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►**B**

COMMISSION DECISION

of 7 May 2002

on common technical specifications for *in vitro*-diagnostic medical devices

(notified under document number C(2002) 1344)

(Text with EEA relevance)

(2002/364/EC)

(OJ L 131, 16.5.2002, p. 17)

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►**M2**	Commission Decision 2009/886/EC of 27 November 2009	L 318	25	4.12.2009
►**M3**	Commission Decision 2011/869/EU of 20 December 2011	L 341	63	22.12.2011
►**M4**	Commission Implementing Decision (EU) 2019/1244 of 1 July 2019	L 193	1	19.7.2019
►**M5**	Commission Implementing Decision (EU) 2020/350 of 28 February 2020	L 63	3	3.3.2020

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►**C1** Corrigendum, OJ L 348, 29.12.2009, p. 94 (2009/886/EC)

▼B

COMMISSION DECISION

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on common technical specifications for *in vitro*-diagnostic medical devices

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(Text with EEA relevance)

(2002/364/EC)

Article 1

The technical specifications set out in the Annex to this Decision are adopted as common technical specifications for *in vitro* diagnostic medical devices in list A of Annex II to Directive 98/79/EC.

Article 2

This Decision is addressed to the Member States.

▼M2

ANNEX

COMMON TECHNICAL SPECIFICATIONS (CTS) FOR *IN VITRO* DIAGNOSTIC MEDICAL DEVICES

1. SCOPE

The common technical specifications set out in this Annex shall apply for the purposes of Annex II List A to Directive 98/79/EC.

2. DEFINITIONS AND TERMS

(Diagnostic) sensitivity

The probability that the device gives a positive result in the presence of the target marker.

True positive

A specimen known to be positive for the target marker and correctly classified by the device.

False negative

A specimen known to be positive for the target marker and misclassified by the device.

(Diagnostic) specificity

The probability that the device gives a negative result in the absence of the target marker.

False positive

A specimen known to be negative for the target marker and misclassified by the device.

True negative

A specimen known to be negative for the target marker and correctly classified by the device.

Analytical sensitivity

Analytical sensitivity may be expressed as the limit of detection, i.e. the smallest amount of the target marker that can be precisely detected.

Analytical specificity

Analytical specificity means the ability of the method to determine solely the target marker.

Nucleic acid amplification techniques (NAT)

The term ‘NAT’ is used for tests for the detection and/or quantification of nucleic acids by either amplification of a target sequence, by amplification of a signal or by hybridisation.

Rapid test

‘Rapid test’ means qualitative or semi-quantitative *in vitro* diagnostic medical devices, used singly or in a small series, which involve non-automated procedures and have been designed to give a fast result.

Robustness

The robustness of an analytical procedure means the capacity of an analytical procedure to remain unaffected by small but deliberate variations in method parameters and provides an indication of its reliability during normal usage.

▼M2

Whole system failure rate

The whole system failure rate means the frequency of failures when the entire process is performed as prescribed by the manufacturer.

▼M5

First-line assay

First-line assay means an assay used to detect a marker or analyte, and which may be followed by a confirmatory assay. Devices intended solely to be used to monitor a previously determined marker or analyte are not considered first-line assays.

Confirmatory assay

Confirmatory assay means an assay used for the confirmation of a reactive result from a first-line assay.

▼M2

Virus typing assay

Virus typing assay means an assay used for typing with already known positive samples, not used for primary diagnosis of infection or for screening.

Sero-conversion HIV samples

Sero-conversion HIV samples mean:

— p24 antigen and/or HIV RNA positive, and

— recognised by all of the antibody screening tests, and

— positive or indeterminate confirmatory assays.

Early sero-conversion HIV samples

Early seroconversion HIV samples mean:

— p24 antigen and/or HIV RNA positive, and

— not recognised by all of the antibody screening tests, and

— indeterminate or negative confirmatory assays.

3. COMMON TECHNICAL SPECIFICATIONS (CTS) FOR PRODUCTS REFERRED TO IN ANNEX II, LIST A OF DIRECTIVE 98/79/EC

3.1. **CTS for performance evaluation of reagents and reagent products for the detection, confirmation and quantification in human specimens of markers of HIV infection (HIV 1 and 2), HTLV I and II, and hepatitis B, C, D**

General principles

▼M5

3.1.1. Devices which detect virus infections shall meet the requirements for sensitivity and specificity set out in Table 1, Table 3, Table 4 and Table 5, which apply to them taking account of the intended purpose of the devices concerned, virus type and entities to be detected (antigen and/or antibody). See also principle 3.1.11 for first-line assays.

▼M2

3.1.2. Devices intended by the manufacturer for testing body fluids other than serum or plasma, e.g. urine, saliva, etc., shall meet the same CTS requirements for sensitivity and specificity as serum or plasma tests. The performance evaluation shall test samples from the same individuals in both the tests to be approved and in a respective serum or plasma assay.

▼M5

3.1.3. Devices for self-testing shall meet the same CTS requirements for sensitivity and specificity as respective devices for professional use. Relevant parts of the performance evaluation shall be carried out (or repeated) by appropriate lay users to validate the operation of the device and the instructions for use. The lay users selected for the performance evaluation shall be representative of the intended users groups.

Performance evaluation of a device for self-testing shall include, for each body fluid claimed for use with the device, e.g. whole blood, urine, saliva, etc., at least 200 lay users that are known positive for the infection and at least 400 lay users that do not know their status, of which at least 200 are at high risk of acquiring the infection. The sensitivity and specificity of the device for self-testing in the hands of lay users shall be defined against the confirmed patient infectious status.

▼M2

3.1.4. All performance evaluations shall be carried out in direct comparison with an established state-of-the-art device. The device used for comparison shall be one bearing CE marking, if on the market at the time of the performance evaluation.

3.1.5. If discrepant test results are identified as part of an evaluation, these results shall be resolved as far as possible, for example:

— by evaluation of the discrepant sample in further test systems,

— by use of an alternative method or marker,

— by a review of the clinical status and diagnosis of the patient, and

— by the testing of follow-up-samples.

3.1.6. Performance evaluations shall be performed on a population equivalent to the European population.

3.1.7. Positive specimens used in the performance evaluation shall be selected to reflect different stages of the respective disease(s), different antibody patterns, different genotypes, different subtypes, mutants, etc.

3.1.8. Sensitivity with true positives and sero-conversion samples shall be evaluated as follows:

3.1.8.1. Diagnostic test sensitivity during sero-conversion has to represent the state of the art. Whether further testing of the same or additional sero-conversion panels is conducted by the notified body or by the manufacturer the results shall confirm the initial performance evaluation data (see Table 1). Sero-conversion panels should start with a negative bleed(s) and should have narrow bleeding intervals.

▼M2

3.1.8.2. For blood screening devices (with the exception of HBsAg and anti-HBc tests), all true positive samples shall be identified as positive by the device to be CE marked (Table 1). For HBsAg and anti-HBc tests the new device shall have an overall performance at least equivalent to that of the established device (see 3.1.4).

3.1.8.3. Regarding HIV tests:

— all sero-conversion HIV samples shall be identified as positive, and

— at least 40 early sero-conversion HIV samples shall be tested. Results should conform to the state of the art.

▼M5

3.1.9. Performance evaluation of first line assays shall include 25 positive (if available in the case of rare infections) 'same day' fresh serum samples (≤ 1 day after sampling).

▼M2

3.1.10. Negative specimens used in a performance evaluation shall be defined so as to reflect the target population for which the test is intended, for example blood donors, hospitalised patients, pregnant women, etc.

▼M5

3.1.11. For performance evaluations for first line assays (Table 1 and Table 3) blood donor populations shall be investigated from at least two blood donation centers and consist of consecutive blood donations, which have not been selected to exclude first time donors.

▼M2

3.1.12. Devices shall have a specificity of at least 99,5 % on blood donations, unless otherwise indicated in the accompanying tables. Specificity shall be calculated using the frequency of repeatedly reactive (i.e. false positive) results in blood donors negative for the target marker.

3.1.13. Devices shall be evaluated to establish the effect of potential interfering substances, as part of the performance evaluation. The potential interfering substances to be evaluated will depend to some extent on the composition of the reagent and configuration of the assay. Potential interfering substances shall be identified as part of the risk analysis required by the essential requirements for each new device but may include, for example:

— specimens representing 'related' infections,

— specimens from multipara, i.e. women who have had more than one pregnancy, or rheumatoid factor positive patients,

— for recombinant antigens, human antibodies to components of the expression system, for example anti-E. coli, or anti-yeast.

3.1.14. For devices intended by the manufacturer to be used with serum and plasma the performance evaluation must demonstrate serum to plasma equivalency. This shall be demonstrated for at least 50 donations (25 positive and 25 negative).

3.1.15. For devices intended for use with plasma the performance evaluation shall verify the performance of the device using all anticoagulants which the manufacturer indicates for use with the device. This shall be demonstrated for at least 50 donations (25 positive and 25 negative).

▼M2

3.1.16. As part of the required risk analysis the whole system failure rate leading to false-negative results shall be determined in repeat assays on low-positive specimens.

3.1.17. If a new *in vitro* diagnostic medical device belonging to Annex II List A is not specifically covered by the common technical specification, the common technical specification for a related device should be taken into account. Related devices may be identified on different grounds, e.g. by the same or similar intended use or by similar risks.

▼M4

3.2. **Additional requirements for HIV and HCV antigen and antibody combined tests**

3.2.1. HIV antigen and antibody combined tests intended for the detection of HIV-1 p24 antigen and HIV-1/2 antibody shall meet the requirements for sensitivity and specificity set out in Table 1 and Table 5.

3.2.2. Hepatitis C virus (HCV) antigen and antibody combined tests intended for the detection of HCV antigen and HCV antibody shall meet the requirements for sensitivity and specificity set out in Table 1 and Table 5. HCV seroconversion panels for the evaluation of HCV antigen and antibody combined tests shall start with one or more negative bleeds and comprise panel members from early HCV infection (HCV core antigen and/or HCV RNA positive but anti-HCV negative). HCV antigen and antibody combined tests shall demonstrate enhanced sensitivity in early HCV infection when compared to HCV antibody only tests.

▼M2

3.3. **Additional requirements for nucleic acid amplification techniques (NAT)**

The performance evaluation criteria for NAT assays can be found in Table 2.

3.3.1. For target sequence amplification assays, a functionality control for each test sample (internal control) shall reflect the state of the art. This control shall as far as possible be used throughout the whole process, i.e. extraction, amplification/hybridisation, detection.

▼M4

3.3.2. The analytical sensitivity or detection limit for NAT assays shall be expressed by the 95 % positive cut-off value. This is the analyte concentration where 95 % of test runs give positive results following serial dilutions of an international reference material, where available, such as a World Health Organisation (WHO) International Standard or reference material calibrated against a WHO International Standard.

3.3.2a. Qualitative HIV NAT assays intended to be used to detect the presence of HIV in blood, blood components, cells, tissues or organs, or in any of their derivatives, in order to assess their suitability for transfusion, transplantation or cell administration shall be designed to detect both HIV-1 and HIV-2.

▼M4

3.3.2b. Qualitative HIV NAT assays, other than virus typing assays, shall be designed to compensate for the potential failure of a HIV-1 NAT target region, e.g. by using two independent target regions.

▼M2

3.3.3. Genotype detection shall be demonstrated by appropriate primer or probe design validation and shall also be validated by testing characterised genotyped samples.

3.3.4. Results of quantitative NAT assays shall be traceable to international standards or calibrated reference materials, if available, and be expressed in international units utilised in the specific field of application.

3.3.5. NAT assays may be used to detect virus in antibody negative samples, i.e. pre-sero-conversion samples. Viruses within immune-complexes may behave differently in comparison to free viruses, for example during a centrifugation step. It is therefore important that during robustness studies, antibody-negative (pre-sero-conversion) samples are included.

3.3.6. For investigation of potential carry-over, at least five runs with alternating high-positive and negative specimens shall be performed during robustness studies. The high positive samples shall comprise samples with naturally occurring high virus titres.

3.3.7. The whole system failure rate leading to false-negative results shall be determined by testing low-positive specimens. Low-positive specimens shall contain a virus concentration equivalent to three times the 95 % positive cut-off virus concentration.

3.4. **CTS for the manufacturer's release testing of reagents and reagent products for the detection, confirmation and quantification in human specimens of markers of HIV infection (HIV 1 and 2), HTLV I and II, and hepatitis B, C, D (immunological assays only)**

3.4.1. The manufacturer's release testing criteria shall ensure that every batch consistently identifies the relevant antigens, epitopes, and antibodies.

▼M5

3.4.2. The manufacturer's batch release testing for first line assays shall include at least 100 specimens negative for the relevant analyte.

▼M2

3.5. **CTS for performance evaluation of reagents and reagent products for determining the following blood group antigens: ABO blood group system ABO1 (A), ABO2 (B), ABO3 (A,B); Rh blood group system RH1 (D), RH2 (C), RH3 (E), RH4 (c), RH5 (e); Kell blood group system KEL1 (K)**

Criteria for performance evaluation of reagents and reagent products for determining the blood groups antigens: ABO blood group system ABO1 (A), ABO2 (B), ABO3 (A,B); Rh blood group system RH1 (D), RH2 (C), RH3 (E), RH4 (c), RH5 (e); Kell blood group system KEL1 (K) can be found in Table 9.

3.5.1. All performance evaluations shall be carried out in direct comparison with an established state-of-the-art device. The device used for comparison shall be one bearing CE marking, if on the market at the time of the performance evaluation.

▼M2

3.5.2. If discrepant test results are identified as part of an evaluation, these results shall be resolved as far as possible, for example:

— by evaluation of the discrepant sample in further test systems,

— by use of an alternative method,

3.5.3. Performance evaluations shall be performed on a population equivalent to the European population.

3.5.4. Positive specimens used in the performance evaluation shall be selected to reflect variant and weak antigen expression.

3.5.5. Devices shall be evaluated to establish the effect of potential interfering substances, as part of the performance evaluation. The potential interfering substances to be evaluated will depend to some extent on the composition of the reagent and configuration of the assay. Potential interfering substances shall be identified as part of the risk analysis required by the essential requirements for each new device.

3.5.6. For devices intended for use with plasma the performance evaluation shall verify the performance of the device using all anticoagulants which the manufacturer indicates for use with the device. This shall be demonstrated for at least 50 donations.

3.6. **CTS for the manufacturer's release testing of reagents and reagent products for determining the blood group antigens: ABO blood group system ABO1 (A), ABO2 (B), ABO3 (A,B); Rh blood group system RH1 (D), RH2 (C), RH3 (E), RH4 (c), RH5 (e); Kell blood group system KEL1 (K)**

3.6.1. The manufacturer's release testing criteria shall ensure that every batch consistently identifies the relevant antigens, epitopes, and antibodies.

3.6.2. Requirements for manufacturers batch release testing are outlined in Table 10.

▼M3

3.7. **CTS for Variant Creutzfeldt-Jakob disease (vCJD) assays for blood screening**

CTS for Variant Creutzfeldt-Jakob disease (vCJD) assays for blood screening are set out in Table 11.

▼M5

Table 1

First-line assays, excluding rapid tests: anti-HIV 1/2, HIV 1/2 Ag/Ab, anti-HTLV I/II, anti-HCV, HCV Ag/Ab, HBsAg, anti-HBc

		anti-HIV 1/2, HIV 1/2 Ag/Ab	Anti-HTLV-I/II	anti-HCV, HCV Ag/Ab	HBsAg	Anti-HBc
Diagnostic sensitivity	Positive specimens	400 HIV-1 100 HIV-2 including 40 non-B-subtypes, all available HIV/1 subtypes shall be represented by at least 3 samples per subtype	300 HTLV-I 100 HTLV-II	400 (positive samples) Including samples from different stages of infection and reflecting different antibody patterns. Genotype 1-4: > 20 samples per genotype (including non-a subtypes of genotype 4); 5: > 5 samples; 6: if available	400 including subtype-consideration	400 including evaluation of other HBV-markers
	Sero-conversion panels	20 panels 10 further panels (at notified body or manufacturer)	To be defined when available	20 panels 10 further panels (at notified body or manufacturer)	20 panels 10 further panels (at notified body or manufacturer)	To be defined when available
Analytical sensitivity	Standards				0,130 IU/ml (WHO International Standard: Third International Standard for HBsAg, subtypes ayw1/adw2, HBV genotype B4, NIBSC code: 12/226)	
Specificity	Unselected donors (including first-time donors)	5 000	5 000	5 000	5 000	5 000
	Hospitalized patients	200	200	200	200	200
	Potentially cross-reacting blood-specimens (RF+, related viruses, pregnant women, etc)	100	100	100	100	100

▼M2

Table 2

NAT assays for HIV1, HCV, HBV, HTLV I/II (qualitative and quantitative; not molecular typing)

HIV1			HCV		HBV		HTLV I/II		Acceptance criteria
NAT	qualitative	quantitative	qualitative	quantitative As for HIV quantitative	qualitative	quantitative As for HIV quantitative	qualitative	quantitative As for HIV quantitative	
Sensitivity Detection limit Detection of analytical sensitivity (IU/ml; defined on WHO standards or calibrated reference materials)	According to EP validation guideline ([1]): several dilution series into borderline concentration; statistical analysis (e.g. Probit analysis) on the basis of at least 24 replicates; calculation of 95 % cut-off value	Detection limit: as for qualitative tests; Quantification limit: dilutions (half-log10 or less) of calibrated reference preparations, definition of lower, upper quantification limit, precision, accuracy, 'linear' measuring range, 'dynamic range'. Reproducibility at different concentration levels to be shown	According to EP validation guideline ([1]): several dilution series into borderline concentration; statistical analysis (e.g. Probit analysis) on the basis of at least 24 replicates; calculation of 95 % cut-off value		According to EP validation guideline ([1]): several dilution series into borderline concentration; statistical analysis (e.g. Probit analysis) on the basis of at least 24 replicates; calculation of 95 % cut-off value		According to EP validation guideline ([1]): several dilution series into borderline concentration; statistical analysis (e.g. Probit analysis) on the basis of at least 24 replicates; calculation of 95 % cut-off value		

▼M2

HIV1			HCV		HBV		HTLV I/II		Acceptance criteria
NAT	qualitative	quantitative	qualitative	quantitative As for HIV quantitative	qualitative	quantitative As for HIV quantitative	qualitative	quantitative As for HIV quantitative	
Genotype/ subtype detection/quantification efficiency	At least 10 samples per subtype (as far as available)	Dilution series of all relevant genotypes/subtypes, preferably of reference materials, as far as available	At least 10 samples per genotype (as far as available)		As far as calibrated genotype reference materials are available		As far as calibrated genotype reference materials are available		
	Cell culture supernatants (could substitute for rare HIV-1 subtypes)	Transcripts or plasmids quantified by appropriate methods may be used.							
	According to EP validation guideline ([1]) as far as calibrated subtype reference materials are available; *in vitro* transcripts could be an option		According to EP validation guideline ([1]) as far as calibrated subtype reference materials are available; *in vitro* transcripts could be an option		According to EP validation guideline ([1]) as far as calibrated subtype reference materials are available; *in vitro* transcripts could be an option		According to EP validation guideline ([1]) as far as calibrated subtype reference materials are available; *in vitro* transcripts could be an option		

▼M2

HIV1			HCV		HBV		HTLV I/II		Acceptance criteria
NAT	qualitative	quantitative	qualitative	quantitative As for HIV quantitative	qualitative	quantitative As for HIV quantitative	qualitative	quantitative As for HIV quantitative	
Diagnostic specificity negative samples	500 blood donors	100 blood donors	500 blood donors		500 blood donors		500 individual blood donations		
Potential cross-reactive markers	By suitable assay design evidence (e.g. sequence comparison) and/or testing of at least 10 human retrovirus (e.g. HTLV)-positive samples	As for qualitative tests	By assays design and/or testing of at least 10 human flavivirus (e.g. HGV, YFV) positive samples		By assays design and/or testing of at least 10 other DNA-virus positive samples		By assay design and/or testing of at least 10 human retrovirus (e.g. HIV-) positive samples		
Robustness		As for qualitative tests							
Cross-contamination	At least 5 runs using alternating high positive (known to occur naturally) and negative samples		At least 5 runs using alternating high positive (known to occur naturally) and negative samples		At least 5 runs using alternating high positive (known to occur naturally) and negative samples		At least 5 runs using alternating high positive (known to occur naturally) and negative samples		

▼M2

HIV1			HCV		HBV		HTLV I/II		Acceptance criteria
NAT	qualitative	quantitative	qualitative	quantitative As for HIV quantitative	qualitative	quantitative As for HIV quantitative	qualitative	quantitative As for HIV quantitative	
Inhibition	Internal control preferably to go through the whole NAT procedure		Internal control preferably to go through the whole NAT procedure		Internal control preferably to go through the whole NAT procedure		Internal control preferably to go through the whole NAT procedure		
Whole system failure rate leading to false-neg results	At least 100 samples virus-spiked with 3 × the 95 % pos cut-off concentration		At least 100 samples virus-spiked with 3 × the 95 % pos cut-off concentration		At least 100 samples virus-spiked with 3 × the 95 % pos cut-off concentration		At least 100 samples virus-spiked with 3 × the 95 % pos cut-off concentration		99/100 assays positive

([1]) European Pharmacopoeia guideline.

Notes: Acceptance criteria for 'whole system failure rate leading to false-neg results' is 99/100 assays positive.For quantitative NATs a study shall be performed on at least 100 positive specimens reflecting the routine conditions of users (e.g. no pre-selection of specimens). Comparative results with another NAT test system shall be generated in parallel.For qualitative NATs a study on diagnostic sensitivity shall be performed using at least 10 sero-conversion panels. Comparative results with another NAT test system shall be generated in parallel.

▼M5

Table 3

Rapid tests: anti-HIV 1/2, HIV 1/2 Ag/Ab, anti-HCV, HCV Ag/Ab, HBsAg, anti-HBc, anti-HTLV I and II

		anti-HIV 1/2, HIV 1/2 Ag/Ab	anti-HCV, HCV Ag/Ab	HBsAg	anti-HBc	anti-HTLV I and II	Acceptance criteria
Diagnostic sensitivity	Positive specimens	Same criteria as in Table 1	Same criteria as in Table 1	Same criteria as in Table 1	Same criteria as in Table 1	Same criteria as in Table 1	Same criteria as in Table 1
	Sero-conversion panels	Same criteria as in Table 1	Same criteria as in Table 1	Same criteria as in Table 1	Same criteria as in Table 1	Same criteria as in Table 1	Same criteria as in Table 1
Diagnostic specificity	Negative specimens	[2]1 000 blood donations 200 clinical specimens 200 samples from pregnant women 100 potentially interfering samples	1 000 blood donations 200 clinical specimens 200 samples from pregnant women 100 potentially interfering samples	1 000 blood donations 200 clinical specimens 200 samples from pregnant women 100 potentially interfering samples	1 000 blood donations 200 clinical specimens 100 potentially interfering samples	1 000 blood donations 200 clinical specimens 200 samples from pregnant women 100 potentially interfering samples	≥ 99 % (anti-HBc: ≥ 96 %)

▼M5

Table 4

Confirmatory and supplementary assays for anti-HIV 1/ 2, HIV 1/2 Ag/Ab, anti-HTLV I and II, anti-HCV, HCV Ag/Ab, HBsAg

		anti-HIV 1/2, HIV 1/2 Ag/Ab confirmatory assays	anti-HTLV I and II confirmatory assays	anti-HCV, HCV Ag/Ab supplementary assays	HBsAg confirmatory assays	Acceptance criteria
Diagnostic sensitivity	Positive specimens	200 HIV-1 and 100 HIV-2 Including samples from different stages of infection and reflecting different antibody patterns	200 HTLV-I and 100 HTLV-II	300 HCV (positive samples) Including samples from different stages of infection and reflecting different antibody patterns. Genotypes 1 – 4: > 20 samples (including non-a subtypes of genotype 4; Genotype 5: > 5 samples; Genotype 6: if available	300 HBsAg Including samples from different stages of infection 20 'high pos' samples (>26 IU/ml); 20 samples in the cut-off range	Correct identification as positive (or indeterminate), not negative
	Sero-conversion panels	15 sero-conversion panels/ low titre panels		15 sero-conversion panels/ low titre panels	15 sero-conversion panels/ low titre panels	
Analytical sensitivity	Standards				Third International Standard for HBsAg, subtypes ayw1/adw2, HBV genotype B4, NIBSC code: 12/226	
Diagnostic specificity	Negative specimens	200 blood donations 200 clinical samples including pregnant women 50 potentially interfering samples, including samples with indeterminate results in other confirmatory assays	200 blood donations 200 clinical samples including pregnant women 50 potentially interfering samples, including samples with indeterminate results in other confirmatory assays	200 blood donations 200 clinical samples including pregnant women 50 potentially interfering samples, including samples with indeterminate results in other supplementary assays	10 false positives as available from the performance evaluation of the first line assay ([1]). 50 potentially interfering samples	No false-positive results/ ([1]) no neutralisation

([1]) Acceptance criteria: no neutralisation for HBsAg confirmatory assay.

▼M4

Table 5

HIV 1 antigen, HIV Ag/Ab, HCV antigen, HCV Ag/Ab

		HIV-1 antigen and HIV Ag/Ab assays	HCV antigen and HCV Ag/Ab assays	Acceptance criteria
Diagnostic sensitivity	Positive specimens	50 HIV-1 antigen positive 50 cell culture supernatants including different HIV-1 subtypes and HIV-2	25 HCV core antigen and/or HCV RNA positive but anti-HCV negative samples, comprising HCV genotypes 1-6 (if a genotype is not available, a justification shall be made)	See general principle in § 3.1.8
	Sero-conversion panels ([1])	20 sero-conversion panels/low titre panels	20 sero-conversion panels/low titre panels	
Analytical sensitivity	Standards	HIV-1 p24 Antigen, First International Reference Reagent, NIBSC code: 90/636	HCV core antigen detection limit shall be investigated using dilutions of the WHO International HCV core antigen Standard: (HCV core Ag product code: PEI 129096/12)	For HIV-1 p24 antigen: ≤ 2 IU/ml
Diagnostic specificity		200 blood donations 200 clinical samples 50 potentially interfering samples	200 blood donations, 200 clinical samples, 50 potentially interfering samples	≥ 99,5 % after neutralisation or, if no neutralisation test available, after resolution of the sample status according to general principles in § 3.1.5

([1]) The total number of seroconversion panels for combined Ag/Ab assays (from tables 1 and 5) need not be greater than 30.

▼M2

Table 6

Serotyping and genotyping assay: HCV

		HCV serotyping and genotyping assay	Acceptance criteria
Diagnostic sensitivity	Positive specimens	200 (positive samples) Including samples from different stages of infection and reflecting different antibody patterns. Genotypes 1 – 4: > 20 samples (including non-a subtypes of genotype 4); 5: > 5 samples; 6: if available	≥ 95 % agreement between serotyping and genotyping ►C1 > 95 % agreement between genotyping and sequencing ◄
Diagnostic specificity	Negative specimens	100	

▼M2

Table 7

HBV markers: anti-HBs, anti HBc IgM, anti-HBe, HBeAg

		Anti-HBs	Anti-HBc IgM	Anti-HBe	HBeAg	Acceptance criteria
Diagnostic sensitivity	Positive specimens	100 vaccinees 100 naturally infected persons	200 Including samples from different stages of infection (acute/chronic, etc.) The acceptance criteria should only be applied on samples from acute infection stage.	200 Including samples from different stages of infection (acute/chronic, etc.)	200 Including samples from different stages of infection (acute/chronic, etc.)	≥ 98 %
	Sero-conversion panels	10 follow-ups or anti-HBs sero-conversions	When available			
Analytical sensitivity	Standards	WHO First International Reference Preparation 1977; NIBSC, United Kingdom			HBe — Referenzantigen 82; PEI Germany	Anti-HBs: < 10 mIU/ml
Diagnostic specificity	Negative specimens	500 Including clinical samples 50 potentially interfering samples	200 blood donations 200 clinical samples 50 potentially interfering samples	200 blood donation 200 clinical samples 50 potentially interfering samples	200 blood donations 200 clinical samples 50 potentially interfering samples	≥ 98 %

▼M2

Table 8

HDV markers: anti-HDV, anti-HDV IgM, delta antigen

		Anti-HDV	Anti-HDV IgM	Delta antigen	Acceptance criteria
Diagnostic sensitivity	Positive specimens	100 Specifying HBV markers	50 Specifying HBV markers	10 Specifying HBV markers	≥ 98 %
Diagnostic specificity	Negative specimens	200 Including clinical samples 50 potentially interfering samples	200 Including clinical samples 50 potentially interfering samples	200 Including clinical samples 50 potentially interfering samples	≥ 98 %

Table 9

Blood group antigens in the ABO, Rh and Kell blood group systems

	1	2	3
Specificity	Number of tests per recommended method	Total number of samples to be tested for a launch product	Total number of samples to be tested for a new formulation, or use of well-characterised reagents
Anti-ABO1 (anti-A), anti-ABO2 (anti-B), anti-ABO3 (anti-A,B)	500	3 000	1 000
Anti-RH1 (anti-D)	500	3 000	1 000
Anti-RH2 (anti-C), anti-RH4 (anti-c), anti-RH3 (anti-E)	100	1 000	200
Anti-RH5 (anti-e)	100	500	200
Anti-KEL1 (anti-K)	100	500	200

Acceptance criteria:

All of the above reagents shall show comparable test results with established reagents with acceptable performance with regard to claimed reactivity of the device. For established reagents, where the application or use has been changed or extended, further testing should be carried out in accordance with the requirements outlined in column 1 (above).

Performance evaluation of anti-D reagents shall include tests against a range of weak RH1 (D) and partial RH1 (D) samples, depending on the intended use of the product.

Qualifications:

Clinical samples: 10 % of the test population
Neonatal specimens: > 2 % of the test population
ABO samples: > 40 % A, B positives
'weak D': > 2 % of RH1 (D) positives

▼M2

Table 10

Batch release criteria for reagents and reagent products to determine blood group antigens in the ABO, Rh and Kell blood group systems

Specificity testing requirements on each reagent

1. **Test reagents**

Blood group reagents	Minimum number of control cells to be tested							
	Positive reactions					Negative reactions		
	A1	A2B	Ax			B	0	
Anti-ABO1 (anti-A)	2	2	2 (*)			2	2	
	B	A1B				A1	0	
Anti-ABO2 (anti-B)	2	2				2	2	
	A1	A2	Ax	B		0		
Anti-ABO3 (anti-A,B)	2	2	2	2		4		
	R1r	R2r	WeakD			r'r	r'r	rr
Anti-RH1 (anti-D)	2	2	2 (*)			1	1	1
	R1R2	R1r	r'r			R2R2	r'r	rr
Anti-RH2 (anti-C)	2	1	1			1	1	1
	R1R2	R1r	r'r			R1R1		
Anti-RH4 (anti-c)	1	2	1			3		
	R1R2	R2r	r'r			R1R1	r'r	rr
Anti-RH 3 (anti-E)	2	1	1			1	1	1
	R1R2	R2r	r'r			R2R2		
Anti-RH5 (anti-e)	2	1	1			3		
	Kk					kk		
Anti-KEL1 (anti-K)	4					3		

(*) Only by recommended techniques where reactivity against these antigens is claimed.

Note: Polyclonal reagents must be tested against a wider panel of cells to confirm specificity and exclude presence of unwanted contaminating antibodies.

Acceptance criteria:

Each batch of reagent must exhibit unequivocal positive or negative results by all recommended techniques in accordance with the results obtained from the performance evaluation data.

2. **Control materials (red cells)**

The phenotype of red cells used in the control of blood typing reagents listed above should be confirmed using established device.

▼M3

Table 11

Variant Creutzfeldt-Jakob disease (vCJD) assays for blood screening

	Material	Number of specimens	Acceptance Criteria
Analytical sensitivity	vCJD brain spikes in human plasma (WHO reference number NHBY0/0003)	24 replicates of each of three dilutions of the material WHO number NHBY0/0003 (1×10^4, 1×10^5, 1×10^6)	23 of the 24 replicates detected at 1×10^4
	vCJD spleen spikes in human plasma (10 % spleen homogenate — NIBSC reference number NHSY0/0009)	24 replicates of each of three dilutions of the material NIBSC number NHSY0/0009 (1×10, 1×10^2, 1×10^3)	23 of the 24 replicates detected at 1×10
Diagnostic sensitivity	A) Specimen from appropriate animal models	As many specimen as reasonably possible and available, and at least 10 specimens	90 %
	B) Specimen from humans with known clinical vCJD	As many specimen as reasonably possible and available, and at least 10 specimens	90 %
		Only in case where 10 specimens are not available: — the number of specimens tested shall be comprised between 6 and 9 — all available specimens shall be tested	no more than one false negative result
Analytical specificity	Potentially cross-reacting blood-specimens	100	
Diagnostic specificity	Normal human plasma samples from area of low BSE exposure	5 000	At least 99,5 %