Change Notification for the UK Blood Transfusion Services

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Amendments to Red Book Chapters 7 and 9

This notification includes the following changes:

	BM-DSG Bone Marrow & Peripheral Blood Stem Cell	CB-DSG Cord Blood	GDRI Geographical Disease Risk Index	TD-DSG Tissue - Deceased Donors	TL-DSG Tissue - Live Donors	WB-DSG Whole Blood & Components	Red Book Guidelines for the BTS in the UK
Chapter 7 Specifications for blood components							
1 7.31: Irradiated components	○	○	○	○	○	○	●
Chapter 9 Microbiology tests for donors and donations: general specifications for laboratory test procedures							
2 9.2: Microbiology screening	○	○	○	○	○	○	●
3 9.3: Specific screening targets	○	○	○	○	○	○	●
4 9.4: Reinstatement of blood donors	○	○	○	○	○	○	●
5 9.7: Recommended standards for environmental monitoring (EM) of processing facilities	○	○	○	○	○	○	●

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Changes are indicated using the key below. This formatting will not appear in the final entry.

original text	«inserted text»	~~deleted text~~

1 Changes apply to the **Guidelines for the Blood Transfusion Services**

Chapter 7: Specifications for blood components

(no changes to sections 7.1 to 7.30)

7.31: Irradiated components

- For the whole of this section X-irradiation may be regarded as equivalent to gamma irradiation. Times when irradiation should be undertaken and the permitted post-irradiation storage times are the same, as are the required labelling and dosing (recommended minimum dose achieved in the irradiation field is 25 Gy, with no part receiving >50 Gy) «(±10% at 95% confidence interval)».

- Note that the X-ray equipment should be dose-mapped prior to release from the factory and at installation, and the manufacturers recommend routine dosimetry at 6-monthly intervals (gamma-irradiation equipment requires annual dosimetry). A radiation-sensitive label specifically for use with X-irradiation is available.

- It is not necessary to irradiate the following components:
    - cryopreserved red cells after washing,
    - plasma components.

- For more information, refer to the BCSH Guidelines on the Use of Irradiated Blood Components.[3]

- Irradiated components not used for the intended recipient can safely be used for recipients who do not require irradiated components provided the other requirements of Chapters 6 and 7 have been satisfied. However, any reduction in shelf life resulting from the irradiation process must be observed.

- Irradiated components should conform to their appropriate specification previously given in this chapter. In addition, the guidelines shown below should be observed.

7.31.1: Description

Irradiated components are components that have been irradiated by a validated procedure.

7.31.2: Technical Information

- Other than for use in intrauterine transfusion, exchange transfusion, or large-volume transfusion of neonates, red cells can be irradiated at any time up to 14 days after collection.

- Platelets can be irradiated at any stage in their storage.

- Granulocytes should be irradiated as soon as possible after production.

- For red cells, platelets and granulocytes the recommended minimum dose achieved in the irradiation field is 25 Gy, with no part receiving >50 Gy «(±10% at 95% confidence interval)».

- Laboratories performing irradiation of blood components must work to a clearly defined specification and are strongly recommended to work closely with a medical physicist. The defined irradiation procedure must be validated and there must be regular monitoring of the blood component dosimetry and the laboratory equipment.

- «Provided the blood dosimetry uncertainty of measurement used by blood establishments is equal to or less than the uncertainty as it was measured in the original study data (Pelzsynski et al, 1994) (±10%), there is no clinical indication to include the uncertainty of measurement within routine mapping to confirm ongoing specification compliance.»

- It is recommended that irradiation of blood components is carried out using dedicated blood irradiation machines. If radiotherapy machines are used, equivalent protocols should be developed.

- Appropriate radiation-sensitive labels should be used as an aid to differentiating irradiated from non-irradiated components. However, it may not be necessary to attach a radiation-sensitive label to every component pack, provided that the irradiation procedure follows a validated, documented and well-controlled system of work that is integrated with the component labelling and release mechanism and permits retrospective audit of each stage of the irradiation process.

- There should be a permanent record of all units irradiated. This should include details of irradiation batch and donation numbers, component type, the site of irradiation, when irradiation was performed and by whom.

(no further changes to Chapter 7)

2 Changes apply to the **Guidelines for the Blood Transfusion Services**

Chapter 9: Microbiology tests for donors and donations: general specifications for laboratory test procedures

(no changes to section 9.1)

9.2: Microbiology screening

Note: The meanings of certain terms used in this section are defined in section 9.2.6.

9.2.1: Screening of donations/donors

Donation/donor screening can be broadly divided into two main categories:

- Mandatory: Absolute requirement prior to the release of components. There are, however, different reasons for a specific infectious marker to be defined as 'mandatory'. These include a UK or European Union regulatory requirement, a specific instruction from the Department of Health, including its Advisory Committees, and an Act of Parliament.
- Additional (also known as Discretionary): Performed because of specific additional and identifiable donor or recipient risk«/regulatory requirement».

Importantly, the mandatory requirements for blood donation and for tissue and stem cell donations are different, with some tests that are defined as 'Additional' for blood donations being 'Mandatory' for non-blood donations (Tables 9.1 and 9.2). Although not required for all donations, where additional screening is required, the results are an integral part of the criteria for the release of that donation/component/product. In addition, for certain donation types, there is the option of quarantine and follow-up serological screening before issue or the inclusion of genomic screening at donation.

Donations and any associated components/products must not be released to stock unless they have been screened and found negative for the mandatory, and any additional, microbiological screening required. In certain circumstances, for certain donation/component types, a reactive screen result may not preclude release of the donations/component.

Table 9.1 – Screening required for blood donations

Infectious agent	Minimum requirement	Comments[1]
HIV 1+2	anti-HIV 1+2+O or HIV 1+2+O Ag/Ab (M) HIV RNA[2]	RNA screening in pools of a maximum of 24 donations[3]
HCV	anti-HCV (M) HCV RNA (M)	RNA screening in pools of a maximum of 24 donations[3]
HBV	HBsAg (M)	DNA screening in pools of a maximum of 24 donations[3]

	HBV DNA[2] anti-HBc [+ anti-HBs] (A)[4]	Donations that are anti-HBc reactive and have anti-HBs >100 mIU/mL, tested in the past 24 months by a UK Blood Service, are considered suitable for release if HBsAg and ID HBV DNA negative
Syphilis	anti-treponemal (M)	
HTLV I/II	anti-HTLV I/II (M)[5]	Serology screening individually or in pools of a maximum of 24 donations[3]
HEV	HEV RNA (M)	RNA screening in pools of a maximum of 24 donations[3]
HCMV	anti-HCMV (A)	Ideally both IgG and IgM, but IgG alone is considered sufficient
Plasmodium sp.	anti-*P. falciparum/vivax* (A)	
Trypanosoma cruzi	anti-*T. cruzi* (A)	
West Nile Virus (WNV)		RNA screening in pools of a maximum of 16 donations[6]
«HAV»	«HAV RNA (A)»	«RNA screening in pools of a maximum of 96 donations»
«Human B19»	«B19 DNA (A)»	«DNA screening in pools of a maximum of 96 donations»
(M) – mandatory (release criteria) for the purpose of these guidelines		
(A) – additional (release criteria) due to specifically identifiable risk		
[1] All microbiology screening performed on individual donations unless specified otherwise		
[2] Although neither are mandatory for blood donations in most of the UK, HIV RNA and HBV DNA are included in nucleic acid screening as the commercial systems available are now triplex assays. HIV RNA is, however, mandated within Scotland.		
[3] The minimum sensitivity of the molecular screening is dependent upon pool size. The maximum validated pool size for use for «mandatory» blood screening within the UK Blood Transfusion Services is 24 donations.		
[4] All blood donors are to be screened for anti-HBc at their first donation or their first donation after the introduction of anti-HBc screening. Anti-HBc screening to be repeated if a donor lapses (over 2 years) or has a new HBV risk.		
[5] anti-HTLV screening is only required for blood donations from previously untested donors and for blood donations destined for use to prepare non-leucodepleted products		
[6] The maximum validated pool size for WNV RNA screening is 16 donations		

(no changes to sections 9.2.2 to 9.2.4)

9.2.5: Confirmatory testing

When a donation is screen reactive for any of the serological or molecular mandatory or additional microbiology tests described above (except for anti-HCMV) samples from the donor/donation must undergo confirmatory testing at a designated reference laboratory.

- For blood, donations that are confirmed positive for anti-HBc from donors with anti-HBs >100 mIU/mL, tested in the past 24 months by a UK Blood Service, are considered suitable for release if HBsAg and ID HBV DNA negative.

- For tissues and cells **either** donations that are anti-HBc reactive and anti-HBs ≥100 mIU/mL are considered suitable for release, **or** donations which are anti-HBc reactive and are HBsAg and ID HBV DNA negative are considered suitable for release without the need for anti-HBs level of ≥100 mIU/mL.

- «Anti-*T. gondii* IgG and IgM screening is recommended for HSC, donor lymphocyte infusions and other therapeutic cells (e.g. selected and cultured products including T-cells, natural killer cells, mesenchymal stem cells, cytotoxic T-lymphocytes, T-regulatory cells, tumour derived cells) and embryonic stem cell lines intended for clinical use derived from human embryos initially created for fertility treatment with the use of IgM positive donors avoided. Confirmation of anti-*T.gondii* IgM only reactivity recommended due to known specificity issues with IgM assays.»

- If HEV «, HAV» or WNV RNA is confirmed in a donor, the donor record must be flagged as 'temporary exclusion' for 6 months. The donor can be reinstated automatically at least 6 months after the date of the index HEV «, HAV» or WNV RNA positive donation: see section 9.4.

- «If human B19 DNA is confirmed in a donor, the donor record must be flagged as 'temporary exclusion' for 4 weeks. The donor can be reinstated automatically at least 4 weeks after the date of the index DNA positive donation: see section 9.4.»

- In all other cases, the donor record must be flagged as 'permanent exclusion risk – not to be used for clinical use' or equivalent.

- In all cases where a positive result is confirmed, arrangements should be made to inform the donor and to ensure that the donor is given appropriate advice.

Note: Autologous stem cell donations may be collected from individuals who are known to be infected with one or more of the infectious agents for which donations are routinely screened. Such individuals are not generally classified as donors for the purposes of these guidelines.

- If a negative, inconclusive or indeterminate result is reported following confirmatory testing, and the initial reactivity is determined by the reference laboratory to be non-specific, use of further donations or the same donation (tissue and stem cell donors only) may be possible, as covered in section 9.4.

(no further changes to section 9.2)

3 Changes apply to the **Guidelines for the Blood Transfusion Services**

9.3: Specific screening targets

(no changes to sections 9.3.1 to 9.3.2)

9.3.3: anti-HCV

- The UK requirement for the minimum level of sensitivity for the performance of anti-HCV screening is that a positive result should be obtained with the UK anti-HCV working standard (19/240 or equivalent), available from NIBSC. Laboratories using «HCV assays» ~~*an assay*~~ of higher analytical or dilutional sensitivity where the working standard reacts too strongly are advised to utilise ~~*the NIBSC HCV working standard 1/8 dilution (19/242 or equivalent) or, if the 1/8 standard reacts too strongly in an assay,*~~ an alternative UKCA or CE marked material intended for such use «which» may be used in place of the working standard if the material has been fully validated by the UK Blood and Tissue Establishment using the material.

- In addition to the assay manufacturer's controls, the UK working standard must be included at least once in each series of tests to demonstrate acceptable sensitivity of the test method.

- No series of tests should be considered acceptable unless the result of the assay manufacturer's and the additional quality control samples have satisfied the criteria laid down.

(no changes to sections 9.3.4 to 9.3.16)

9.3.17: Additional screening of plasma intended for fractionation

9.3.17.1: Human Parvovirus B19 DNA

- There is currently no specific UK requirement for the minimum level of sensitivity for the performance of human B19V DNA screening. If screening is performed in minipools, UK Blood Services must ensure that human B19V DNA can be detected at a level that will ensure less than 10^4 IU/mL of B19V DNA in the homogenous plasma pool. A clinical virology immunodeficiency multiplex working reagent including Human B19 DNA (2.4×10^4 IU/mL) is available from NIBSC («15/130» ~~*12/130*~~ or equivalent).

- The assay must include a specific internal control for each test performed.

- No series of tests should be considered acceptable unless the manufacturer's QC requirements in the IFU have been met, and the results of any additional quality control samples used have satisfied the criteria laid down.

(no further changes to section 9.3)

4 Changes apply to the **Guidelines for the Blood Transfusion Services**

9.4: Reinstatement of blood donors

9.4.1: Donors whose samples are confirmed positive

- Donors whose blood samples are confirmed positive cannot normally be reinstated, even after successful treatment, as screening test reactivity will persist in serological assays, for example anti-HCV and TPHA.

- For blood, donations that are confirmed positive for anti-HBc from a donor with anti-HBs >100 mIU/mL, tested in the past 24 months in a UK Blood Service, are considered suitable for release if HBsAg and ID HBV DNA negative.

- For tissues and cells **either** donations that are anti-HBc confirmed positive and anti-HBs ≥100 mIU/mL are considered suitable for release, **or** donations which are anti-HBc reactive and are HBsAg and ID HBV DNA negative do not require an anti-HBs level of ≥100 mIU/mL to be considered suitable for release.

- Donors with confirmed HEV «, HAV» or WNV infection should be deferred for 6 months from the date of first detection of HEV/«HAV/»WNV RNA. These donors may be reinstated without further testing 6 months from the date of the index RNA positive donation.

- If a previously confirmed HEV infected donor is tested prior to the end of the 6-month deferral period and found to be HEV RNA negative on individual testing and HEV IgG positive at ≥1 IU/ml using the PEI International standard for HEV IgG (HEV IgM may or may not still be present), the donor may be reinstated immediately.

- «Donors with confirmed human B19 DNA should be deferred for 4 weeks from the date of first detection of B19 DNA. These donors may be reinstated without further testing 4 weeks from the date of the index DNA positive donation.»

(no further changes to section 9.4)

5 Changes apply to the **Guidelines for the Blood Transfusion Services**

9.7: Recommended standards for environmental monitoring (EM) of processing facilities

(no changes to sections 9.7.1 to 9.7.3)

9.7.4: Alert and action limits

9.7.4.1 Controlled Rooms (Cleanrooms)

In cleanroom facilities, alert and action limits must be set for the results of particulate and microbiological monitoring. «Action» ~~*Alert*~~ limits are specified in Annex 1 of the EU Guidelines to GMP (Manufacture of Sterile Medicinal Products).[8]

Action limits are initially set in alignment with EU GMP Annex 1 guidance values. However, if trend data for Grade B, C or D GMP areas indicates a consistently lower value, the action limits may be lowered to improve control. Alert limits must also be set to provide a warning of a possible deviation from normal operating conditions that may not require direct action but may need to be monitored more closely.

Alert limits must be established based on results of Performance Qualification (PQ) tests or trend data and must be subject to periodic review.

(no changes to sections 9.7.4.2 to 9.7.6)

9.7.7: Process simulations

Validation of aseptic processing must include a process simulation test using a nutrient medium. The process simulation test must imitate as closely as possible the routine process including all critical subsequent manufacturing steps. It must also take into account various interventions known to occur during the routine process as well as worst-case situations. Process simulation tests must be performed as initial validation with three consecutive satisfactory tests and repeated at defined intervals and after any significant modification to the heating, ventilation and air conditioning (HVAC) system, equipment or process.

Normally process simulation tests «should» ~~*must*~~ be repeated twice a year (per shift and process). Acceptance criteria must be defined and documented, and any investigated.

(no further changes to section 9.7)