 (0.27-0.37)	0.06		1/36 (3%)	
B4004-xxx-10	0.10 (0.089-0.12)	0.02			

Table 4.27. P0283 HBV-DNA genotype D (BQC standard)
Replacement of P0011 BQC standard dilution panel above (table 2.26)

Sample-id	cp/mL (95% CI)	IU/mL
B4274-xxx-01	300 (256-352)	56.2
B4274-xxx-02	100 (85.0-117)	18.7
B4274-xxx-03	30.0 (25.6-35.2)	5.62
B4274-xxx-04	10.0 (8.50-11.7)	1.87
B4274-xxx-05	3.00 (2.56-3.52)	0.56
B4274-xxx-06	1.00 (0.85-1.12)	0.19
B4274-xxx-07	0.30 (0.25-0.35)	0.06
B4274-xxx-08	0.10 (0.085-0.11)	0.02

Table 4.28. P0115 HBV-DNA genotype D1 (WHO reference panel member 5086/08-10)

Sample-id	cp/mL (95% CI)	IU/mL	Tigris Ultrio Plus	cobas S201 MPX 1.0
B4115-xxx-01	283 (179-445)	53		
B4115-xxx-02	94.2 (59.8-148)	17.7	6/6 (100%)	6/6 (100%)
B4115-xxx-03	28.3 (17.9-44.5)	5.3	12/12 (100%)	12/12 (100%)
B4115-xxx-04	9.42 (5.98-14.8)	1.77	7/12 (58%)	12/12 (100%)
B4115-xxx-05	2.83 (1.79-4.45)	0.53	4/12 (33%)	9/12 (75%)
B4115-xxx-06	0.94 (0.60-1.48)	0.18	2/12 (17%)	3/12 (25%)
B4115-xxx-07	0.28 (0.17-0.45)	0.05		
B4115-xxx-08	0.094 (0.060-0.15)	0.02		

Table 4.29. P0116 HBV-DNA genotype D3 (WHO reference panel member 5086/08-11)

Sample-id	cp/mL (95% CI)	IU/mL	Tigris Ultrio Plus	cobas S201 MPX 1.0
B4116-xxx-01	308 (247-384)	57.8		
B4116-xxx-02	103 (82.5-128)	19.3		
B4116-xxx-03	30.8 (24.7-38.4)	5.78	6/6 (100%)	6/6 (100%)
B4116-xxx-04	10.3 (8.25-12.8)	1.93	9/12 (75%)	12/12 (100%)
B4116-xxx-05	3.08 (2.47-3.84)	0.58	7/12 (58%)	9/12 (82%)
B4116-xxx-06	1.03 (0.82-1.28)	0.19	1/12 (8%)	6/12 (50%)
B4116-xxx-07	0.31 (0.25-0.38)	0.06	0/12 (0%)	2/12 (17%)
B4116-xxx-08	0.10 (0.082-0.13)	0.02		

Table 4.30. P0117 HBV-DNA genotype D1 (WHO reference panel member 5086/08-12)

Sample-id	cp/mL (95% CI)	IU/mL	Tigris Ultrio Plus	cobas S201 MPX 1.0
B4117-xxx-01	318 (209-484)	59.6		
B4117-xxx-02	106 (69.6-161)	19.9	6/6 (100%)	6/6 (100%)
B4117-xxx-03	31.8 (20.9-48.4)	5.96	12/12 (100%)	12/12 (100%)
B4117-xxx-04	10.6 (6.96-16.1)	1.99	9/12 (75%)	11/12 (92%)
B4117-xxx-05	3.18 (2.09-4.84)	0.6	7/12 (58%)	11/12 (92%)
B4117-xxx-06	1.06 (0.70-1.61)	0.2	3/12 (25)	3/12 (25%)
B4117-xxx-07	0.32 (0.21-0.48)	0.06		
B4117-xxx-08	0.11 (0.070-0.16)	0.02		

Table 4.31. P0012 HBV-DNA genotype E (BQC standard)

Sample-id	cp/mL (95% CI)	IU/mL	Tigris Ultrio	Tigris Ultrio Plus	Panther Ultrio Elite
B4005-xxx-01	3213 (2906-3561)	603			
B4005-xxx-02	1068 (966-1183)	200	12/12 (100%)		
B4005-xxx-03	321 (291-356)	60.3	12/12 (100%)	12/12 (100%)	
B4005-xxx-04	107 (96.6-118)	20	12/12 (100%)	35/35 (100%)	18/18 (100%)
B4005-xxx-05	32.1 (29.1-35.6)	6.03	9/12 (75%)	36/36 (100%)	18/18 (100%)
B4005-xxx-06	10.7 (9.66-11.8)	2	6/12 (50%)	32/36 (89%)	17/18 (94%)
B4005-xxx-07	3.21 (2.91-3.56)	0.6	2/12 (17%)	16/35 (46%)	12/18 (67%)
B4005-xxx-08	1.07 (0.97-1.18)	0.2	0/12 (0%)	5/36 (14%)	2/18 (11%)
B4005-xxx-09	0.32 (0.29-0.36)	0.06		1/36 (3%)	
B4005-xxx-10	0.11 (0.097-0.12)	0.02			

Table 4.32. P0284 HBV-DNA genotype E (BQC standard)

Replacement of P0012 BQC standard dilution panel above (table 4.31)

Sample-id	cp/mL (95% CI)	IU/mL
B4275-xxx-01	300 (271-332)	56.2
B4275-xxx-02	100 (90.0-111)	18.7
B4275-xxx-03	30.0 (27.1-33.2)	5.62
B4275-xxx-04	10.0 (9.00-11.1)	1.87
B4275-xxx-05	3.00 (2.71-3.32)	0.56
B4275-xxx-06	1.00 (0.90-1.11)	0.19
B4275-xxx-07	0.30 (0.27-0.33)	0.06
B4275-xxx-08	0.10 (0.090-0.11)	0.02

Table 4.33. P0118 HBV-DNA genotype E1 (WHO reference panel member 5086/08-13)

Sample-id	cp/mL (95% CI)	IU/mL	Tigris Ultrio Plus	cobas S201 MPX 1.0
B4118-xxx-01	304 (242-383)	57.1		
B4118-xxx-02	101.5 (80.6-128)	19	6/6 (100%)	6/6 (100%)
B4118-xxx-03	30.4 (24.2-38.3)	5.71	12/12 (100%)	12/12 (100%)
B4118-xxx-04	10.1 (8.06-12.8)	1.9	7/12 (58%)	12/12 (100%)
B4118-xxx-05	3.04 (2.42-3.83)	0.57	5/12 (42%)	9/12 (75%)
B4118-xxx-06	1.01 (0.81-1.28)	0.19	2/12 (17%)	3/12 (25%)
B4118-xxx-07	0.30 (0.24-0.38)	0.06		
B4118-xxx-08	0.10 (0.08-0.13)	0.02		

Table 4.34. P0013 HBV-DNA genotype F (BQC standard)

Sample-id	cp/mL (95% CI)	IU/mL	Tigris Ultrio	Tigris Ultrio Plus	Panther Ultrio Elite
B4006-xxx-01	3607 (2315-5624)	677			
B4006-xxx-02	1205 (774-1880)	226	12/12 (100%)		
B4006-xxx-03	361 (232-562)	67.7	12/12 (100%)	12/12 (100%)	
B4006-xxx-04	121 (77.4-188)	22.6	12/12 (100%)	36/36 (100%)	
B4006-xxx-05	36.1 (23.2-56.2)	6.77	10/12 (83%)	36/36 (100%)	18/18 (100%)
B4006-xxx-06	12.1 (7.74-18.8)	2.26	5/12 (42%)	34/36 (94%)	15/18 (83%)
B4006-xxx-07	3.61 (2.32-5.62)	0.68	2/12 (17%)	16/36 (44%)	5/18 (28%)
B4006-xxx-08	1.21 (0.77-1.88)	0.23	1/12 (8%)	11/36 (31%)	5/18 (28%)
B4006-xxx-09	0.36 (0.23-0.56)	0.07		2/36 (6%)	1/18 (6%)
B4006-xxx-10	0.12 (0.077-0.18)	0.02			

Table 4.35. P0285 HBV-DNA genotype F (BQC standard)

Replacement of P0013 BQC standard dilution panel above (table 4.34)

Sample-id	cp/mL (95% CI)	IU/mL
B4276-xxx-01	300 (193-468)	56.2
B4276-xxx-02	100 (64-156)	18.7
B4276-xxx-03	30.0 (19.3-46.8)	5.62
B4276-xxx-04	10.0 (6.40-15.6)	1.87
B4276-xxx-05	3.00 (1.93-4.68)	0.56
B4276-xxx-06	1.00 (0.64-1.56)	0.19
B4276-xxx-07	0.30 (0.19-0.47)	0.06
B4276-xxx-08	0.10 (0.064-0.16)	0.02

Table 4.36. P0119 HBV-DNA genotype F3 (WHO reference panel member 5086/08-14)

Sample-id	cp/mL (95% CI)	IU/mL	Tigris Ultrio Plus	cobas S201 MPX 1.0
B4119-xxx-01	310 (193-496)	58.1		
B4119-xxx-02	103 (64.4-165)	19.4	6/6 (100%)	6/6 (100%)
B4119-xxx-03	31.0 (19.3-49.6)	5.81	12/12 (100%)	8/12 (67%)
B4119-xxx-04	10.3 (6.44-16.5)	1.94	12/12 (100%)	2/12 (17%)
B4119-xxx-05	3.10 (1.93-4.96)	0.58	6/12 (50%)	0/12 (0%)
B4119-xxx-06	1.03 (0.64-1.65)	0.19	6/12 (50%)	0/12 (0%)
B4119-xxx-07	0.31 (0.19-0.50)	0.06		
B4119-xxx-08	0.10 (0.064-0.17)	0.02		

Table 4.37. P0014 HBV-DNA genotype G (BQC standard)

Sample-id	cp/mL (95% CI)	IU/mL	Tigris Ultrio	Tigris Ultrio Plus	Panther Ultrio Elite
B4007-xxx-01	3188 (2650-3834)	598			
B4007-xxx-02	1063 (883-1278)	199	12/12 (100%)		
B4007-xxx-03	319 (265-383)	59.8	12/12 (100%)	12/12 (100%)	
B4007-xxx-04	106 (88.3-128)	19.9	12/12 (100%)	35/35 (100%)	
B4007-xxx-05	31.9 (26.5-38.3)	5.98	12/12 (100%)	36/36 (100%)	18/18 (100%)
B4007-xxx-06	10.6 (8.83-12.8)	1.99	7/12 (58%)	34/36 (94%)	15/18 (83%)
B4007-xxx-07	3.19 (2.65-3.83)	0.6	3.12 (25%)	15/35 (43%)	11/18 (61%)
B4007-xxx-08	1.06 (0.88-1.28)	0.2	1/12 (8%)	8/36 (22%)	3/18 (17%)
B4007-xxx-09	0.32 (0.27-0.38)	0.06		2/36 (6%)	0/18 (0%)
B4007-xxx-10	0.11 (0.088-0.13)	0.02			

Table 4.38. P0286 HBV-DNA genotype G (BQC standard)

Replacement of P0014 BQC standard dilution panel above (table 4.37)

Sample-id	cp/mL (95% CI)	IU/mL
B4277-xxx-01	300 (249-361)	56.2
B4277-xxx-02	100 (83-120)	18.7
B4277-xxx-03	30.0 (25-36)	5.62
B4277-xxx-04	10.0 (8.3-12)	1.87
B4277-xxx-05	3.00 (2.5-3.6)	0.56
B4277-xxx-06	1.00 (0.83-1.20)	0.19
B4277-xxx-07	0.30 (0.25-0.36)	0.06
B4277-xxx-08	0.10 (0.083-0.12)	0.02

Table 4.39. P0120 HBV-DNA genotype G (WHO reference panel member 5086/08-15)

Sample-id	cp/mL (95% CI)	IU/mL	Tigris Ultrio Plus	cobas S201 MPX 1.0
B4120-xxx-01	300 (173-519)	56.2		
B4120-xxx-02	100 (57.7-173)	18.7	6/6 (100%)	6/6 (100%)
B4120-xxx-03	30.0 (17.3-51.9)	5.62	12/12 (100%)	12/12 (100%)
B4120-xxx-04	10.0 (5.77-17.3)	1.87	10/12 (83%)	11/12 (92%)
B4120-xxx-05	3.00 (1.73-5.19)	0.56	2/12 (17%)	5/12 (42%)
B4120-xxx-06	1.00 (0.58-1.73)	0.19	1/12 (8%)	1/12 (8%)
B4120-xxx-07	0.30 (0.17-0.52)	0.06		
B4120-xxx-08	0.10 (0.058-0.17)	0.02		

Expected Lower limit of detection (LOD)

For establishing the 95% and 50% LOD by probit analysis[21] it is recommend to test the panel members in at least 12 and preferably in 24 or 48 replicates. Panel members ranging from at least one concentration of 100% reactivity to at least one concentration below 50% reactivity should be used for a reliable probit analysis. Apply Log transformation of the concentrations in copies or IU/mL before interpreting the number of

reactive and nonreactive results by probit analysis. It is recommended to report both the 50% and 95% LOD and compare these with the historically established values presented in tables 5.1 to 5.4 for the different HBV-DNA genotype reference panels.

Table 5.1 Detection limits on HBV-DNA genotype A standard dilution panels in Procleix Ultrio assay versions and cobas MPX assay versions

HBV-DNA standard	panel	NAT method	n	50% LOD (CI) cp/mL	95% LOD (CI) cp/mL
S0010 Eurohep HBV-DNA genotype A2	P0001	Ultrio	48	9.4 (5.0-18.0)	93.9 (40.9-493)
	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)
	P0001	TaqScreen 1.0	12	2.3 (1.3-3.8)	14.1 (7.2-56.6)
	P0272	cobas MPX	48	1.7 (1.0-2.4)	10.3 (6.2-28.8)
WHO HBV-DNA 97/750 genotype A2	P0023	Ultrio	32	13.1 (6.3-32.0)	101 (38.7-1020)
	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)
	P0023	cobas MPX	12	1.8 (0.93-2.8)	8.0 (4.4-37.4)
S0011 VQC-Sanquin HBV-DNA genotype A2	S2384	Ultrio	48	27.2 (14.3-105)	235 (153-407)
	P0007	Ultrio	24	15.7 (7.0-33.9)	208 (77.6-2022)
	S2384	Ultrio Plus	12	5.7 (3.4-9.7)	49.4 (27.4-103)
	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)
	S2384	TaqScreen 1.0	12	2.8 (1.7-4.8)	24.5 (13.7-50.9)
	P0007	cobas MPX	24	1.9 (1.3-2.7)	13.0 (7.7-29.6)
S0043 BioQ HBV-DNA genotype A2 inactivated	P0031	Ultrio	58	56.5 (31.5-104)	715 (316-3046)
	P0031	Ultrio Plus	24	6.6 (2.7-17.4)	64 .2 (22.4-109)
	P0031	Ultrio Elite	25	5.7 (4.0-8.2)	40.8 (24.3-91.7)
	P0031	cobas MPX	12	2.4 (1.4-4.2)	18.6 (9.1-75.9)
	P0251	TaqScreen 2.0	12	2.8 (1.5-4.3)	23.8 (12.4-99.3)
WHO HBV-DNA genotype A2 5086/08-3	P0108	Ultrio Plus	12	3.0 (1.8-5.1)	22.1 (12.7-40.8)
	P0108	TaqScreen 1.0	12	1.7 (1.1-2.8)	9.5 (5.7-16.8)
WHO HBV-DNA genotype A1 5086/08-1	P0106	Ultrio Plus	12	3.1 (1.9-5.2)	22.9 (13.2-41.9)
	P0106	TaqScreen 1.0	12	1.8 (1.1-2.9)	9.8 (6.0-17.0)
WHO HBV-DNA genotype A1 5086/08-2	P0107	Ultrio Plus	12	4.3 (2.5-7.3)	31.4 (17.9-58.5)
	Po107	TaqScreen 1.0	12	6.3 (3.7-10.7)	34.4 (19.8-63.7)

Table 5.2. Detection limits on HBV-DNA genotype B and C standard dilution panels in Procleix Ultrio assay versions and cobas MPX assay versions

HBV-DNA standard	panel	NAT method	n	50% LOD (CI) cp/mL	95% LOD (CI) cp/mL
S0098 BioQ HBV-DNA genotype B	S2385	Ultrio	24	5.3 (3.6-7.8)	49.9 (30.7-94.2)
	P0009	Ultrio	12	3.3 (1.9-5.5)	23.6 (13.6-45.9)
	S2385	Ultrio Plus	12	3.1 (1.8-5.4)	29.4 (16.0-62.8)
	P0009	Ultrio Plus	36	2.8 (2.1-3.8)	20.3 (13.6-45.9)
	P0009	Ultrio Elite	18	2.7 (1.8-4.1)	34.5 (22.1-58.0)
	S2385	TaqScreen 1.0	12	6.4 (3.7-10.9	59.5 (32.1-129)
WHO HBV-DNA genotype B1 5086/08-4	P0109	Ultrio Plus	12	5.0 (3.1-8.2)	36.6 (21.9-64.7)
	P0109	TaqScreen 1.0	12	3.8 (2.4-6.1)	20.9 912.8-35.9)
WHO HBV-DNA genotype B2 5086/08-5	P0110	Ultrio Plus	12	3.6 (2.2-6.1)	26.7 (15.6-48.4)
	P0110	TaqScreen 1.0	12	3.5 (2.2-5.6)	19.3 (11.9-33.0)
WHO HBV-DNA genotype B4 5086/08-6	P0111	Ultrio Plus	12	4.4 (2.6-7.2)	32.1 (19.0-57.4)
	P0111	TaqScreen 1.0	12	3.3 (2.1-5.2)	18.0 (11.1-30.8)
S0057 BioQ HBV-DNA genotype C	S2386	Ultrio	24	10.0 (6.4-15.5)	64.3 (37.8-137)
	P0010	Ultrio	12	14.3 (6.3-32.9)	115 (48.7-368)
	S2386	Ultrio Plus	12	4.2 (2.3-7.8)	27.3 (14.0-66.9)
	P0010	Ultrio Plus	36	4.6 (2.9-7.6)	37.4 (20.3-93.4)
	P0010	Ultrio Elite	18	5.0 (2.4-10.2)	40.0 (18.6-114)
	S2386	TaqScreen 1.0	12	2.9 (1.6-5.4)	19.0 (9.7-47.2)
WHO HBV-DNA genotype C2 5086/08-7	P0112	Ultrio Plus	12	7.3 (4.3-12.3)	53.2 (30.6-97.9)
	P0112	TaqScreen 1.0	12	2.4 (1.5-3.8)	13.2 (8.1-22.6)
WHO HBV-DNA genotype C2 5086/08-8	P0113	Ultrio Plus	12	4.0 (2.3-6.7)	29.2 (16.9-53.2)
	P0113	TaqScreen 1.0	12	2.4 (1.5-3.9)	13.2 (7.9-23.1)
WHO HBV-DNA genotype C2 5086/08-9	P0114	Ultrio Plus	12	3.5 (2.1-5.9)	25.6 (14.9-46.6)
	P0114	TaqScreen 1.0	12	1.6 (1.0-2.6)	8.7 (5.1-15.4)

Table 5.3. Detection limits on HBV-DNA genotype D and E standard dilution panels in Procleix Ultrio assay versions and cobas MPX assay versions

HBV-DNA standard	panel	NAT method	n	50% LOD (CI) cp/mL	95% LOD (CI) cp/mL
S0107 Eurohep HBV-DNA genotype D	P0002	Ultrio	48	3.5 (2.2-5.8)	20.9 (11.0-72.0)
	P0002	Ultrio Plus	48	2.2 (1.1-4.0)	25.3 (10.9-142)
S0058 BioQ HBV-DNA genotype D	S2387	Ultrio	24	15.2 (11.0-21.2)	80.8 (53.1-144)
	P0011	Ultrio	12	14.9 (6.7-32.9)	123 (53.3-371)
	S2387	Ultrio Plus	12	5.1 (3.2-8.3)	27.5 (16.4-53.7)
	P0011	Ultrio Plus	36	4.6 (2.9-7.3)	37.9 (20.9-91.1)
	P0011	Ultrio Elite	18	5.3 (2.8-10.2)	44.1 (21.6-118)
	S2387	TaqScreen 1.0	12	1.6 (1.0-2.6)	8.4 (4.9-16.6)
WHO HBV-DNA genotype D1 5086/08-10	P0115	Ultrio Plus	12	4.8 (2.8-7.9)	34.9 (20.4-63.0)
	P0115	TaqScreen 1.0	12	1.6 (0.9-2.7)	8.7 (5.2-15.4)
WHO HBV-DNA genotype D3 5086/08-11	P0116	Ultrio Plus	12	3.5 (2.1-6.0)	25.9 (14.9-47.9)
	P0116	TaqScreen 1.0	12	1.0 (0.6-1.6)	5.3 (3.2-9.2)
WHO HBV-DNA genotype D1 5086/08-12	P0117	Ultrio Plus	12	2.7 (1.6-4.5)	19.6 (11.4-35.4)
	P01117	TaqScreen 1.0	12	1.5 (0.9-2.5)	8.1 (4.8-14.3)
S0059 BioQ HBV-DNA genotype E	S2388	Ultrio	24	9.4 (6.3-14.0)	110 (64.3-225)
	P0012	Ultrio	12	11.4 (7.3-17.9)	58.6 (35.9-107)
	S2388	Ultrio Plus	12	4.6 (2.6-8.3)	54.2 (28.0-124)
	P0012	Ultrio Plus	36	3.2 (2.4-4.1)	16.2 (11.3-26.1)
	P0012	Ultrio Elite	18	2.5 (1.7-3.7)	12.7 (8.2-21.7)
	S2388	TaqScreen 1.0	12	2.1 (1.1-3.8)	23.9 (12.2-54.3)
WHO HBV-DNA genotype E1 5086/08-13	P0118	Ultrio Plus	12	4.3 (2.6-7.2)	31.9 (18.7-57.4)
	P0118	TaqScreen 1.0	12	1.6 (0.9-2.9)	8.7 (5.2-15.4)

Table 5.4. Detection limits on HBV-DNA genotype F and G standard dilution panels in Procleix Ultrio assay versions and cobas MPX assay versions

HBV-DNA standard	panel	NAT method	n	50% LOD (CI) cp/mL	95% LOD (CI) cp/mL
S0060 BioQ HBV-DNA genotype F	S2389	Ultrio	24	11.9 (8.4-16.9)	78.8 (50.5-143)
	P0013	Ultrio	12	11.2 (6.8-18.6)	82.2 (47.2-161)
	S2389	Ultrio Plus	12	2.6 (1.6-4.2)	17.0 (9.8-34.4)
	P0013	Ultrio Plus	36	2.7 (2.0-3.6)	19.8 (13.3-33.1)
	P0013	Ultrio Elite	18	3.8 (2.5-5.7)	27.6 (17.0-50.1)
	S2389	TaqScreen 1.0	12	5.3 (3.3-8.8)	35.2 (20.2-71.6)
WHO HBV-DNA genotype F3 5086/08-14	P0119	Ultrio Plus	12	1.5 (1.0-2.6)	11.0 (6.2-20.3)
	P0119	TaqScreen 1.0	12	22.2 (13.4-37.0)	122 (71.4-222)
S0061 BioQ HBV-DNA genotype G	S2390	Ultrio	24	4.6 (3.1-6.7)	44.3 (29.9-86.1)
	P0014	Ultrio	12	6.2 (3.8-10.0)	36.0 (21.3-67.9)
	S2390	Ultrio Plus	12	1.8 (1.0-3.2)	17.7 (9.5-38.7)
	P0014	Ultrio Plus	36	2.6 (2.0-3.5)	15.3 (10.6-25.0)
	P0014	Ultrio Elite	18	2.9 (2.0-4.3)	17.0 (10.9-29.7)
	S2390	TaqScreen 1.0	12	7.2 (4.2-12.4)	96.6 (37.3-154)
WHO HBV-DNA genotype G 5086/08-15	P0120	Ultrio Plus	12	4.8 (2.8-8.2)	35.2 (20.2-64.9)
	P0120	TaqScreen 1.0	12	3.3 (2.0-5.4)	18.1 (10.9-31.6)

Limit of quantification (LOQ) of viral load assays

The HBV-DNA reference panels may also be used to check the LOQ of a viral load assay. The LOQ of a viral load assay is the lowest amount of nucleic acid in a sample which can be quantitatively determined with sufficient precision and accuracy.

- **Checking amplification efficiency**.
  For quantitative NAT methods the relation between ^{2}log(concentration) and ^{2}log(quantitative results) or Ct value can be judged using linear regression. Ideally the slope of the curve should be -1.00. If the result is different consider to remove lower concentrations with intermittent reactivity. The slope is accepted when the confidence interval on the slope overlaps -1.00
- **Calculation of precision**.
  The precision becomes less with lower concentrations approaching the LOQ and 95% LOD of the viral load assay. One could calculate the SD of replicate viral load tests for each concentration and compare this with the values in the package insert of the NAT method to be evaluated.

Accuracy

The P0001 HBV-DNA Eurohep genotype A and P0007 HBV-DNA VQC-Sanquin genotype A standard dilution panels can best be used to examine the accuracy of a quantitative NAT method for reporting values in copies/mL in the lower viral load range. The P0004 WHO 97/750 standard dilution panel P0004 can best be used for reporting accuracy of values

reported in IU/mL. The accuracy is highest when the measured values are equal to the nominal values.

Limitations

The cross calibration of the reference panels in copies/mL was based on testing of HBV genotype standards in the previous bDNA 3.0 assay as reference method. The 95% and 50% LODs may change when calibration would be based on other quantitative NAT methods. The IU values assigned to the reference panels were based on the 1st WHO HBV-97/746 standard and a conversion factor of 5.33 copy/IU. However cross calibration of different HBV standards may be dependent on the quantitative NAT method used. Therefore LODs and copy/IU conversion factors may change when the 3rd WHO HBV genotype A standard (or other standards) are used.

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