L.N. 30 of 2004

PRODUCT SAFETY ACT (ACT NO. V OF 2001)

In Vitro Diagnostic Medical Devices (Amendment) Regulations, 2004

IN exercise of the powers conferred by articles 38 to 40 of the Product Safety Act, the Minister of Finance and Economic Affairs, on the advice of the Malta Standards Authority, has made the following regulations:-

1. The title of these regulations is the In Vitro Diagnostic Medical Devices (Amendment) Regulations, 2004, and they shall be read and construed as one with the In Vitro Diagnostic Medical Devices Regulations, 2002, hereinafter referred to as "the principal regulations". Citation. L.N. 61 of 2002.

2. (1) Immediately after regulation 3.1.15 of the principal regulations, there shall be inserted the following: Amends regulation 3 of the principal regulations.

"3.1.15.1. Where, in these regulations, reference is made to harmonised standards, this is also meant to refer to the common technical specifications;".

(2) Immediately after regulation 3.1.25 of the principal regulations, there shall be inserted the following:

"3.1.26. "common technical specification" means a technical specification for a relevant device referred to in a list in Annex II of the Directive, set out in Schedule II to these regulations, which has been adopted in accordance with the procedure set out in Article 7(2) of the Directive and published in the OJ, as set out in Schedule XI to these regulations;".

3. (1) Immediately after regulation 5.2 of the principal regulations, there shall be inserted the following: Amends regulation 5 of the principal regulations.

"5.3. A device shall be treated as complying with an essential requirement if as respects that requirement, it complies with the relevant national standard, unless there are reasonable indications that the device does not comply with that requirement.

5.4. Without prejudice to regulation 5.3 of these regulations, a device specified in List A or B of Annex II of the Directive, set out in Schedule II hereto, shall be treated as complying with the relevant essential requirements if the device is designed and manufactured in conformity with the common technical specifications drawn up for the device, unless there are reasonable indications that the device does not comply with those requirements.

5.4.1. A device to which regulation 5.4 of these regulations, relates shall be treated as having been manufactured in accordance with the common technical specifications drawn up for the device if, for justifiable reasons, it is not so manufactured but is manufactured in accordance with technical specifications that are at least equivalent to such common technical specifications, unless there are reasonable indications that the device does not comply with those requirements.

5.4.1.1. The technical specifications set out in Schedule XI to these regulations are adopted as common technical specifications for devices in list A of Schedule II to these regulations.";

(2) Regulation 5.3 of the principal regulations shall be renumbered as regulation 5.5 thereof.

Adds Schedule XI to the principal regulations.

4. (1) Immediately after Schedule X to the principal regulations, there shall be inserted the following new Schedule:

"Schedule XI

Based on the Annex of Commission Decision 2002/364/EC of 7 May 2002 on common technical specifications for *in-vitro* diagnostic medical devices

CTS - COMMON TECHNICAL SPECIFICATIONS FOR IN VITRO-DIAGNOSTIC MEDICAL DEVICES

1. SCOPE

These Common Technical Specifications are for the list of devices referred to in Annex II, list A:

- reagents and reagent products, including related calibrators and control materials, for determining the following blood groups: ABO system, Rhesus (C, c, D, E, e) anti-Kell,

- reagents and reagent products, including related calibrators and control materials, 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 and D.

2. DEFINITIONS

(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

In the context of the CTS it may be expressed as the limit of detection: i.e. the smallest amount of the target marker that can be precisely detected.

Analytical specificity

The ability of the method to determine solely the target marker.

Nucleic acid amplification techniques (NAT)

In the context of this document 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

In this context the term "rapid test" is understood to mean those tests which can only be used singly or in a small series and which have been designed to give a rapid result for near patient testing.

Robustness

The robustness of an analytical procedure is a measure of its capacity 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 is the frequency of failures when the entire process is performed as prescribed by the manufacturer.

3. COMMON TECHNICAL SPECIFICATIONS (CTS) FOR PRODUCTS DEFINED 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 and/or diagnostic tests, shall meet the same requirements for sensitivity and specificity (see Table 1).

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 device with acceptable performance. Once the CE marking of IVDs is established, the device used for comparison shall be CE marked, 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 etc.

3.1.8. For blood screening devices (with the exception of HBsAg tests), all true positive samples shall be identified as positive by the device to be CE marked (Table 1). For HbsAg tests the new device shall have an overall performance at least equivalent to that of the established device (see principle 3.1.4). Diagnostic test sensitivity during the early infection phase (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).

3.1.9. 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.

3.1.10. 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.

3.1.11. 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.

3.1.12. 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.

3.1.13. 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.

3.1.14. 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.

3.1.15. 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.

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

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

3.2.1. 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.

3.2.2. 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 materials.

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

3.2.4. 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.

3.2.5. 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.

3.2.6. 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 of samples with naturally occurring high virus titres.

3.2.7. 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 3 x the 95 % positive cut-off virus concentration.

3.3. **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)**

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

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

3.4. CTS for performance evaluation of reagents and reagent products for determining the blood group antigens: ABO system (A, B), Rhesus (C, c, D, E, e) and Kell (K)

Criteria for performance evaluation of reagents and reagent products for determining the blood groups: ABO system (A,B), Rhesus (C, c, D, E, e) and Kell (K) can be found in Table 9.

3.4.1. All performance evaluations shall be carried out in direct comparison with an established device with acceptable performance. Once the CE marking of IVDs is established, the device used for comparison shall be CE marked, if on the market at the time of the performance evaluation.

3.4.2. 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.

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

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ANNEX

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

3.5.2. Requirements for manufacturer's 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 three samples per subtype	300 HTLV I 100 HTLV II	400 including genotypes 1a-4a: at least 20 samples/genotype genotypes 4 non-a and 5: at least 10 samples/genotype	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				0,5 ng/ml (French/UK standard until WHO available)	
Specificity	Unselected donors (including 1st 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)**

HIV 1			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-log 10 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) Cell culture supernatants (could substitute for rare HIV 1 subtypes)	Dilution series of all relevant genotypes/subtypes, preferably of reference materials, as far as available Transcripts or plasmids quantified by appropriate methods may be used	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		
	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		

NAT	HIV 1		HCV		HBV		HTLV I/II		Acceptance criteria
	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 assays 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		
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 whlole 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.

Nota: Acceptance criteria for 'whole system failure rate leading to false-neg results' is 99/100 assays positive.

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/III	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
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 Including samples from different stages of infection and reflecting different anti-body patterns	200 HTLV I and 100 HTLV II	300 HCV Including samples from different stages of infection and reflecting different anti-body patterns genotypes 1 - 4a: 15 samples; genotypes 4 (non a), 5: five samples; six: if available	300 HBsAG Including samples from different stages of infection 20 'high pos' samples (> 50 ng HBsAg/ml); 20 samples in the cut-off range	Correct identification as positive (or indeterminate), not negative
	Sero-conversion panels	15 seroconversion panels/ low titre panels		15 seroconversion panels/ low titre panels	15 seroconversion panels/ low titre panels	
Analytical sensitivity	Standards				HBsAg standards (AdM, NIBSC, WHO)	
Diagnostic specificty	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 pontentially 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	20 false-positives in the corresponding screening assay (1) 50 potentially interfering samples	No false-positive results/ (1) no neutralisation

(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	
Diagnostic specificity	Standards	ADM or 1st international reference	< 50 pg/ml
Diagnostic specificity		200 blood donations 200 clinical samples 50 potentially interfering samples	≥ 99,5 % after neutralisation

Table 6: **Serotyping Assay: HCV**

		HCV 1 serotyping assay	Acceptance criteria
Diagnostic sensitivity	Positive specimens	200 incl. genotypes 1-4a: > 20 samples. 4 (non a); 5: > 10 samples, 6: if available	≥ 95 % agreement between serotyping and genotyping
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.)	200 including samples from different stages of infection (acute/chronic etc.)	200 including samples from different stages of infection (acute/chronic etc.)	≥ 98 %
	Sero-con-version panels	10 follow-ups or anti/HBs sero-conversions	When available			
Analytical sensitivity	Standards	WHO standard			PEI standard	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 donations 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 Groups ABO, Rhesus (C, c, D, E, e) and Kell**

	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-A, B and AB	500	3 000	1 000
Anti-D	500	3 000	1 000
Anti-C, c, E	100	1 000	200
Anti-e	100	500	200
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 week RhD and partial Rh 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 Rhesus positives

Table 10: **Batch release criteria for Blood Groups ABO, Rhesus (C, c, D, E, e), and Kell**

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-A	2	2	2 (*)			2	2	
	B	A1B				A1	0	
Anti-B	2	2				2	2	
	A1	A2	Ax	B		0		
Anti-AB	2	2	2	2		4		
	R1r	R2r	WeakD			R'r	r"r	rr
Anti-D	2	2	2 (*)			1	1	1
	R1R2	R1r	r'r			R2R2	r"r	rr
Anti-C	2	1	1			1	1	1
	R1R2	R1r	r'r			R1R1		
Anti-c	1	2	1			3		
	R1R2	R2r	r"r			R1R1	r'r	rr
Anti-E	2	1	1			1	1	1
	R1R2	R2r	r"r			R2R2		
Anti-e	2	1	1			3		
	Kk					kk		
Anti-K	4					3		

(*) Only by recommended techniques where reactivity against these antigents 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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