II

(Acts adopted under the EC Treaty/Euratom Treaty whose publication is not obligatory)

DECISIONS

COMMISSION

COMMISSION DECISION

of 27 November 2009

amending Decision 2002/364/EC on common technical specifications for in vitro diagnostic medical devices

(notified under document C(2009) 9464)

(Text with EEA relevance)

(2009/886/EC)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on *in vitro*-diagnostic medical devices [1], and in particular the second subparagraph of Article 5(3) thereof,

Whereas:

(1) The common technical specifications for in vitro diagnostic medical devices are laid down in Commission Decision 2002/364/EC [2].

(2) In the interest of public health and in order to reflect technical progress including the evolution in the performance and analytical sensitivity of devices, it is appropriate to revise the common technical specifications laid down in Decision 2002/364/EC.

(3) The definition of rapid test should be refined in order for it to be more precise. For the sake of clarity further definitions should be included.

(4) To bring the common technical specifications in line with current scientific and technical practices it is necessary to update a number of scientific and technical references.

(5) The requirements for HIV screening assays should be clarified. In order to ensure that the performance criteria appropriate to today's technology is reflected in the common technical specifications it is necessary to add requirements for HIV antibody/antigen combined tests and further specification of the sample requirements for certain assays.

(6) The Annex to Decision 2002/364/EC should therefore be amended accordingly and, for the purpose of clarity, be replaced.

(7) Due to an administrative error, Commission Decision 2009/108/EC of 3 February 2009 amending Decision 2002/364/EC on common technical specifications for *in vitro*-diagnostic medical devices [3] was adopted without the European Parliament being given the possibility to exercise its right of scrutiny in accordance with Article 8 of Council Decision 1999/468/EC of 28 June 1999 laying down the procedures for the exercise of implementing powers conferred on the Commission [4]. Therefore, Decision 2009/108/EC should be replaced by this Decision.

(8) Manufacturers whose devices are already on the market should be given a transitional period in order to adapt to the new common technical specifications. On the other hand, in the interest of public health, manufacturers who so wish should be able to apply the new common technical specifications before the expiry of the transitional period.

(9) The measures provided for in this Decision are in accordance with the opinion of the committee set up by Article 6(2) of Council Directive 90/385/EEC [5],

[1] OJ L 331, 7.12.1998, p. 1.
[2] OJ L 131, 16.5.2002, p. 17.
[3] OJ L 39, 10.2.2009, p. 34.
[4] OJ L 184, 17.7.1999, p. 23.
[5] OJ L 189, 20.7.1990, p. 17.

HAS ADOPTED THIS DECISION:

Article 1

The Annex to Decision 2002/364/EC is replaced by the text in the Annex to this Decision.

Article 2

Decision 2009/108/EC is repealed.

Article 3

This Decision shall apply from 1 December 2010 for those devices first placed on the market prior to 1 December 2009.

It shall apply from 1 December 2009 for all other devices.

However, Member States shall allow manufacturers to apply the requirements set out in the Annex before the dates set out in the first and second paragraphs.

Article 4

This Decision is addressed to the Member States.

Done at Brussels, 27 November 2009.

For the Commission

Günter VERHEUGEN

Vice-President

ANNEX

'*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.

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.

Confirmation assay

Confirmation assay means an assay used for the confirmation of a reactive result from a screening assay.

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

3.1.1. Devices which detect virus infections placed on the market for use as either screening or diagnostic tests, shall meet the requirements for sensitivity and specificity set out in Table 1. See also principle 3.1.11 for screening assays.

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.

3.1.3. Devices intended by the manufacturer for self-test, i.e. home use, 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.

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.

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.

3.1.9. Performance evaluation of screening assays shall include 25 positive (if available in the case of rare infections) "same day" fresh serum and/or plasma samples (≤ 1 day after sampling).

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.

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

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).

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.

3.2. **Additional requirements for HIV antibody/antigen combined tests**

3.2.1. HIV antibody/antigen combined tests intended for anti-HIV and p24 antigen detection which include claims for single p24 antigen detection shall follow Table 1 and Table 5, including criteria for analytical sensitivity for p24 antigen.

3.2.2. HIV antibody/antigen combined tests intended for anti-HIV and p24 detection which do not include claims for single p24 detection shall follow Table 1 and Table 5, excluding criteria for analytical sensitivity for p24.

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.

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 for example a WHO standard or calibrated reference material.

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.

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

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.

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.

Table 1

"Screening" assays: anti-HIV 1 and 2, anti-HTLV I and II, anti-HCV, HBsAg, anti-HBc

		Anti-HIV-1/2	Anti-HTLV-I/II	Anti-HCV	HBsAg	Anti-HBc
Diagnostic sensitivity	Positive specimens	400 HIV-1 100 HIV-2 including 40 non-B subtypes, all available HIV/1 subtypes should 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 subtypeconsideration	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 (Second International Standard for HBsAg, subtype adw2, genotype A, NIBSC code: 00/588)	
Specificity	Unselected donors (including first-time donors)	5 000	5 000	5 000	5 000	5 000
	Hospitalised patients	200	200	200	200	200
	Potentially cross-reacting blood-specimens (RF+, related viruses, pregnant women, etc.)	100	100	100	100	100

Table 2

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

	HIV1		HCV		HBV		HTLV I/II		
NAT	qualitative	quantitative	qualitative	quantitative As for HIV quantitative	qualitative	quantitative As for HIV quantitative	qualitative	quantitative As for HIV quantitative	Acceptance criteria
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		
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		

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	
	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		
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							

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	
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		
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.

Table 3

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

		Anti-HIV 1/2	Anti-HCV	HBsAg	Anti-HBc	Anti-HTLV I/II	Acceptance criteria
Diagnostic sensitivity	Positive specimens	Same criteria as for screening assays	Same criteria as for screening assays	Same criteria as for screening assays	Same criteria as for screening assays	Same criteria as for screening assays	Same criteria as for screening assays
	Sero-conversion panels	Same criteria as for screening assays	Same criteria as for screening assays	Same criteria as for screening assays	Same criteria as for screening assays	Same criteria as for screening assays	Same criteria as for screening assays
Diagnostic specificity	Negative specimens	1 000 blood donations	1 000 blood donations	1 000 blood donations	1 000 blood donations	1 000 blood donations	≥ 99 % (anti-HBc: ≥ 96 %)
		200 clinical specimens	200 clinical specimens	200 clinical specimens	200 clinical specimens	200 clinical specimens	
		200 samples from pregnant women	200 samples from pregnant women	200 samples from pregnant women		200 samples from pregnant women	
		100 potentially interfering samples	100 potentially interfering samples	100 potentially interfering samples	100 potentially interfering samples	100 potentially interfering samples	

Table 4

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

		Anti-HIV confirmatory assay	Anti-HTLV confirmatory assay	HCV supplementary assay	HBsAg confirmatory assay	Acceptance criteria
Diagnostic sensitivity	Positive specimens	200 HIV-1 and 100 HIV-2	200 HTLV-I and 100 HTLV-II	300 HCV (positive samples)	300 HBsAg	Correct identification as positive (or indeterminate), not negative
		Including samples from different stages of infection and reflecting different antibody patterns		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	Including samples from different stages of infection 20 "high pos" samples (> 26 IU/ml); 20 samples in the cut-off range	
	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				Second International Standard for HBsAg, subtype adw2, genotype A, NIBSC code: 00/588	
Diagnostic specificity	Negative specimens	200 blood donations	200 blood donation	200 blood donations	10 false positives as available from the performance evaluation of the screening assay (1).	No false-positive results/ (1) no neutralisation
		200 clinical samples including pregnant women 50 potentially interfering samples, including samples with indeterminate results in other confirmatory assays	200 clinical samples including pregnant women 50 potentially interfering samples including samples with indeterminate results in other confirmatory assays	200 clinical samples including pregnant women 50 potentially interfering samples including samples with indeterminate results in other supplementary assays	50 potentially interfering samples	

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

Table 5

HIV 1 antigen

		HIV-1 antigen assay	Acceptance criteria
Diagnostic sensitivity	Positive specimens	50 HIV-1 Ag-positive 50 cell culture supernatants including different HIV-1 subtypes and HIV-2	Correct identification (after neutralisation)
	Sero-conversion panels	20 sero-conversion panels/low titre panels	
Analytical sensitivity	Standards	HIV-1 p24 Antigen, First International Reference Reagent, NIBSC code: 90/636	≤ 2 IU/ml
Diagnostic specificity		200 blood donations 200 clinical samples 50 potentially interfering samples	≥ 99,5 % after neutralisation

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 ≥ 95 % agreement between genotyping and sequencing
Diagnostic specificity	Negative specimens	100	

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 %

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

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.'

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