

## Change Notification for the UK Blood Transfusion Services

**Date of Issue:** 13 February 2023

**Implementation:** to be determined by each Service

Guidelines for the Blood Transfusion Services

### Revised chapters

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## Chapter 9 Microbiology tests for donors and donations

Blood donations make up the majority of donations collected and processed by the UK **«Blood and Tissue Establishments»** ~~transfusion services~~, but tissue and stem cell donations are **«now»** a **«significant»** ~~growing~~ part of their portfolio. While the screening requirements for blood, tissues and stem cells largely overlap, there are some important differences that should be acknowledged and incorporated into any guidelines.

For the purpose of these guidelines, tissue donations include all of the types of tissue normally retrieved from living or deceased donors, and stem cell donations include haemopoietic progenitor cells (HPC) and therapeutic cells (TP). These guidelines therefore specify the screening requirements for blood, tissue and stem cell donations managed by the UK **«Blood and Tissue Establishments»** ~~transfusion services~~.

### 9.1: General requirements

All screening must be performed within Blood Safety and Quality Regulations<sup>1</sup> (BSQR) compliant laboratories and meet any other appropriate regulatory requirements.

Secure and effective procedures must be in place to ensure that:

- all donations, any subsequent components/products and their laboratory samples are correctly identified by barcoded and eye readable numbers
- donations can be linked to their donor
- information about previous test results which would preclude issue of a subsequent donation cannot be automatically overridden by a subsequent negative test result
- donor samples are suitably stored under appropriate conditions of temperature and time to preserve the targets for which they will be screened
- the screening assays used are properly evaluated and validated
- tests are appropriately performed and controlled, and the results properly and accurately recorded, using validated procedures
- test results and other relevant test information are retained for the appropriate period, as set out in the BSQR<sup>1</sup> **«and any other appropriate regulations»** ~~or equivalent~~
- appropriate confirmatory testing is available to investigate screen reactivity
- relevant data relating to screening and confirmatory test results are reported to a centralised surveillance system, allowing the monitoring of trends in screening test reactivity and confirmed positive results.

#### 9.1.1: Test reagents **«kits and equipment»**

All assays used must be **«UKCA or»** CE marked and must have been assessed in respect of sensitivity and **«if appropriate or necessary,»** specificity and deemed suitable by the UK Blood **«and Tissue Establishments»** ~~Transfusion Services~~ kit evaluation groups (NHSBT KEG or SNBTS/NIBTS MTEG) for the detection of the required markers in the donation types being screened. Unless specifically validated for alternative use/performance, test kits and reagents must be stored and used according to the manufacturer's instructions.

Each new manufacturer's lot of each assay **«must»** ~~should~~ be assessed prior to being accepted and put into use **«(Lot Release Testing – LRT). Each additional delivery of an existing lot should be assessed before use (Delivery Acceptance Testing – DAT). Each manufacturer's batch/lot of microbiology test kits must be shown to conform with nationally established minimum criteria for specificity and sensitivity prior to being accepted for use for screening»**.

Additionally, all testing laboratories must ensure that the expected standard of performance of the assays used is being achieved **«through the use of the appropriate Quality Control (QC) samples and the statistical monitoring of assay control and QC sample results. Appropriate reactivity with manufacturers' and QC samples must be demonstrated with every series of tests.»** ~~by using appropriate assay batch pre-acceptance testing, delivery acceptance testing and statistical monitoring of test results on defined quality control samples.~~ All test procedures must be documented and an inventory maintained of kits and reagents in stock, including supplier, batch number, expiry date, date of receipt, version number of product insert and record of pre-acceptance testing.

Procedures must ensure the traceability of the batch number and manufacturer of kits and reagents and the serial number of equipment used to test every donation.

Equipment must be validated, calibrated and maintained. Appropriate records for these activities must be made and retained as defined in extant regulations (currently 30 years).

~~Appropriate reactivity with manufacturers' and any external control samples must be demonstrated with every series of tests.~~

A series/batch of tests is defined as the number of tests set up at the same time, under the same conditions and processed in a similar manner:

- Where the microplate format is used each plate constitutes a series of tests even if only a few wells are used.
- Where a closed system is used the size of a series/batch of tests must be determined by each individual Service through an appropriate risk assessment.

#### **9.1.2: Recording and reporting of results**

The laboratory final output should indicate the result of every test performed, using a system that provides positive sample identification. Each test result should be recorded by a system that does not require transcription. If manual completion of screening is performed it must be thoroughly documented and controlled and the results handled electronically following the same basic principles applied to fully automated testing.

#### **9.1.3: Release of tested components/products**

Standard procedures must ensure that no donations, or components/products prepared from them, can be released for issue until all the required laboratory tests (mandatory and additional) have been completed, documented and approved within a validated system of work. Compliance with this requirement can only be achieved by the use of a validated computerised system that requires the input of valid and acceptable test results for all the mandatory and required laboratory tests to permit the release of each individual donation.

**Table 9.1 Screening required for blood donations**

Infectious agent	Minimum requirement	Comments <sup>1</sup>
HIV 1+2	anti-HIV 1+2 «+O» or HIV 1+2 «+O» Ag/Ab (M) HIV RNA <sup>2</sup>	RNA screening in pools of a maximum of «24» 48 donations <sup>3</sup>
HCV	anti-HCV (M) HCV RNA (M)	RNA screening in pools of a maximum of «24» 48 donations <sup>3</sup>
HBV	HBsAg (M) HBV DNA <sup>2</sup> anti-HBc [+ anti-HBs] (A) <sup>4</sup>	DNA screening in pools of a maximum of «24» 48 donations <sup>3</sup> 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 Ab (M)	
HTLV I/II	anti-HTLV I/II («M» A) <sup>5</sup>	«Serology screening individually or in pools of a maximum of 24 donations <sup>3</sup> » <i>ID or screening in pools of a maximum of 48 donations**</i>
HEV	HEV RNA («M» A)	«RNA» screening in pools of a maximum of 24 donations <sup>3</sup>
HCMV	anti-HCMV (A)	Ideally both IgG and IgM, but IgG alone is considered sufficient
Plasmodium sp.	anti- <i>P.falciparum/vivax</i> (A)	
Trypanosoma cruzi	anti- <i>T.cruzi</i> (A)	
West Nile Virus (WNV)	WNV RNA (A)	RNA screening in pools of a maximum of 16 donations <sup>6</sup>
(M) – mandatory (release criteria) for the purpose of these guidelines		
(A) – additional «(release criteria)» due to specifically identifiable risk		
« <sup>1</sup> All microbiology screening performed on individual donations unless specified otherwise»		
<sup>2</sup> Although neither are mandatory for blood donations in most of the UK, HIV RNA and HBV DNA are included in <del>the</del> nucleic acid «screening» <del>amplification techniques (NAT) screen</del> as the commercial systems available are now triplex assays. HIV RNA is «however» mandated within Scotland.		
<sup>3</sup> The minimum sensitivity of the molecular screening is dependent upon pool size. The maximum validated pool size for use for blood screening within the UK Blood Transfusion Services is «24» 48 donations.		
<sup>4</sup> All blood donors are to be screened for anti-HBc at their first donation or their 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.		
<sup>5</sup> 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		
<sup>6</sup> The maximum validated pool size for WNV «RNA» <del>NAT</del> screening is 16 donations.		

**Table 9.2 Screening required for tissue and stem cell donations<sup>1</sup>**

Infectious agent	Minimum requirement	Comments <sup>1,2</sup>
HIV 1+2	anti-HIV 1+2 «+O» or HIV 1+2 «+O» Ag/Ab (M) HIV RNA (O)	«Stem cell donors: as for blood donors» <del>Maximum pool size of 24 donations**</del>
HCV	anti-HCV (M) HCV Ag and/or HCV Ag/Ab (O) HCV RNA (O)	«Stem cell donors: as for blood donors» <del>Maximum pool size of 24 donations**</del>
HBV	HBsAg (M) anti-HBc «(M)» [+ anti-HBs <sup>2</sup> ] («O» <del>M</del> ) HBV DNA <sup>3</sup> (O)	«Stem cell donors: as for blood donors (for HBsAg and HBV DNA, anti-HBc mandatory for stem cell donors) Either: donations that are anti-HBc reactive and have anti-HBs ≥100 mIU/mL are considered suitable for release Or: donations that 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 <sup>3</sup> » <del>Donations that are anti-HBc reactive and have anti-HBs &gt;100 mIU/mL are considered suitable for release</del>
Syphilis	anti-treponemal <del>Ab</del> (M)	
HTLV I/II	anti-HTLV I/II(M) <sup>4,5</sup>	«Serology screening individually or in pools of a maximum of 24 donations <sup>4</sup> » <del>ID or maximum pool size of 24 donations**</del>
«HEV»	«HEV RNA (A)»	«RNA screening in pools of a maximum of 24 donations <sup>4</sup> »
HCMV	anti-HCMV (A)	Ideally both IgG and IgM, but IgG alone is considered sufficient
Plasmodium sp.	anti- <i>P.falciparum/vivax</i> (A) « <i>Plasmodium spp</i> DNA (A) <sup>7</sup> »	
Trypanosoma cruzi	anti- <i>T.cruzi</i> (A)	
West Nile Virus (WNV)	WNV RNA (A)	Maximum pool size of 16 donations <sup>6</sup>
(M) – mandatory «(release criteria) for the purpose of these guidelines»		
(A) – additional «(release criteria)» due to specifically identifiable risk		
(O) – optional, genomic screening for HIV, HCV and HBV nucleic acids is not mandated but can be performed on the original donation sample as an alternative to 180 days' quarantine and follow-up serological testing		
« <sup>1</sup> All microbiology screening performed on individual donations unless specified otherwise»		
<sup>2</sup> UK screening requirements. Other testing, e.g. Epstein-Barr virus, toxoplasmosis, may be required as additional tests depending upon specific additional risk and/or special requests for individual recipients. For certain product types that are exported there may be additional end user «screening» <del>testing</del> requirements.		
« <sup>3</sup> anti-HBc reactive tissue and stem cell donations do not need to have an anti-HBs level ≥100 mIU/ml to be considered suitable for release if both HBsAg and ID HBV NAT are negative on screening»		
<sup>4</sup> All screening of deceased tissue donations should be performed on individual samples. Anti-HTLV I/II screening of surgical tissues/stem cells may be performed using pools of a maximum of 24 samples. «HEV RNA screening of surgical tissues may be performed using pools of a maximum of 24 samples.» <del>HBV DNA screening should be on individual samples.</del>		
<sup>5</sup> Not mandatory for avascular tissue donations but may be considered good practice.		
<sup>6</sup> The maximum validated pool size for WNV RNA screening is 16 donations.		
« <sup>7</sup> Certain tissues and cord bloods from donors with malaria risk and which are found to be malaria antibody positive may be released for use if additional testing for malaria DNA is performed and malaria DNA is not detected (see Tissue Donor Selection Guidelines <sup>3</sup> )»		

## 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» test to be defined as 'mandatory'. These include a «UK or» European Union 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.

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» tests are 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» testing 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» tested 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.

### 9.2.2: Deceased neonatal and infant tissue donors

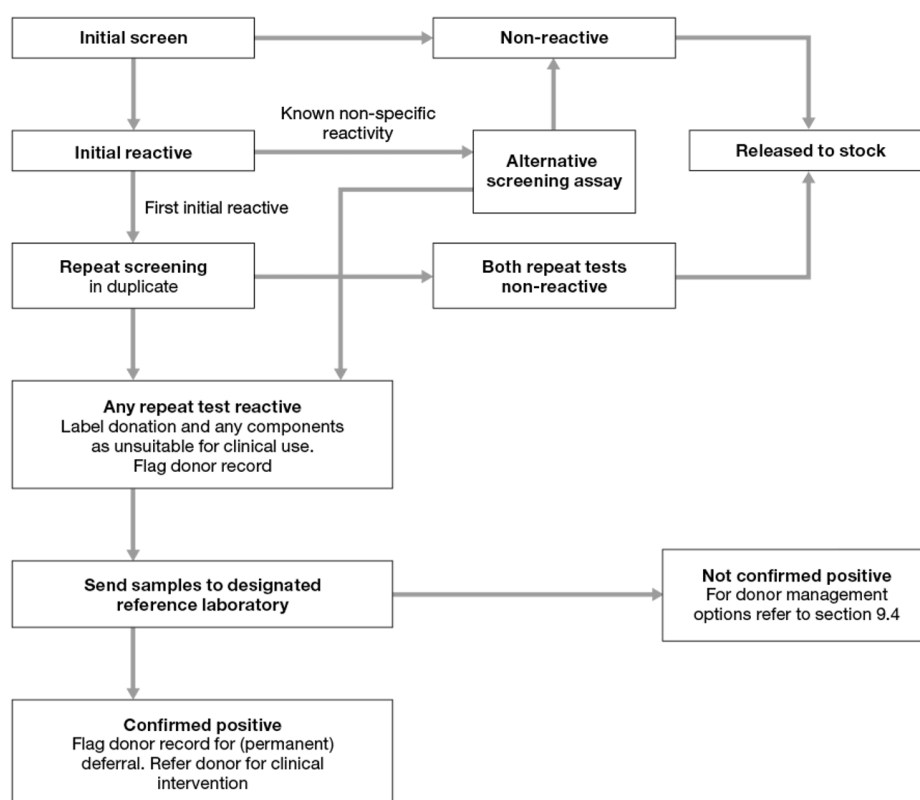
- Full microbiology screening of a maternal sample is always required.
- For still births and «for» neonates «up to 28 days» less than 48 hours after birth, no microbiology screening of the neonate is required.
- ~~For neonates between 48 hours and 28 days after birth, a neonatal sample is only required when there are identifiable risks of possible viral transmission. In this scenario only nucleic acid amplification techniques (NAT) testing of the sample is required.~~
- For infants more than 28 days after birth, full microbiology screening of an infant's sample is required.

### 9.2.3: Serology screening algorithms

#### 9.2.3.1: Blood donations

- No «donation» sample which «is» tests initially reactive for the first time in the routine screening assay can be released for clinical use unless subsequently shown to have a negative result on both tests in duplicate repeat testing using the same assay.
- Blood donations «which» that are reactive on one or both of the repeat tests are unsuitable for use and must be labelled as biological hazard/not for transfusion.
- «Donations» Samples which «are» test initially reactive in the routine screening assay, but which originate from donors who have been previously investigated in a reference laboratory and have been shown to be demonstrating non-specific reactivity, may be «screened using» tested on a second (alternative) screening assay of at least equal sensitivity to the primary screening assay, and can be considered suitable for clinical use if the reaction in the alternative screening assay is negative.

See flowchart for screening of blood donations provided in Figure 9.1.



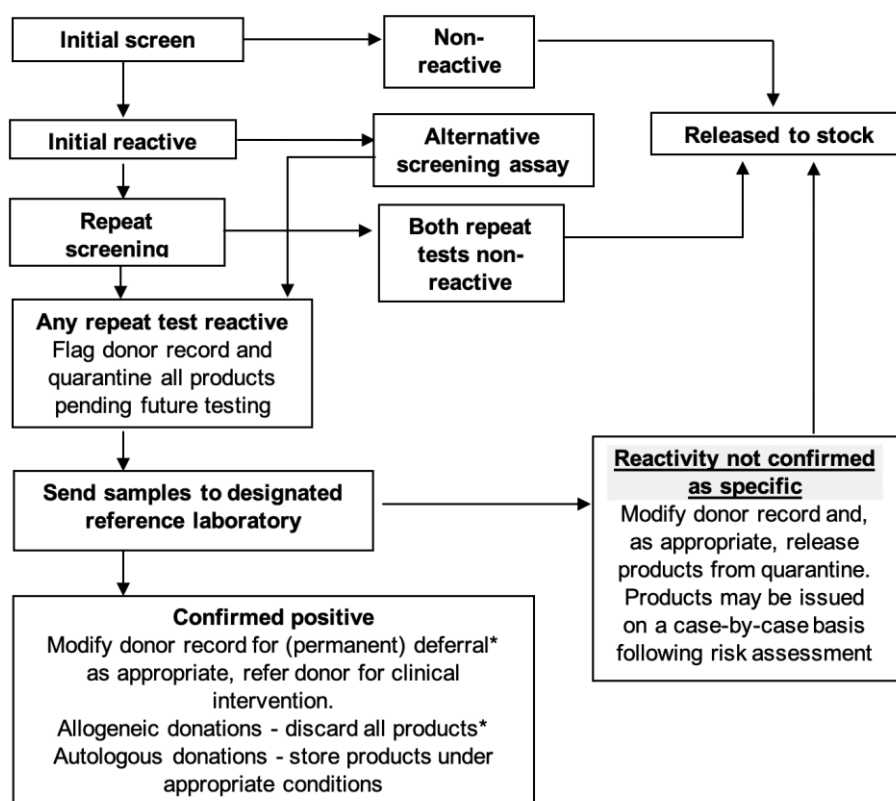
**Figure 9.1 Serology screening: blood donations**

### 9.2.3.2: Tissue and stem cell donations

- All initially reactive samples (see Figure 9.2) must be re-tested in duplicate using either the same assay or using an alternative assay that has been specifically evaluated to have at least equal sensitivity and ideally is based on different antigens and/or antibodies, and/or principles.
- Donations that are non-reactive on both of the repeat tests can be considered suitable for clinical use.
- Donations that are reactive on one or both of the repeat tests may in some clinical circumstances, and depending on the confirmatory results, be considered suitable for use (SaBTO «[Microbiological Safety Guidelines 2020<sup>3</sup>](#)» [Guidelines 2011](#)).

### 9.2.4: Molecular screening algorithm

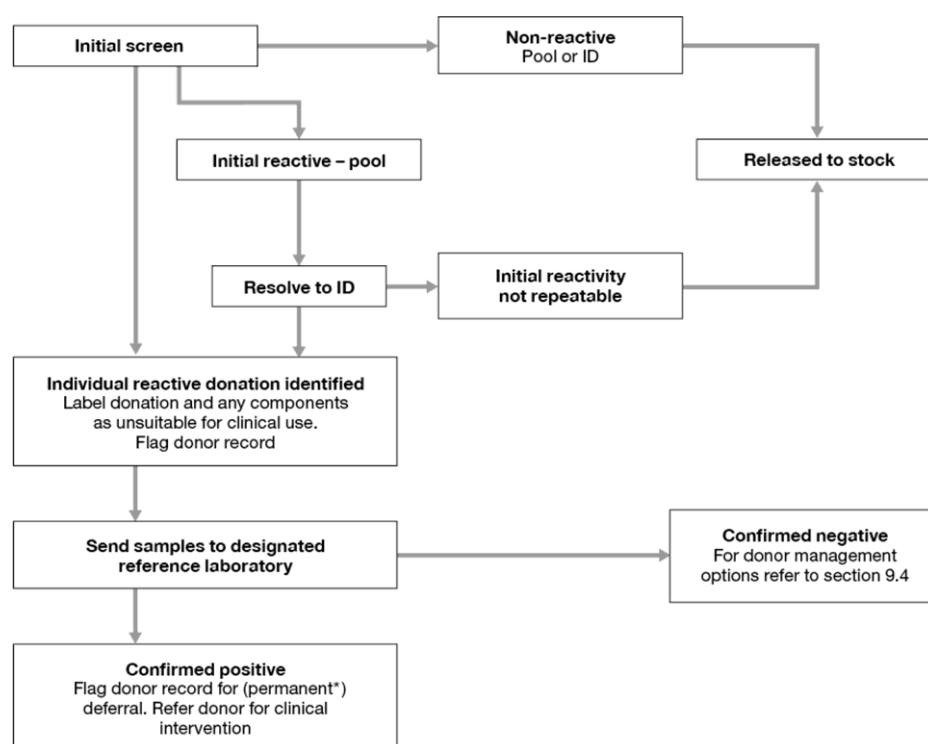
- All initially reactive pool samples (see Figures 9.3 and 9.4) must be resolved to an individual (or more) reactive donation«(s)». All other non-reactive donation«(s)» can be considered suitable for clinical use.
- Individual reactive donations are unsuitable for clinical use and must be labelled as biological hazard/not for transfusion.
- Stem cell donations from known infected individuals that are reactive on screening may in some clinical circumstances be considered suitable for use (SaBTO «[Microbiological Safety Guidelines 2020<sup>3</sup>](#)» [Guidelines 2011](#)).



**Figure 9.2 Serology screening: tissue and stem cell donors/donations**

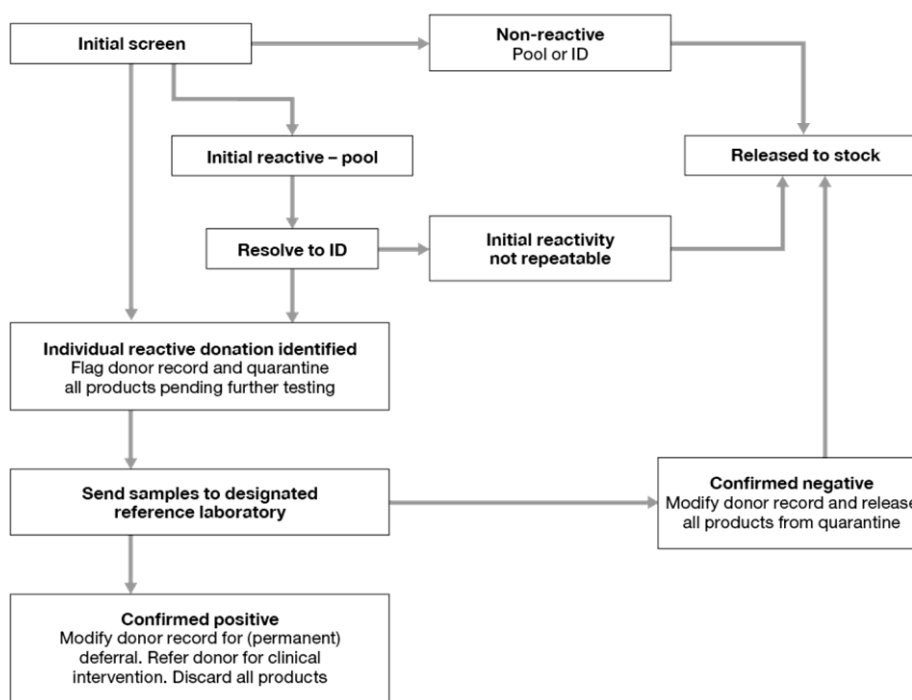
«\*Tissue/stem cell donors/donations confirmed to be anti-HBc reactive, and which are HBsAg and ID HBV DNA negative may be considered suitable for release»





**Figure 9.3 Molecular screening: blood donations**

«\*Donors confirmed to be HEV or WNV RNA positive need only be deferred for 6 months from initial detection.»



**Figure 9.4 Molecular screening for tissue and cell donors**

### 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 ~~and anti-HBc, where anti-HBs is present at a level  $\geq 100$  mIU/mL~~), 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  $\geq 100$  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  $\geq 100$  mIU/mL.»
- If HEV 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 or WNV RNA 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.

#### 9.2.5.1: Specific requirements for HBsAg confirmation

The designated reference laboratory should, «~~when~~ ~~where~~ appropriate, perform specific neutralisation tests for HBsAg to ensure that donors with low-level HBsAg reactivity «, in the absence of other HBV markers,» are not incorrectly «reported» ~~described~~ as non-specifically reactive.

### 9.2.6: Definitions

Term	Definitions
Non-reactive (NR)	A sample whose reactivity when first tested falls «below» <del>inside</del> the assay cut-off as defined by the manufacturer's instructions. May also be referred to as a 'Negative' test result
Initial reactive (IR)	Any sample whose reactivity when first tested falls «above» <del>outside</del> the cut-off as defined by the manufacturer's instructions
Repeat reactive (RR)	Any sample reactive on two or more occasions either in the same screening «assay» <del>test</del> (duplicate) or in two or more screening «assays» <del>tests</del> that are used in combination sequentially, to determine the suitability of a donation for release for clinical use
Alternative assay «screening» <del>testing</del>	When a «second assay for the same screening target and» a <del>test</del> of similar <del>modality</del> <del>and</del> sensitivity is used sequentially to screen a sample which is either IR or RR in a first screening assay
Confirmatory testing	«Full investigation, in a designated reference laboratory» <del>Further testing</del> of a repeat reactive sample <del>using a number of different assays in a reference laboratory to</del> «determine» <del>define</del> whether the reactivity is specific to the «infectious agent» <del>microbe</del> being screened for and indicative of «current or past infection in the donor» <del>potential infectivity</del>
Positive	A sample whose reactivity in confirmatory testing meets pre-defined criteria. This may indicate current or past infection
Inconclusive	A sample whose reactivity in confirmatory testing is not sufficient and/or specific enough to determine whether it reflects infection or possible non-specific reactivity

Negative	A sample <b>«whose screen reactivity, on investigation»</b> which is either <b>«not demonstrable or»</b> <del>non-reactive in confirmatory testing or whose reactivity in confirmatory testing</del> is deemed not to reflect infection
<b>«Individual nucleic acid test (ID-NAT)»</b>	<b>Molecular screening of a donation as an individual sample cf. pooled testing»</b>

### 9.3: Specific **«screening targets» assays**

#### 9.3.1: HBsAg

- The UK specification for the minimum level of sensitivity for the performance of HBsAg screening is 0.2 IU/mL. A UK HBsAg working standard (07/288 or equivalent) containing 0.2 IU/mL HBsAg is available from the National Institute for Biological Standards and Control (NIBSC). Laboratories using an assay of high analytical or dilutional sensitivity where the working standard reacts too strongly are advised to utilise the NIBSC HBsAg monitoring standard (07/286 or equivalent) set at 0.05 IU/mL in place of the working standard.
- 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.
- ~~Each manufacturer's batch/lot of HBsAg test kits must be shown to conform with nationally established minimum criteria for specificity and sensitivity prior to being accepted for use for screening.~~

#### 9.3.2: anti-HIV 1+2 or HIV 1+2 Ag/Ab combination

- «Screening for both HIV p24 antigen and antibody to HIV 1+2+O in a»** ~~The HIV 1+2 Ag/Ab~~ combination assay is recommended ~~for use within the UK Blood Services~~ as the serological screening **«approach for HIV within the UK Blood Services» assay of choice.**
- The UK requirement for the minimum level of sensitivity for the performance of HIV 1+2 serological screening is that a positive result should be obtained with the UK anti-HIV 1 working standard, available from NIBSC (99/750 or equivalent). Laboratories using an assay of higher analytical or dilutional sensitivity where the working standard reacts too strongly are advised to utilise the NIBSC HIV working standard 1/5 dilution (99/710 or equivalent) in place of the working standard. There is no specific requirement to demonstrate individual anti-HIV 2 or HIV p24 Ag reactivity.
- 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.
- ~~Each manufacturer's batch/lot of HIV test kits must be shown to conform with nationally established minimum criteria for specificity and sensitivity prior to being accepted for use for screening, including demonstrating specific anti-HIV 2 reactivity and, as appropriate specific HIV p24 Ag reactivity.~~

#### 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» 06/488** or equivalent), available from NIBSC. Laboratories using 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» 06/490** 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 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.

- ~~Each manufacturer's batch/lot of anti-HCV test kits must be shown to conform with nationally established minimum criteria for specificity and sensitivity prior to being accepted for use for screening.~~

#### 9.3.4: anti-HTLV I/II

- The UK requirement for the minimum level of sensitivity for the performance of anti-HTLV I/II screening is that a positive result should be obtained with the UK anti-HTLV working standard, available from NIBSC (03/104 or equivalent).
- 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.
- ~~Each manufacturer's batch/lot of anti-HTLV I/II test kits must be shown to conform with nationally established minimum criteria for specificity and sensitivity prior to being accepted for use for screening.~~

#### 9.3.5: Syphilis antibody

- The UK requirement for the minimum level of sensitivity for the performance of syphilis (specific treponemal antibody) screening is that, ~~in the absence of a specifically defined UK working standard produced by NIBSC~~, a positive result should be obtained with the appropriate **«syphilis Ab standard available from NIBSC (QCRSYPHQC1 (20/B767), QCRSYPHQC2 (17/B713) or equivalent)»** ~~Health Protection Agency (HPA) syphilis quality control preparation.~~
- In addition to the assay manufacturer's controls, the **«NIBSC» HPA** syphilis **«antibody»** quality control preparation 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.
- ~~Each manufacturer's batch/lot of anti-treponemal test kits must be shown to conform with nationally established minimum criteria for specificity and sensitivity prior to being accepted for use for screening.~~

#### 9.3.6: Malarial antibody

**«Donations collected from donors with an identified malarial risk may be released if the donation has been collected following the exclusion period set out in the JPAC Donor Selection Guidelines<sup>3</sup> and malarial antibody is not detected on screening. These guidelines also identify specific situations when donations may be released if malarial antibody is detected and additional testing for malarial DNA is then performed and malarial DNA not detected, and situations when donations may be collected at a timepoint within the standard exclusion period.»**

~~The exclusion period for donors from malarial areas is given in the Joint UKBTS/HPA Professional Advisory Committee (JPAC) Donor Selection Guidelines.<sup>3</sup> These guidelines specify situations where donations may only be released if a test for malarial antibodies is negative.~~

- The UK requirement for the minimum level of sensitivity for the performance of malarial antibody (anti-*P.falciparum/vivax*) screening is that, ~~in the absence of a specifically defined UK working standard produced by NIBSC~~, a positive result should be obtained with the **«malarial Ab standard available from NIBSC (QCRMALQC1 (13/B627) or equivalent)»** ~~HPA malaria antibody quality control preparation.~~
- In addition to the assay manufacturer's controls, the **«NIBSC» HPA** malaria antibody quality control preparation 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.
- ~~Each manufacturer's batch/lot of malarial antibody test kits must be shown to conform with nationally established minimum criteria for specificity and sensitivity prior to being accepted for use for screening.~~

#### 9.3.7: anti-*T.cruzi* «antibody»

The deferral criteria for donors from *T.cruzi* endemic areas are given in the JPAC Donor Selection Guidelines<sup>3</sup>. Donors at risk of *T.cruzi* must be tested for anti-*T.cruzi* and negative results obtained prior to the release of any donation for clinical use.

- The UK requirement for the minimum level of sensitivity for the performance of anti-*T.cruzi* screening is that, in the absence of a specifically defined UK working standard produced by NIBSC, a positive result should be obtained with a formally validated in-house anti-*T.cruzi* quality control preparation. **«*T.cruzi* international standards are available from NIBSC (09/188 and 09/186 or equivalent).**»
- In addition to the assay manufacturer's controls, the anti-*T.cruzi* quality control preparation 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.
- ~~Each manufacturer's batch/lot of anti-*T.cruzi* test kits must be shown to conform with nationally established minimum criteria for specificity and sensitivity prior to being accepted for use for screening.~~

### 9.3.8: anti-HBc

The exclusion period for blood donors who have had body piercing, acupuncture etc. are given in the JPAC Donor Selection Guidelines<sup>3</sup>. ~~Certain of these categories may require donations to be tested for anti-HBc and negative results obtained prior to release of any blood component for clinical use.~~ **«All blood donors are to be screened for anti-HBc at their first donation or their 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.»** Tissue and stem cells donations have anti-HBc screening as a mandatory requirement.

- The UK requirement for the minimum level of sensitivity for the performance of anti-HBc screening is that, ~~in the absence of a specifically defined UK working standard produced by NIBSC,~~ a positive result should be obtained with the **«appropriate anti-HBc standard available from NIBSC (QCRTHBcQC1 (16/B704) and QCRTHBcQC2 (14/B651) or equivalent).**» ~~HPA anti-HBc quality control preparation.~~
- In addition to the assay manufacturer's controls, the **«NIBSC» HPA** anti-HBc quality control preparation 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.
- ~~Each manufacturer's batch/lot of anti-HBc test kits must be shown to conform with nationally established minimum criteria for specificity and sensitivity prior to being accepted for use for screening.~~
- **«Blood» donations «which are confirmed positive» found to be reactive for anti-HBc should be tested for anti-HBs «; Tissue and stem cell donations found to be reactive for anti-HBc alone may not require additional anti-HBs testing»** (see section 9.3.10).

### 9.3.9: anti-HCMV

- The UK requirement for the minimum level of sensitivity for the performance of anti-HCMV screening is that, ~~in the absence of a specifically defined UK working standard produced by NIBSC,~~ a positive result should be obtained with the **«anti-CMV standard available from NIBSC (QCRCMVQC1 (18/B731) or equivalent).**» ~~HPA anti-HCMV quality control preparation.~~
- In addition to the assay manufacturer's controls, the **«NIBSC» HPA** anti-HCMV quality control preparation 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.
- ~~Each manufacturer's batch/lot of anti-HCMV test kits must be shown to conform with nationally established minimum criteria for specificity and sensitivity prior to being accepted for use for screening.~~

### 9.3.10: anti-HBs

**«Blood» donations «confirmed positive» found to be reactive for anti-HBc with levels of anti-HBs <100 mIU/mL are deemed unsuitable for release, whereas « blood donations confirmed positive for anti-HBc with anti-HBs levels ≥100 mIU/mL tested in the past 24 months by a UK Blood Service» those with levels >100 mIU/mL can be considered suitable for release «if HBsAg and ID HBV DNA negative.**

**In the case of tissue and stem cell donations ONLY, there is no requirement for an anti-HBs level of ≥100 mIU/ml if both HBsAg and HBV DNA negative on individual donation [non-pooled] screening.»**

- The UK requirement for the minimum level of sensitivity for the performance of anti-HBs testing is that, ~~in the absence of a specifically defined UK working standard produced by NIBSC,~~ a positive result should be obtained with the **«anti-HBs standard available from NIBSC (QCRHBsQC1 or equivalent).»** ~~HPA anti-HBs quality control preparation.~~
- In addition to the assay manufacturer's controls, the **«NIBSC»** ~~HPA~~ anti-HBs quality control preparation 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.

#### **9.3.11: Hepatitis C virus RNA ~~(HCV-NAT)~~**

- The UK requirement for the minimum level of sensitivity for the performance of HCV **«RNA screening»** ~~NAT~~ is 5000 IU/mL in an individual donation. **«A multiplex working reagent (HBV DNA, HCV RNA, HIV RNA) is available from NIBSC (14/198 or equivalent).»** ~~An HCV international standard is available from the NIBSC.~~
- The assay must include a specific internal control for each sample tested.
- No series of tests should be considered acceptable unless the result of the assay manufacturer's and any additional quality control samples have satisfied the criteria laid down.
- ~~Each manufacturer's batch/lot of HCV RNA test kits must be shown to conform with nationally established minimum criteria for specificity and sensitivity prior to being accepted for use for screening~~

#### **9.3.12: Hepatitis B virus DNA ~~(HBV-NAT)~~**

- There is currently no specific UK requirement for the minimum level of sensitivity for the performance of HBV **«DNA screening»** ~~NAT~~. **«A multiplex working reagent (HBV DNA, HCV RNA, HIV RNA) is available from NIBSC (14/198 or equivalent).»** ~~An HBV international standard is available from the NIBSC.~~
- The assay must include a specific internal control for each sample tested.
- No series of tests should be considered acceptable unless the result of the assay manufacturer's and any additional quality control samples have satisfied the criteria laid down.
- ~~Each manufacturer's batch/lot of HBV DNA test kits must be shown to conform with nationally established minimum criteria for specificity and sensitivity prior to being accepted for use for screening.~~

#### **9.3.13: Human immunodeficiency virus RNA ~~(HIV-NAT)~~**

- There is currently no specific UK requirement for the minimum level of sensitivity for the performance of HIV **«RNA screening»** ~~NAT~~. **«A multiplex working reagent (HBV DNA, HCV RNA, HIV RNA) is available from NIBSC (14/198 or equivalent).»** ~~An HIV international standard is available from the NIBSC.~~
- The assay must include a specific internal control for each sample tested.
- **«The assay must utilise two separate targets within the HIV genome to minimise any risk of failure of detection due to sequence changes in the primer or probe binding regions.»**
- No series of tests should be considered acceptable unless the result of the assay manufacturer's and any additional quality control samples have satisfied the criteria laid down.
- ~~Each manufacturer's batch/lot of HIV RNA test kits must be shown to conform with nationally established minimum criteria for specificity and sensitivity prior to being accepted for use for screening.~~

#### **9.3.14: Hepatitis E virus RNA ~~(HEV-NAT)~~**

- There is currently no specific UK requirement for the minimum level of sensitivity for the performance of HEV **«RNA screening. An HEV RNA international standard is available from the Paul Ehrlich Institute (PEI) (6329/10 or equivalent).»** ~~NAT~~
- The assay must include a specific internal control for each sample tested



- No series of tests should be considered acceptable unless the result of the assay manufacturer's and any additional quality control samples have satisfied the criteria laid down
- ~~Each manufacturer's batch/lot of HEV RNA test kits must be shown to conform with nationally established minimum criteria for specificity and sensitivity prior to being accepted for use for screening~~

### 9.3.15: West Nile virus RNA ~~(WNV NAT)~~

The exclusion criteria for donors from a WNV risk area is given in the JPAC Donor Selection Guidelines<sup>3</sup>. These guidelines specify some situations where donations may only be released if a test for WNV RNA is negative. WNV RNA screening can be performed on donations provided by donors within the exclusion period and the donations released if WNV RNA negative.

- There is currently no specific UK requirement for the minimum level of sensitivity for the performance of WNV NAT. **«A WNV international standard is available from NIBSC (18/206 or equivalent).»**
- The assay must include a specific internal control for each sample tested.
- No series of tests should be considered acceptable unless the result of the assay manufacturer's and any additional quality control samples have satisfied the criteria laid down.
- ~~Each manufacturer's batch/lot of WNV RNA test kits must be shown to conform with nationally established minimum criteria for specificity and sensitivity prior to being accepted for use for screening.~~

### 9.3.16: Other infectious agents

The JPAC Donor Selection Guidelines<sup>3</sup> may identify other infectious agents and specify some situations when screening may be applied in addition to donor deferral. In such situations any screening performed must:

- use assays specifically evaluated and validated for the screening of the donation type
- identify and utilise an independent quality control in each series of tests in addition to the manufacturer's assay controls
- ensure that the results of the assay manufacturer's and the additional quality control samples have satisfied the criteria laid down prior to release of the results
- ~~require that each manufacturer's batch/lot of kits must be shown to conform with nationally established minimum criteria for specificity and sensitivity prior to being accepted for use for screening.~~

### «9.3.17: Additional screening of plasma intended for fractionation

**All plasma pools intended for the manufacture of medicines are subjected to microbiological screening as described in the current European Pharmacopoeia Monograph on Human Plasma for Fractionation. Dependent on which product the plasma pool is being used to produce, to limit the viral burden in-process screening of the first homogenous plasma pool for both hepatitis A Virus (HAV) RNA and Human Parvovirus B19 (B19V) DNA is performed. A maximum level for B19 DNA has been defined in the European Pharmacopoeia, but not for HAV RNA.**

**There is no mandatory requirement to screen donations for HAV and Human B19V, although UK Blood services may elect to screen donations in minipools to reduce the risk of discard of larger plasma pools.**

#### 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<sup>4</sup> IU/ml of B19V DNA in the homogenous plasma pool. A clinical virology immunodeficiency multiplex working reagent including Human B19 DNA (2.4 x 10<sup>4</sup> IU/mL) is available from NIBSC (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.**

### 9.3.17.2: Hepatitis A virus RNA

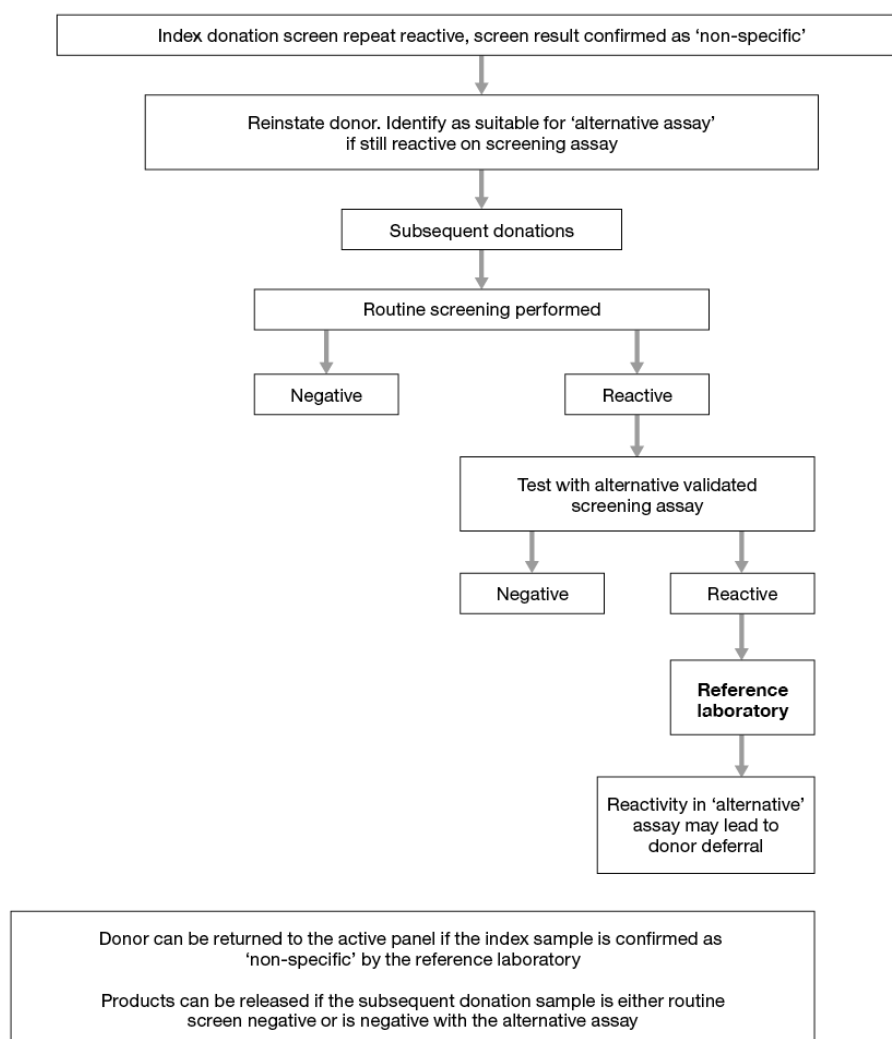
There is currently no specific UK requirement for the minimum level of sensitivity for the performance of HAV NAT. If screening is performed in minipools, UK Blood Services must ensure that HAV RNA can be detected at a level that will ensure a negative HAV NAT in the homogenous plasma pool. Currently HAV RNA standardised run control material is not available from NIBSC or PEI.

- 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.»

### 9.4: Reinstatement of blood donors

Where a blood donation sample is found to be repeatedly reactive on screening «(except for anti-HCMV)», the donation and any components must not be released for clinical use. «For anti-HBc/anti-HBs exceptions see 9.2.5.» The donor's record must be flagged in accordance with standard operating procedures to prevent the issue of subsequent donations while awaiting the results of confirmatory testing in the reference laboratory. The screen repeat reactive sample must be sent to a designated reference laboratory for confirmatory testing.

If the donation sample is determined by the reference laboratory to be demonstrating non-specific reactivity, subsequent donations from the donor may be considered suitable for issue provided that the associated donation samples are negative in the primary or an alternative screening assay (Figure 9.5).



**Figure 9.5 Action chart – blood donor reinstatement following confirmation of screen reactivity as non-specific**



#### 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 acute HBV infection may be reinstated provided that they meet the criteria for an individual with previous (recovered) hepatitis B virus infection laid out in the current edition of the UK Donor Selection Guidelines~~
- Donors with confirmed HEV or WNV infection should be deferred for 6 months from the date of first detection of HEV/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 UI/ml using the PEI International standard for HEV IgG (HEV IgM may or may not still be present)», the donor may be reinstated immediately.

#### 9.4.2: Donors whose samples are repeatedly reactive, but concluded after reference testing to represent non-specific reactivity

Where a blood donation sample is found to be repeatedly reactive on screening, the donation and any components must not be released for clinical use.

- The donor's record must be flagged in accordance with standard operating procedures to prevent the issue of subsequent donations while awaiting the results of confirmatory testing in the reference laboratory
- The screen repeat reactive sample must be sent to a designated reference laboratory for confirmatory testing
- If the donation sample is determined by the reference laboratory to be demonstrating non-specific reactivity, subsequent donations from the donor may be considered suitable for issue provided that the associated donation samples are negative in the primary or an alternative screening assay (Figure 9.5).
- «Blood donations in which reactivity in an anti-HBc screening assay is subsequently confirmed as non-specific do not require any additional screening (unless the donor lapses, has a defined exposure incident or reports a hepatitis-like illness). The confirmed negative result can impart anti-HBc negative 'status' to the donor's record.»

#### 9.4.3: Process to reinstate a confirmed non-specific reacting blood donor

A donor with screen reactivity that is confirmed by the reference laboratory as 'non-specific' may be immediately returned to active status with no restrictions on any subsequent donations (see Figure 9.5).

However, in order to reinstate a donor whose sample remains reactive in the original screening assay but confirmed by the reference laboratory to be demonstrating non-specific reactivity, the Blood Service must have the facilities to run appropriate alternative screening assays and to the same standard as primary screening. The following conditions must be met for this to be acceptable:

- The alternative assay must be of equivalent sensitivity to the original screening assay in which the index donation gave a repeatable non-specific reaction and conform to the UK requirements for microbiology screening tests.
- Donations taken subsequent to the return of the donor to the active panel may be used provided that the donation is non-reactive by the alternative assay.
- The donor's record must remain flagged with the information identifying previous non-specific reactivity for the marker.
- «For anti-HBc confirmed non-specific reactivity, 'anti-HBc negative' status can be applied. No additional screening is required in subsequent donations unless the donor lapses, has a defined exposure incident or reports a hepatitis-like illness.»

## 9.5: Recommended standards for the reduction of bacterial contamination of blood components

In recent years bacterial contamination of blood has been significantly reduced by the introduction of improved donor arm cleansing using 70% isopropyl alcohol/2% chlorhexidine gluconate applied as a single-step procedure, and diversion of the first 20–30 mL of the blood donation. The risk of bacterial contamination can be further reduced, but not eliminated, by screening of blood.

### 9.5.1: Arm cleansing

There should be an effective, specified and validated method of arm cleansing, using an approved skin-cleansing system. 70% isopropyl alcohol/2% chlorhexidine gluconate is recommended by the National Evidence-Based Guidelines for Preventing Healthcare-Associated Infections in NHS Hospitals in England<sup>4</sup>. Adherence to the principles, protocols and practices relating to the correct use of the specified skin-cleansing system shall be regularly audited by periodic bacterial sampling and observation, and corrected if found to be lacking.

*Periodic bacterial sampling of the skin of donors' arms may be carried out as an audit of correct use of the specified skin-cleansing system. If such sampling is performed, it will give an indication of how well staff are complying with the use of the system. In practice, it should be expected that bacterial sampling after skin cleansing with 70% isopropyl alcohol/2% chlorhexidine gluconate will reveal bacteria at a rate of no greater than 2 cfu per standard contact plate. Such levels may be difficult to achieve with other cleansing systems. Consistent finding of higher levels may require a review of compliance/re-education of relevant staff and further observational audits.*

*Periodic bacterial sampling may also take the form of anonymous sampling of staff fingertips after hand hygiene and after dealing with donors to assess levels of hand contamination and effectiveness of hand washing and decontamination in practice. Findings can then be fed back to staff as an educational tool.*

### 9.5.2: Diversion of donation

A minimum of 20 mL of the first part of every blood donation should be diverted into a side-arm pouch, in order to minimise the level of bacterial skin contaminants in the collection bag. This diverted volume can be used as a source of blood samples for mandatory and other testing of the donation.

### 9.5.3: Screening of platelet components

There should be a means of detecting bacterial contamination of platelet components, using validated methods. The key requirements of a detection system are (i) effective sample size, (ii) a rapid test result or automated **«continuous monitoring» 24-hour readout** with alarm notification and (iii) reliable detection of bacteria at a level indicating **«potential» emerging** risk to recipient.

Bacterial culture using an automated microbial detection system represents the most widely used and efficient method for screening of components. Its key feature is the continuous monitoring of **«incubated culture bottles» incubation** to allow immediate withdrawal of contaminated **«and associated»** units.

**«The use of an automated microbial detection system using the following protocol has been shown to give a substantial risk reduction regarding transfusion transmission of bacteria in platelet components<sup>5</sup>. This requires a minimum hold period of at least 36 hours before sampling and a minimum of 8ml inoculated into both anaerobic and aerobic culture bottles. Continuous incubation and monitoring need to be performed until the end of shelf life, which can be extended from 5 to 7 days.»**

*The following protocols are considered to be optimal for single and two test systems for the screening of platelets using an automated microbial detection system. Both require the use of a minimum 16 mL sample for aerobic and anaerobic culture and allow a 7-day shelf life. A two-test protocol is the ideal method for optimal performance, but this has significant operational issues. A single test protocol with a minimum hold period of 36 hours before sampling will allow extension of shelf life of the product to 7 days providing incubation and monitoring is continued for the duration. Services may choose to initiate testing earlier than the 36-hour holding period (e.g. 18 hours), but these platelets will not qualify for a 7-day shelf life unless a second test is performed.*

#### 9.5.3.1: Single-test **«protocol» system**

1. Platelet components are held for at least 36 hours after collection
2. Minimum 8 mL samples are inoculated into each aerobic and anaerobic bottle.
3. If samples are negative after a minimum of 6 hours of incubation, release product on a negative-to-date basis with 7-day shelf life and continue incubation and monitoring for the shelf life of the product.

4. A **suitable** protocol must be in place for confirmation of the presence of contamination.

~~5. Discard unused platelets on Day 8. (Time-expired units may be referred to the relevant bacteriology laboratory for surveillance testing.)~~

### 9.5.3.2: Two-test system

~~1. Platelet components are held for at least 18 hours after collection.~~

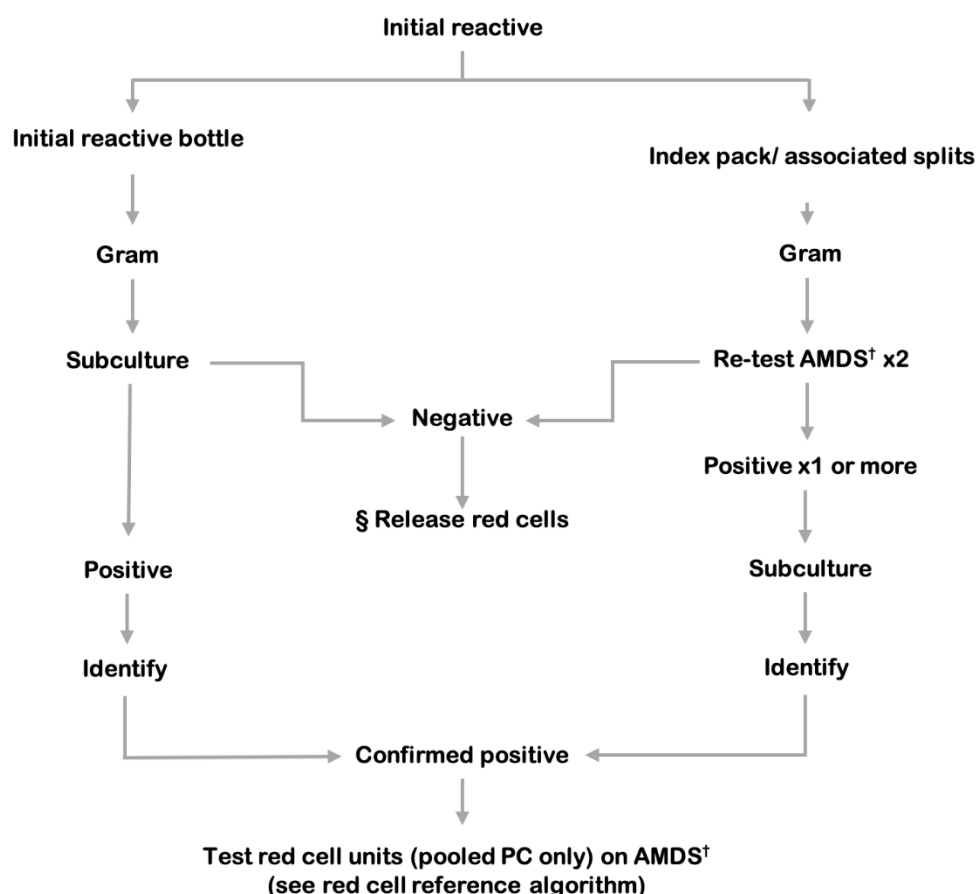
~~2. Minimum 8 mL samples are inoculated into each aerobic and anaerobic bottle.~~

~~3. If samples are negative after 24 hours of incubation, release product on a negative-to-date basis with 5-day shelf life and continue incubation and monitoring for the shelf life of the product.~~

~~4. A suitable protocol must be in place for confirmation of the presence of contamination.~~

~~5. Re-sample and test remaining stock at 4 days after collection and if negative at 24 hours release for use with a 7-day shelf life.~~

~~6. Discard unused platelets on Day 8. (Time-expired units may be referred to the relevant bacteriology laboratory for surveillance testing.)~~



**Figure 9.6 Platelet components testing algorithm.** If the index pooled platelet component is not available to re-test, the associated red cell unit «must» **should** be tested.

§ Release of red cells requires a negative result from both the index culture bottles and testing of the platelet component.

† AMDS: Automated microbial detection system, re-test aerobic and anaerobic culture in duplicate.

The following definitions of screening test results are recommended.

**Initial reactive:** «Index culture bottle/s, from initial screening, with positive signal from an automated microbial detection system.» ~~Positive bottle or bottles from which bacteria are isolated on initial screen.~~

**Repeat reactive:** «Repeat culture bottle/s, from repeat sampling of the index unit, with positive signal from an automated microbial detection system.» ~~Positive bottle or bottles from repeat testing of the index unit from which bacteria are isolated.~~

**«Associated reactive:** Associated culture bottle/s, from sampling of associated components, with positive signal from an automated microbial detection system.»

**Confirmed positive:** «Matching speciation from positive subculture of the initial reactive AND the repeat reactive OR the associated reactive.» ~~Bacteria detected from the initial and repeat tests which are of the same species.~~

**Indeterminate «positive:** A combination of results that includes positive subculture, but does not satisfy the definition for 'confirmed positive'» ~~Bacteria detected in only the initial or repeat test, but not both, or bacteria detected in the initial or repeat reactives which cannot be matched at species level.~~

- «Positive subculture from the initial reactive, BUT no positive signal from sampling of the index or associated components OR no index or associated components returned for sampling.
- Positive subculture from ONLY ONE of the initial reactive OR the repeat reactive OR the associated reactive.
- Non-matching speciation from positive subcultures of the initial reactive AND the repeat reactive OR the associated reactive.

*(In most cases there is positive subculture from the initial reactive bottle. but the index unit is not available for culture because it has been transfused.)*

**Indeterminate negative:** Negative subculture from the initial reactive, BUT no index unit available for testing.

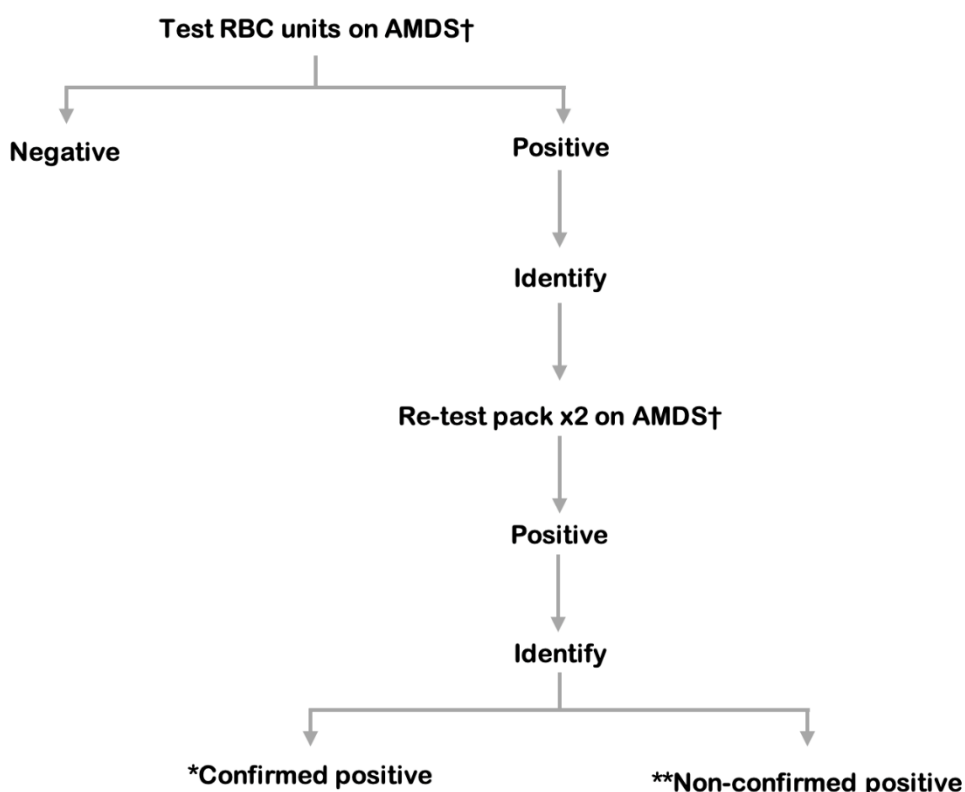
*(Where assessed, negativity would also require no organisms on Gram stain and negative growth curves from the automated microbial detection system)»*

**False positive:** «Negative subculture from the initial reactive AND no signal from repeat sampling of the index unit.» ~~A positive signal is obtained for a culture bottle but no bacteria are detected on subculture.~~

**False negative:** «Negative screening test to the end of the incubation period, BUT positive subculture from sampling of the platelet unit during investigation of a visually abnormal unit OR a post-transfusion reaction.» ~~Initial test negative but component associated with a post-transfusion reaction is subsequently positive on re-testing.~~

«When the initial reactive result is generated, any associated components (plasma, red cells etc. from the same donation) must be quarantined pending the result of repeat sampling and a recall procedure should be initiated for any platelet units or other components already issued.»

~~If the initial test is positive any components (plasma, red cells etc.) from the same donation must be quarantined pending the result of the repeat test and a recall procedure should be initiated for any platelet units or other components already issued.~~



**Figure 9.7 Red blood cell «reference» ~~reference~~ algorithm**

\* Confirmed positive: a match at species level on the initial RBC test and re-test.

\*\* Non-confirmed positive: negative repeat test and no match at species level with the PC confirmed positive result.

† AMDS: Automated microbial detection system, re-test aerobic and anaerobic culture in duplicate.

Release of red cells requires a negative result from both the index culture bottles and testing of the platelet component.

«Testing» ~~The~~ algorithms shown in Figures 9.6 and 9.7 are « **guidelines and may be modified to be Blood Service specific.** » ~~recommended for the confirmation of bacterial contamination of platelet components or red blood cells using an automated microbial detection system.~~

## 9.6: Recommended standards for microbiological screening

### 9.6.1: Tissues

All microbiological culture testing is subject to quality control tests in accordance with national accreditation standards and guidelines. This ensures that the risk of disease transmission is minimised and that tissue allografts are suitable for their intended use.

A written policy documenting the bacteriological acceptance criteria for specified tissues «**must**» ~~should~~ be drawn up in consultation with a designated microbiologist.

Tissues must be screened for bacterial and fungal contamination by validated methods in accredited laboratories. Samples for bacterial screening (e.g. swab culture, bone chips etc.) «**must**» ~~should~~ be obtained aseptically and placed in appropriate culture media at the time of retrieval or processing. Samples «**must**» ~~should~~ be culture tested before and after exposure to decontaminating agents by enrichment liquid cultures to maximise the recovery of aerobic and anaerobic bacteria, and fungi. If pathogenic, highly virulent bacteria are recovered (e.g. *Clostridium* spp. *Streptococcus pyogenes*, *Staphylococcus aureus*,

*Candida* spp.) the tissue **«must» ~~should~~** not be used for transplantation unless it is effectively sterilised by a process such as gamma irradiation. **«It is considered good practice to test cardiovascular tissues for the presence of *Mycobacterium* spp.»** Cardiovascular tissues must be tested for the presence of *Mycobacterium* spp. Tissues contaminated with opportunist species of low virulence must be decontaminated by a validated process. Tissues which cannot be terminally sterilised (e.g. heart valves, amnion, menisci, osteochondrals) must be discarded if post-decontamination tests prove positive. An exception is cryopreserved skin allografts, which can be transplanted if non-pathogenic bacteria are present.

If no suitable sample is available for screening for bacterial and fungal contamination, then the products **«must» ~~should~~** be handled in the same way as those which have positive culture results for highly virulent bacteria: either discard or terminal sterilisation with a process such as gamma irradiation.

If a tissue fails culture testing, other tissues from the same donor **«must» ~~should~~** be discarded unless processed separately or an assessment of the risk shows otherwise.

### 9.6.2: Cord blood

Cord blood donations are subject to the NetCord-FACT International Standards for Cord Blood Collection, **«Banking» ~~Processing~~** and Release for Administration. <sup>«6»<sup>5</sup></sup> Cord blood collections must be screened for bacterial (aerobic and anaerobic) and fungal contamination using a system permissive for the growth of these microorganisms (European Pharmacopoeia 2.6.27). All **«unrelated»** donations **«collected for public banking found»** positive for microbial growth **«must» ~~should~~** be discarded. Identification of any organism isolated needs to be undertaken and results reviewed by a microbiologist to identify potential sources of contamination. A trend analysis of contamination rates **«must» ~~should~~** be performed periodically to maintain quality.

### 9.6.3: Stem cells

Stem cell products (peripheral blood stem cells, bone marrow **«and»<sup>7</sup>**, whole blood ~~and directed cords~~) are subject to the FACT-JACIE International Standards for **«Haematopoietic»** Cellular Therapy Product Collection, Processing, and Administration. <sup>«7»<sup>6</sup></sup>

All products (fresh and cryopreserved) must be tested for microbial contamination (European Pharmacopoeia 2.6.27) unless the total sample volume is specifically requested by the transplant surgeon to optimise dose for the recipient. Microbial isolates recovered from products **«must» ~~should~~** be identified to species level and antimicrobial susceptibilities determined ~~and stored in a cryobank~~. A trend analysis of data **«must» ~~should~~** be reviewed by a **«relevant experts» ~~microbiologist~~** to identify potential sources of contamination.

### 9.6.4: **Autologous** Serum eye drops

Eye drops made from ~~diluted autologous~~ serum are used to treat ocular surface disorders. The serum is diluted with saline **«or used neat»** and **«dispensed» ~~bottled~~** under **«closed»** aseptic conditions and bacteriologically tested (European Pharmacopoeia 2.6.27). **«Samples must be tested for sterility in accordance with regulations»** ~~It is recommended that 5% of batches should be tested for sterility by culture for aerobic and anaerobic bacteria.~~ Identification of positive cultures needs to be performed and advice sought from a medical microbiologist regarding the suitability of a product for use via a quality concession.

## 9.7: Recommended standards for environmental monitoring **«(EM)»** of processing facilities

**«EM» ~~Environmental monitoring~~** programmes must be in place for both uncontrolled and controlled **«(GMP graded areas)»** processing facilities and must meet the requirements of appropriate regulatory bodies. ~~They must form part of the quality management system ensuring that products are processed to the highest possible standards.~~ Uncontrolled facilities include blood-processing laboratories and controlled facilities include cleanrooms used for the aseptic processing of tissues, ~~and~~ stem cells **«and associated products»**.

The main aim of microbiological **«EM» ~~environmental monitoring~~** is to provide a means of monitoring trends over time thereby ensuring that processing facilities continue to operate within acceptable bioburden **«limits and comply with GMP recommended limits for microbial contamination and airborne particulate concentration for controlled (GMP Graded) areas.»** ~~levels. Individual test results, whether high or low counts, are rarely significant.~~ **«The EM programme must form part of the quality risk management system (QRM) ensuring that products are processed to the highest possible standards and that microbial, particulate and pyrogen contamination associated with microbes is prevented in the final product.»**

**The EM programme must be part of the contamination control strategy document. The locations, frequency, volume and duration of monitoring must be determined based on a risk assessment method (EU GMP i.e. Hazard Analysis Critical Control Points (HACCP)) and from the results obtained during room qualification.»**



### 9.7.1: Key elements of an «EM» ~~environmental monitoring~~ programme

The monitoring programmes must define and document:

- The sites to be monitored and the rationale behind the selection of these sites.
- «The formal risk assessment study for each process and GMP processing area listing the Critical Control Points, which must be monitored
- A location map of monitoring sites on local data sheets.
- Airflow visualisation studies (i.e. smoke tests) to define EM sites (N/A uncontrolled rooms).»
- The types of samples to be taken and the techniques used.
- The monitoring frequency and the conditions under which the monitoring is to be performed, i.e. in the 'at rest' or 'in operation' states «as defined by EU GMP Annex 1<sup>8</sup>. Routine monitoring for clean rooms, clean air devices and personnel must be performed "in operation" during processing (N/A uncontrolled rooms)».
- Which personnel are authorised to perform «EM» ~~environmental monitoring~~.
- The incubation regime for samples.
- The setting of limits (alert and action «limits» ~~levels~~). «Alert limits for controlled rooms must be established based on results of Performance Qualification (PQ) tests or trend data and must be subject to periodic review.»
- The requirement for data and trend analysis.
- A procedure for the investigation of «out-of-specifications (OOS)» ~~out-of-limit~~ results including the identification of colony growth and the possible causes of the contamination.
- A procedure for corrective «and preventative» action in the event of «OOS» ~~out-of-limit~~ results. «A root-cause analysis (RCA) followed by a corrective and preventive action (CAPA) protocol.»

### 9.7.2: Monitoring techniques

Monitoring must be performed using standardised techniques and the main areas of sampling «must» ~~should~~ include:

- Surface sampling using contact and swab plates with the latter being used in areas inappropriate for contact plates.
- «Passive» air sampling using settle plates and, in addition, in «GMP graded areas» ~~cleanroom environments~~, active air sampling and particle counting.
- Glove prints for assessing potential transfer of bacterial contamination to sterile product during aseptic processing «in GMP grade A and B areas.» ~~(cleanrooms)~~.

« Viable and Non-viable EM techniques must comply with EU GMP Annex 1. Guidance and QRM principles.<sup>8</sup>»

In controlled facilities, monitoring for fungal in addition to bacterial contamination must, as a minimum, be achieved through the use of settle plates with media «and incubation regimens» specific for each type of contamination.

### 9.7.3: Culture media

Culture media used for «EM» ~~environmental monitoring~~ must be appropriate for the type of environment in which it is to be used, i.e. irradiated and triple wrapped media for use in cleanrooms, and for the range of organisms likely to be isolated. Media used for post-disinfection monitoring must contain agents, «that will» either individually or in combination, ~~that will~~ neutralise any residual surface disinfectant. Neutralising agents must be validated against the disinfectant(s) in use within the facility. Media storage must be in compliance with the manufacturer's recommendations and the monitored facility must be able to provide monitoring data to show that these storage requirements are «being» met.

### 9.7.4: Alert and action «limits» ~~levels~~

#### «9.7.4.1 Controlled Rooms (Cleanrooms)»

In cleanroom facilities, «alert and action» limits must be set for the results of both particulate and microbiological monitoring. «Alert» ~~These~~ limits are specified in Annex 1 of the EC Guidelines to GMP (Manufacture of Sterile Medicinal Products).<sup>«8»<sup>7</sup></sup>

«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.» ~~The action levels for microbiological monitoring in controlled rooms are taken as the limits given in the EU Guide.~~ Alert «limits» ~~levels~~ must also be set in order 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.

#### 9.7.4.2 Uncontrolled facilities

Action limits» ~~In uncontrolled facilities, action levels~~ must be established using historical data. The monitoring programmes must define how the «action limits» ~~alert levels~~ in controlled rooms and the action levels in uncontrolled rooms are to be determined.

#### 9.7.5: Data and trend analysis

«Trends may include:

- Increasing numbers of action or alert limit breaches
- Consecutive breaches of limits
- Regular but isolated breaches of limits that may have a common cause
- Changes in flora type and numbers»

Monitoring results must be entered on a suitable database to allow data and trend analysis. The results must be reviewed by staff of the monitored facility on a regular basis with a formal documented review being held «on a six-monthly basis» ~~at a minimum of four times a year.~~ This formal review must involve senior cleanroom/processing staff and representatives from the quality and microbiology departments.

#### 9.7.6: Cleanroom gowning

«EM» ~~Environmental monitoring~~ programmes for controlled rooms also need to include procedures for:

- The qualification of staff with respect to cleanroom gowning for grade A and B environments
- «The assessment and confirmation of compliance with aseptic gowning procedures. This must be reassessed periodically, at least annually and must involve both visual and microbiological assessment (using surface monitoring methods for locations such as hands (glove prints), arms, neck and chest)
- The monitoring of personnel after critical operations.»
- The monitoring of staff upon leaving an aseptic area as a means of assessing operator bioburden «limits» ~~levels~~.
- ~~Gowning qualification and~~ Exit suit monitoring «must» ~~should~~ be performed for each cleanroom operator on a regular basis with the frequency, sampling method(s) used and monitoring sites clearly defined in the procedures.

#### 9.7.7: Process simulations

Validation of aseptic processing «must» ~~should~~ include a process simulation test using a nutrient medium. The process simulation test «must» ~~should~~ imitate as closely as possible the routine process including all critical subsequent manufacturing steps. It «must» ~~should~~ also take into account various interventions known to occur during the routine process as well as worst-case situations. Process simulation tests «must» ~~should~~ 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 «must» ~~should~~ be repeated twice a year (per shift and process). «Acceptance criteria must» ~~Alert and action levels~~ should be defined and documented and any contamination investigated.

#### 9.7.8: Cleaning and disinfection

Cleaning/disinfection validation «must» ~~should~~ be performed ~~in order~~ to confirm the effectiveness of a cleaning/disinfection programme. As part of the validation, pre- and post-cleaning/disinfection «EM must» ~~environmental monitoring should~~ be used to verify the acceptability of the frequency and efficiency of the programme in terms of microbiological contamination.



Pre- and post-«EM» limits «must» ~~should~~ be established and documented within the cleaning/disinfection programme. The monitoring results «must» ~~should~~ be reviewed and, where limits have been exceeded, the contamination investigated «using RCA and CAPA» ~~and corrective action~~ implemented.

Typically, three consecutive applications of the cleaning/disinfection procedure «must» ~~should~~ be performed and shown to be successful in order to prove that the method is validated.

The cleaning and disinfection of controlled rooms is particularly important and «must» ~~should~~ be performed in accordance with a written programme. Where disinfectants are used, more than one type «must» ~~should~~ be employed on a rotational basis. «Disinfectants must be validated for their effectiveness and compatibility with the cleaning agents used. A sporicidal disinfectant must be included as one of the rotational disinfectants if practical.» Detergents and disinfectants «must» ~~should~~ be monitored for microbial contamination and, when used in grade A and B areas, «must» ~~should~~ be sterile prior to use «and where possible single use».

## 9.8: Investigation of suspected bacterial contamination of blood components

Suspected cases of bacterial contamination of blood components may be notified by reports from the hospital of a significant transfusion reaction or, following a severe reaction, the identification of bacteria either within the pack or in a patient's blood culture.

A record of the original notification, clinical details and investigations carried out by the hospital must be made by the Blood Centre. The pack remains «must» ~~should~~ be sealed and transported as soon as possible to a specialist bacteriology laboratory along with any bacterial isolates subsequently recovered from the patient's blood. If the patient has died without blood samples being obtained after the transfusion, it may be necessary for a post-mortem blood sample to be collected.

The contents of the pack, or if empty, a 20 mL «sterile» ~~saline~~ wash out of the pack, «must» ~~should~~ be sampled in the laboratory taking care to minimise the introduction of contaminants. A Gram stain may be informative but the sample «must» ~~should~~ be cultured for bacteria (aerobic and anaerobic) and fungi using a system permissive for the growth of these microorganisms. If cultures prove negative no further action/investigation is necessary.

Where bacterial contamination is indicated, action must be taken to safeguard the safety of the blood supply by recalling all other components from the same donation(s) and these must be subjected to bacterial investigation. The possible source of a contamination needs to be investigated in consultation with a specialist microbiologist and appropriate swabs and other samples from the donor obtained for culture. If isolates of the same species are obtained from the pack and donor these must be submitted for molecular typing to establish the strain identity and possible route of transmission. Further decisions about the use of subsequent donations from the donor will depend on the circumstances and the type of contamination. An assessment «must» ~~should~~ be carried out on a case-by-case basis to determine the risk of bacterial contamination through the use of further blood donations from the donor, and appropriate action taken.

## 9.9: References

«

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2. SaBTO (2020). Microbiological Safety Guidelines Available at [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/876161/SaBT\\_O-microbiological-safety-guidelines.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/876161/SaBT_O-microbiological-safety-guidelines.pdf)
3. Joint United Kingdom Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee's (JPAC) Donor Selection Guidelines. Available at [www.transfusionguidelines.org.uk](http://www.transfusionguidelines.org.uk)
4. Pratt RJ, Pellowe CM, Wilson JA, Loveday HP, Harper PJ, Jones SR, McDougall C, Wilcox MH. (2007). epic2: National Evidence-Based Guidelines for Preventing Healthcare-Associated Infections in NHS Hospitals in England. Journal of Hospital Infection, 65, S1–S64.
5. McDonald C, Allen J, Brailsford S, Roy A, Ball J, Moule R, Vasconcelos M, Morrison R, Pitt T. (2017) Bacterial screening of platelet components by National Health Service Blood and Transplant, an effective risk reduction measure. Transfusion, 57(5):1122-1131
6. NetCord-FACT International Standards for Cord Blood Collection, Banking and Release for Administration, seventh edition 2019. Available at [www.factwebsite.org](http://www.factwebsite.org)
7. FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration eighth edition 2021. Available at <https://www.ebmt.org/accreditation/jacie-standards>

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- ~~3. Joint UKBTS/HPA Professional Advisory Committee's (JPAC) Donor Selection Guidelines. Available at [www.transfusionguidelines.org.uk](http://www.transfusionguidelines.org.uk).~~
- ~~4. Pratt RJ, Pellowe CM, Wilson JA, Loveday HP, Harper PJ, Jones SR, McDougall C, Wilcox MH. (2007). epic2: National Evidence-Based Guidelines for Preventing Healthcare-Associated Infections in NHS Hospitals in England. *Journal of Hospital Infection*, 65, S1–S64.~~
- ~~5. NetCord-FACT International Standards for Cord Blood Collection, Processing and Release for Administration, fourth edition 2010. Available at [www.factwebsite.org](http://www.factwebsite.org).~~
- ~~6. FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing, and Administration, fifth edition 2012. Available at [www.jacie.org/Standards](http://www.jacie.org/Standards).~~
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The following changes apply to:

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## **Chapter 10** Investigation of suspected transfusion-transmitted infection

### **10.1 General considerations**

The guidelines in this section apply to reports of possible transfusion-transmitted infection (TTI) arising from blood or blood components supplied by the UK Blood Transfusion Services. Any suspected cases of TTI should be documented and fully assessed to determine whether further investigation of donors and/or donation samples is required or warranted. The guidance contained within this section covers the action to be taken **«by blood services» at the Blood Centre** in such cases.

Suspected cases of bacterial contamination of blood components may be notified by reports from the hospital of a significant transfusion reaction or, following a reaction, the identification of bacteria either within the pack or in a patient's blood culture. Reports will normally be received close to the time of transfusion of the blood component, when other components from the same blood donation may be in stock at either a Blood Centre or a hospital.

Because non-bacterial TTI may be asymptomatic, cases may not be recognised or detected until months or years after the transfusion. Many cases come to light through incidental screening of a patient who has received a blood component transfusion in the past or specific testing on development of late clinical features of the infection in question. Cases may therefore be notified by sources other than the hospital blood transfusion laboratory, but close liaison will be required with the reporting clinician and with the hospital blood transfusion laboratory that supplied the blood component **«(s)»** for transfusion.

#### **10.1.1: Documentation**

Reports of possible TTI must be recorded and retained. Details of the notification should be confirmed in writing by the reporter. For each report, confirmation of clinical and laboratory details will be required. Ideally, these should take the form of copies of the relevant recipient blood tests and computer printouts of transfusion records. Other forms of reporting of donation numbers (by letter, typed lists etc.) should be avoided in view of the risk of transcription errors.

#### **10.2: Assessment of validity of the possible diagnosis of TTI**

Clinical and laboratory details of the case should be reviewed to assess the validity of a diagnosis of possible TTI. Further information or test results may be required and requested at this stage.

Investigation of reported cases of TTI can be extremely time-consuming and impact on several different areas. In general, no investigation of archived samples or contact with involved donors should take place until all necessary information has been made available. However, in cases where complete details are not immediately available and a full assessment cannot be made, there should be consideration of the need to prevent issue of any further components from involved blood donors. Similarly, there should be consideration of the need to recall any in-date components from the same/recent donations to prevent their transfusion pending a decision about whether full investigation is necessary.

#### **10.3: Non-bacterial TTI: identification of possible infectious donations**

When a decision has been made to conduct an investigation into a reported non-bacterial TTI case, it may be possible to obtain sufficient information by reviewing results of testing of subsequent donations from the involved donor(s). If this is not the case, consideration should be given as to which donors require further investigation, and whether this can be satisfactorily carried out with samples already available **at the Blood Centre** from the index or any subsequent donation. This decision is dependent on the premise that subsequent samples may conclusively demonstrate the development of infectious markers (e.g. antibodies) in one of the implicated donors. It is expected that Blood Establishments will retain samples from each donation for a minimum period of 3 years in a suitable frozen archive. The retrieval of samples from this archive must be fully documented and be restricted mainly to such investigations.

If further investigation is required, and suitable blood samples are not available from the donor, then the decision may be made to contact the donor(s) and request further samples.

Decisions for each case and each donor will be on an individual basis depending upon the circumstances, timing, assessed likelihood of TTI and resources required. In cases of doubt, there should be a mechanism to ensure that there is a system for review and agreement on the way forward **«, taking expert advice as necessary»**.

In instances where there is doubt whether a donor has been the source of a TTI, specialised molecular genotyping of both implicated donor and infected recipient may be necessary to prove conclusively whether TTI did indeed occur.

#### 10.4: Investigation of possible bacterial TTI

Refer to «Chapter 9,» section 9.8 for details of laboratory investigations.

#### 10.5: Closing TTI investigations

Each investigation must be formally closed, with a conclusion and written notification to the reporter and any other interested party. In those cases where the recipient has been discharged from hospital, agreement should be reached as to who will notify the recipient: normally the «GP» ~~general practitioner~~, or another clinician. It must be remembered that confidentiality of donor details is paramount and no information should be released which could lead, either directly or indirectly, to identification of «any» ~~the~~ donor.

In cases of proven transmission, the recipient (or family, in the case of fatal cases) should be provided with an explanation of the cause of the transmission and should be given the opportunity of a meeting with relevant staff, in keeping with «Health Service» ~~NHS~~ guidelines following a serious adverse event. «Details of» legal implications and the availability of any ex-gratia payment schemes should be provided, as appropriate.

Each case investigated must be reported to the appropriate surveillance system: NHSBT/UKHSA transfusion-transmitted infection surveillance scheme for England and Wales, SNBTS National Microbiology Reference Unit for Scotland, Northern Irish Blood Transfusion Centre for Northern Ireland. These reports are collated and published in the annual report of the Serious Hazards of Transfusion (SHOT) scheme.

#### 10.6: Look-back investigations

Look-back investigations are initiated on recognition that there may have been a risk of transmitting infection from a donor to a recipient. Such a situation may arise in the following circumstances:

- donors identified as infected through the introduction of a new screening test applied to all donations
- donors identified to be infected through seroconversion during their blood donation career
- donors identified to be infected and reported to the Blood Service from an outside source
- donors identified to be responsible for transmission of infection to a recipient.

##### 10.6.1: General principles for look-back investigations

National lookback investigations, following introduction of a new screening test, should be managed through a generic system which incorporates the following steps:

- identification of potentially infectious donations
- identification of all blood components prepared from those donations
- documentation of the fate of the blood components
- notification of hospital transfusion laboratories in receipt of involved blood components
- identification of the fate of the component at the hospital, including details of any identified recipient
- for recipients not known to be dead, a procedure for notification, generally following notification of the «GP» ~~general practitioner~~/hospital clinician
- a protocol for management of recipient notification and testing (if required)
- notification of recipient test results to recipient and other interested parties.

Look-back investigations following identification of a donor who has seroconverted and/or been responsible for transmission of infection and/or is identified through post-donation information should be carried out using the same principles.

Wherever possible, retrospective testing of stored samples should be carried out in order to identify those donations which must be included in the look-back. If samples can be tested, look-back should be performed to include the last seronegative donation, unless there is evidence about the timing of infection which would make such action unnecessary, e.g. a documented negative test result after the last negative blood donation, a clear history of risk exposure post-dating the last seronegative donation etc.

If retained samples are not available for testing, then case-by-case decisions on the number of donations to be included in the look-back will be influenced by the dates of donations and the availability of the particular hospital transfusion records.

#### **10.6.2: Documentation and reporting**

All cases of look-back should be documented in the same fashion as investigation of TTI. There should be a full audit trail of decisions made and actions taken.

Where look-back results in the identification of infected recipients, a report should be made to the surveillance system as appropriate, and cases included in the annual SHOT report.

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## Chapter 19 Tissue banking: general principles

### 19.1: Regulatory environment in the UK

The whole process of tissue banking is now covered by legislation. The EU Directive on Tissues and Cells ~~(2004/23/EC)<sup>1</sup>~~ and its associated Commission Directives ~~(2006/17/EC and 2006/86/EC)<sup>2,3</sup> have been~~ «were» transposed into UK law as the Human Tissue (Quality and Safety for Human Application) Regulations 2007<sup>4</sup> «, (as amended), referred to as the **Quality & Safety Regulations<sup>1</sup>**». These regulations lay down standards of quality and safety for all aspects of banking of human tissues and cells intended for human applications. «**The UK retained the same quality and safety standards after 1 January 2021.**»

In addition, the Human Tissue Act 2004<sup>2,5</sup> applies throughout the UK with the exception of Scotland, where the Human Tissue (Scotland) Act 2006<sup>3,6</sup> applies «, **and the Human Transplantation Act (Wales) 2013<sup>4</sup> applies in Wales.**»

All Tissue Establishments need to be licensed by the 'Competent Authority', which in the case of the UK is the Human Tissue Authority (HTA). Under the Human Tissue Act the HTA issues its expected standards in the form of 'Directions'<sup>5,7</sup> and 'Codes of Practice'<sup>6,8</sup> to Tissue Establishments. HTA expected standards are contained in the Guide to Quality and Safety Assurance for Human Tissues and Cells for Patient Treatment<sup>5,7</sup> which is implemented via Directions and is periodically updated.

Every Tissue Establishment must designate a responsible person (termed the Designated Individual) who shall be responsible for ensuring that all activities relating to human tissues and cells intended for human application are in accordance with the laws in force in the UK. It is therefore the responsibility of the Designated Individual to ensure that all the requirements of the HTA are met in a timely and comprehensive manner. «**The Designated Individual may if necessary, delegate some of these responsibilities to appropriately trained and qualified individuals (Persons Designate), for example if the Tissue Establishment is located on multiple sites.**»

### 19.2: Reference documents for tissue banking

The advice contained in these guidelines is believed to represent acceptable practice at the time of writing. It is policy to revise these guidelines as new developments occur. However, it may not be possible to do so at the time of such change and the guidelines should therefore be used with due regard to current acceptable practice.

The guidelines in Chapters 19–21 apply to tissue banking activities within the Transfusion Services of the UK. They must be read in conjunction with the other sections of the guidelines including regulatory environment in the UK, quality in Blood and Tissue Establishments, microbiology tests for donors and donations and labelling of human tissue products.

Reference should be made to the current version of the JPAC *Donor Selection Guidelines*<sup>7,9</sup> available at [www.transfusionguidelines.org.uk](http://www.transfusionguidelines.org.uk).

Other key documents relating to tissue banking are listed in the references at the end of this chapter. «<sup>8-13</sup>»<sup>10,11,12,13,14,15,16</sup>

### 19.3: Data protection and confidentiality

Living donors and families of deceased donors must be told that information relating to the donation will be stored in accordance with the Data Protection Act (DPA) 2018<sup>14</sup> ~~1998<sup>17</sup>~~ and may be shared with relevant health professionals.

Tissue Establishments shall take the necessary measures to ensure that all data, collated within the scope of all their banking activities and to which third parties have access, have been rendered anonymous so that neither donor nor recipients remain identifiable.

### 19.4: References

«

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2. **Human Tissue Act 2004 (except Scotland). Available at [www.legislation.gov.uk](http://www.legislation.gov.uk)**
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5. Human Tissue Authority: Directions given under the Human Tissue Act 2004 to establishments licensed under the Quality and Safety Regulations, available at <https://www.hta.gov.uk/guidance-professionals/codes-practice-standards-and-legislation/legal-directions>
  - 001/2021 implementing the ‘Guide to Quality and Safety Assurance for Human Tissues and Cells for Patient Treatment’
6. Human Tissue Authority: Codes of Practice, available at [www.hta.gov.uk](http://www.hta.gov.uk):
  - Code A. Guiding principles and the fundamental principle of consent
  - Code F, parts 1 and 2. Donation of solid organs and tissues for transplantation
  - Code E. Research
  - Code of practice on the Human Transplantation (Wales) Act 2013
7. Joint UKBTS/NIBSC Professional Advisory Committee’s (JPAC) Donor Selection Guidelines. Available at [www.transfusionguidelines.org.uk](http://www.transfusionguidelines.org.uk):
  - Tissue donor selection guidelines: living donors (TDSG-LD)
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14. Data Protection Act 2018. Available at <https://www.gov.uk/data-protection>

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- ~~1. Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. OJ, L 102, 07.04.2004, p48.~~
- ~~2. Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells. OJ, L 038, 09.02.2006, p40.~~
- ~~3. Commission Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells. OJ, L 294, 25.10.2006, p32.~~
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  - ~~• Code 2. Donation of solid organs for transplantation~~
  - ~~• Code 5. Disposal of human tissue~~
  - ~~• Code 8. Import and export of human bodies, body parts and tissue~~
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## Chapter 20 Tissue banking: selection of donors

### 20.1: General considerations

The overall responsibility for applying the policies for the selection and care of tissue donors lies with the **«Tissue Establishment authorised»** ~~tissue bank designated~~ clinician, who must have relevant clinical experience and will be familiar with the various legal statutes and relevant documents which apply to tissue banking (see Chapter 19). The **«Tissue Establishment authorised»** ~~tissue bank designated~~ clinician must consult with relevant specialist advisors as appropriate.

The **«authorised»** ~~designated~~ clinician will rely on procedures and documentation that enable the appropriate medical and behavioural history to be acquired, to prevent microbial infection and transmission of disease **«(for example) (including malignant or neurodegenerative disease) to the recipient»<sup>1,2</sup>**. Decisions on donor assessment should be consistent with JPAC Donor Selection Guidelines.<sup>«3»<sup>†</sup></sup>

Tissues must be procured, transported, processed, stored and distributed according to the **«regulatory»** requirements **«specified in Chapter 19 of»** ~~stated in~~ these guidelines ~~(the Red Book)~~.

Procedures must be in place to document a complete audit trail from donor to recipient. Tissue **«Establishments»** ~~banks~~ must ensure that tissues can be traced from the donor to the point of issue. It is the responsibility of the hospital to **«ensure procedures are in place to»** document the fate of the tissue from its receipt to its use or discard. **«Tissue Establishments should have end user agreements in place with all hospitals to whom they provide tissue to ensure hospitals are aware of these requirements and have agreed to comply with them, and systems in place, such as periodic audit, to ensure this is being done. Evidence of such checks should be retained by Tissue Establishments.»** This will ensure that the audit trail can be followed in both directions. Clinicians caring for the recipients of tissues associated with risks identified following the issue of tissue must be informed where pertinent. Mechanisms should be in place to ensure that confidentiality is maximised.

UK Blood Transfusion Services **«Tissue Establishments»** ~~tissue banks~~ may collect tissues from donors referred to them by **«Specialist Nurse Practitioners for Organ or Tissue Donation or another Tissue Establishment and may also refer donors to other Tissue Establishment.»** ~~a third party such as a donor transplant coordinator or another tissue bank and may also refer donors to other tissue banking agencies such as a cornea or research bank.~~ Whenever information regarding donor medical and behavioural history and/or consent for donation is obtained by, or on behalf of, a third party this must be subject to a written agreement between the parties involved. The agreement must specify what information is required regarding the medical and behavioural history of the donor and consent for donation, the standards for obtaining this information and the responsibilities of both parties in ensuring that the information is accurate and properly documented. The information should, as a minimum, be provided in accordance with the guidance in this document **«, regulatory requirements»** and the current JPAC Donor Selection Guidelines.<sup>«3»<sup>†</sup></sup> It is the responsibility of the designated clinician to determine the **«Tissue Establishment's»** ~~bank's~~ policy for the referral of donors. **«Donors must be excluded from donation if any of the criteria defined in Annex A of the HTA's Guide to Quality and Safety Assurance for Tissues and Cells for Patient Treatment<sup>4</sup> apply, unless the donation is justified on the basis of a documented risk assessment process approved by the establishment's Designated Individual.»**

### 20.2: Consent

Consent must be obtained and documented by appropriately trained professionals competent in the issues and processes of tissue donation. No coercion or inducement to donate **«can»** ~~must~~ be applied during the consent procedure. The statutory requirements for consent are detailed in the relevant national legislation: ~~the Human Tissue Act (2004)<sup>2</sup> and the Human Tissue (Scotland) Act 2006<sup>3</sup>~~. Further detailed guidance is laid out in the ~~current version of the Human Tissue Authority Code of Practice on Consent<sup>4</sup> and in the Guide to Quality and Safety Assurance for Human Tissues and Cells for Patient Treatment<sup>5</sup>~~ **«Human Tissue Authority Codes of Practice: Code A Guiding Principles and the Fundamental Principle of Consent<sup>5</sup>, Codes F part one and two<sup>6</sup>, the Code of Practice on the Human Transplantation (Wales) Act 2013<sup>7</sup>, and in the Guide to Quality and Safety Assurance for Human Tissues and Cells for Patient Treatment.<sup>4</sup>»**

Living donors must be competent to give consent before donations can be accepted **«, and be provided with the opportunity to consider and receive responses to any questions they may have»**. Where donors are not competent **«to provide consent»**, national legislation and the guidance of the Human Tissue Authority (HTA) must be followed. When a deceased person (while alive and competent) has explicitly consented **«/given authorisation»** to donation of organs and tissues then that consent **«/authorisation»** is sufficient for the activity to be lawful. Where the **«decision or»** wishes of the deceased **«person»** are unknown, the **«Human Tissue Authority Codes of Practice should be followed which reflect the legal requirements in each UK nation.»** ~~Human Tissue Acts rank persons in a qualifying relationship for the purpose of obtaining consent to organ and tissue donation. The consent of the nominated representative or the highest ranking person at the time of death should be sought. In circumstances where this person does not wish to deal with the issue of~~

~~consent, or is unable to do so, the next person in the ranking order is approached, but it is advisable to record this in the notes.~~

Consent **«/authorisation where donated tissue is to be used for transplantation»** must cover retrieval, testing, storage, discard and access to medical records. If the tissue may be used for **«non-clinical purposes, as specified in the HTA Code of Practice A»** ~~research and development, or teaching~~, specific consent **«/authorisation»** must be obtained for this as well. ~~Explicit information must be given if tissues are to be retrieved for specific commercial use.~~ Living donors and families of deceased donors must be informed that information relating to the donation will be stored in accordance with the Data Protection Act **«(2018)»** ~~(1998)»~~ and may be shared with relevant healthcare professionals.

For deceased donors, information to be supplied to the next of kin regarding various aspects of tissue donation which forms the basis of consent should include the following:

- that reconstruction will be performed following retrieval
- **«generic»** ~~explicit~~ information on which tissue is to be retrieved and the clinical purpose to which it is **«likely»** to be **«used»** ~~put~~
- if tissue is found to be unsuitable for clinical transplantation it will be discarded via local discard policies or, if permission is granted, it may be used for research or educational purposes
- that the donor will be tested for markers of microbial infection including HIV **«, hepatitis, HTLV and other infections»** and after individual case assessment, those relevant contacts will be informed in the event of a relevant confirmed positive result
- that details of medical and behavioural history will be sought from additional professional sources and recorded.

Where the Coroner (the Procurator Fiscal in Scotland) is in legal possession of the body, permission must be requested to undertake the retrieval. **«It is good practice if this can be done in writing.»**

## 20.3: Medical and behavioural history

The information noted in the following two subsections for living and deceased donors should be reviewed by the designated clinician who is familiar with the relevant standards in the field of tissue banking (see Chapter 19).

### 20.3.1: For living donors

Medical and behavioural history must be sought by appropriately trained professionals and in compliance with the following guidance.

- Information may be obtained from the donor by either face-to-face interview or by recorded telephone interview by appropriately trained **«Tissue Establishment»** ~~tissue bank~~ staff. This must allow for the exclusion of lifestyle infectious risks. During interviews, a mechanism should be in place to ensure that confidentiality is maximised.
- The interview must be conducted while the donor is free from the effect of anaesthetic, hypnotic or narcotic medication. The donor must be mentally competent to give an accurate history.
- If the medical interview is not done at the time of admission for surgery, a system must be in place to capture any relevant medical and behavioural history changes that may occur in the interval between interview and donation.
- A standard questionnaire to elicit the medical and behavioural history must be used.
- Donors should be selected according to the JPAC *Donor Selection Guidelines*. **«3»**<sup>4</sup>
- The completed questionnaire must be retained as part of the **«Tissue Establishment»** ~~tissue bank~~ donor record.
- **«If considered necessary, and they are available,»** the medical records, ~~if available,~~ must be consulted to review the medical and behavioural history and the medical examination.

Further medical history may be sought, where appropriate, from:

- the general practitioner
- any other relevant medical personnel.

### 20.3.2: For deceased donors

The cause of death and the medical and behavioural history should elicit whether the donor meets the selection criteria outlined in the JPAC *Donor Selection Guidelines*<sup>«3»4</sup>. Modifications for the behavioural and medical history questions may be needed when accepting paediatric donors. Where the deceased donor is less than 18 months of age, or breast fed within the 12-month period prior to donation, the mother's risk for transmissible disease must also be evaluated. Information must be sought from the following sources by appropriately trained professionals and must be documented using a standard form:

- The donor's next of kin or other person identified as the most likely to be in possession of relevant information. **«This may not necessarily be the same person(s) as defined in the hierarchy of consent/authorisation »**
- The medical notes if the donor was admitted to hospital prior to death.
- The general practitioner.
- The post-mortem (where one is undertaken). If no post-mortem is undertaken, the cause of death of the donor, as ascertained from the medical notes, must be documented in the **«Tissue Establishment»** ~~issue-bank~~ donor record.

A record must be made of how the donor was identified (e.g. toe tag, wristband) and by whom. The deceased donor's external appearance should be thoroughly examined at the time of retrieval. The appearance must be documented with respect to the donor's medical and behavioural history, including the presence of any obvious medical intervention, scars, tattoos, skin or mucosal lesions, jaundice, infection, trauma or needle tracks.

The date and time of death must be documented, and where applicable the time the body was refrigerated.

### 20.4: Tissue-specific donor considerations

Reference must be made to the JPAC *Donor Selection Guidelines*<sup>«3»4</sup> document for ages and other specific donor requirements for different tissues.

### 20.5: Donor testing

The general principles of microbiological testing and the specific testing requirements for tissue donors are covered in **«Annex B of the HTA's Guide to Quality and Safety Assurance for Tissues and Cells for Patient Treatment, and»** Chapter 9 **«of this guide»**. Testing must be completed in a licensed Tissue Establishment or under a third-party agreement between the testing laboratory and the licensed Tissue Establishment. If a third-party laboratory is used to perform any aspect of donor testing, the specific requirements and responsibilities of both parties in achieving them must be defined in a written agreement. Such testing should, as a minimum, be performed in accordance with **«regulatory requirements and»** the guidance in this document. There should be protocols for assuring the veracity and security of the sample, labelling, and supporting documentation. The time from sample acquisition to **«initial processing,»** testing or freezing of the sample should be minimised and must be **«compliant»** ~~consistent~~ with test kit manufacturers' recommendations. **«Any deviations from these must be»** ~~or~~ validated for the purpose. Due consideration should be given to dilution of the sample (see section 20.7).

~~Additional discretionary testing may be required (e.g. for malaria, Chaga's disease or West Nile Virus), dependent on the donor's travel history. RhD testing may be required on donors if the retrieved tissues will contain residual red cells or red cell membranes at the time of implantation.~~

The **«Tissue Establishment»** ~~issue-bank~~ should have a documented policy to follow in the case of donors with reactive screening tests. There should be protocols for alternative or confirmatory testing and acceptance or rejection of donations.

A positive result should be notified urgently to the source **«Tissue Establishment»** ~~bank~~, Specialist Nurse Organ Donation or supplier of the tissue or cells so that clinicians in all centres that have received material from the same donor can be informed and take appropriate action. Where tissue or cells from a donor have been sent to other **«Tissue Establishments»** ~~banks~~ or centres, these **«Tissue Establishments»** ~~banks~~ or centres must be told about the positive result. Reports of positive tests should be included in the routine donor surveillance programmes and notified to the **«relevant public health authority»** ~~HTA~~ (see section 21.8).

**«In addition to mandatory tests done on all donor samples, additional discretionary testing may be required (e.g. for malaria, Chagas disease or West Nile Virus), dependent on the donor's travel history. RhD testing may be required on donors if the retrieved tissues will contain residual red cells or red cell membranes at the time of implantation. Discretionary tests, where undertaken, must be undertaken in accordance with the requirements set out above, to ensure that results can be relied upon.»**

## 20.6: Living donor samples

All blood samples from living **«tissue»** donors must be acquired using positive donor identification by an individual trained to ensure the security of the sample and supporting documentation. Living **«tissue»** donors can be tested by either a single sample taken at the time of donation where testing includes a nucleic acid amplification technique (NAT) **«for, as a minimum, HIV, HBV and HCV,»** or by two samples including a post **«180-day»** quarantine sample where additional NAT testing is not required. **«For guidance relating to living stem cell donors, please see Chapter 22.»**

Where only a single sample is tested the 'donation sample' must be obtained at the time of donation or, if not possible, within 7 days post-donation.

Where two samples are tested the **«post 180-day sample»** ~~'post-quarantine sample'~~ is required after an interval of at least 180 days from the date of donation. In these circumstances of repeat testing, the donation sample can be taken up to 30 days prior to and 7 days after donation. When the donation blood sample is taken prior to the date of tissue donation a system must be in place to ensure that the pre-quarantine sample reflects the risk status at the time of donation. **«Tissue must not be released from quarantine until the results from both the donation sample and the post 180-day sample have been reviewed and accepted in accordance with defined procedures.»**

For amnion donation only a maternal sample is required, i.e. a cord blood sample is not required.

## 20.7: Deceased donor samples

Appropriate mechanisms must be in place to ensure:

- The secure identification of samples obtained from hospital laboratories. Where there is doubt about the identity of a blood sample from a tissue donor (inadequate labelling), DNA profiling may be accepted as an accurate method for confirming the identity of the blood sample.
- Documentation of the date and time the sample was taken, the name of the individual and laboratory supplying the sample and sample storage conditions.

An ante-mortem blood sample, up to 7 days preceding death, is always preferable to a post-mortem sample for testing. Where no ante-mortem sample is available, then a post-mortem sample can be used. Samples for testing must not be taken more than 24 hours post-mortem and the time from sampling to testing or freezing of the sample should be minimised and must be consistent with the test kit manufacturer's recommendations or validated for the purpose.

The anatomical site from which the post-mortem sample was obtained **«should»** ~~must~~ be documented. The sample appearance should be documented. If the sample appears dilute or grossly haemolysed, a repeat sample, preferably from an alternative site, should be obtained if possible. Tissue **«Establishments»** ~~banks~~ should have a protocol for post-mortem sampling, clearly defining preferred sites for sampling (e.g. cardiac puncture or femoral vessel puncture and avoiding sites close to intravenous lines).

Where a deceased donor with significant blood loss has received ante-mortem transfusions, a pre-transfusion sample should be used whenever possible for testing. If a pre-transfusion sample is not available, **«Tissue Establishments»** ~~tissue banks~~ must employ an algorithm incorporating the timing, nature and volume of the fluids infused and the donor's own blood volume to assess any resultant plasma dilution (see the JPAC *Donor Selection Guidelines*<sup>3,4</sup> for an example of a deceased donor intravenous fluid report form). Samples of blood estimated to be more than 50% dilute are not suitable for testing **«unless the testing procedure is validated»**.

For post-mortem samples, concluded test results other than negative **«for current infection»** will debar tissues from release unless a superior sample can be obtained (e.g. obtained ante-mortem or closer to the time of death), and this sample is tested and negative results are obtained. The acquisition of the 'superior' sample must be subject to the same requirements given above. **«There must be a documented process for the resolution of discrepant test results, underpinned by a risk assessment authorised by the Designated Individual.»**

**For neonatal sample requirements for testing, see Chapter 9.»**

~~In the case of deceased neonatal or infant tissue donors the following blood samples are required:~~

- ~~• A maternal sample is required when an infant is less than 18 months of age or when an older child has been breast fed within the 12-month period prior to donation.~~
- ~~• For still births and neonates less than 48 hours after birth, no sample is required.~~
- ~~• For neonates between 48 hours and 28 days after birth, a sample is only required if there are identifiable risks of possible viral transmission, e.g. receiving blood components/products or undergoing a surgical procedure.~~
- ~~• For infants more than 28 days after birth, a sample is always required.~~

## 20.8: Follow-up

There is a duty of care to the donor and/or donor's family. For donors who on confirmatory testing have positive or indeterminate results, there should be protocols in place for contacting, **«informing» counselling** and referring the donor, ~~or relevant contacts of the deceased donor,~~ for further investigation and treatment as appropriate. **«Similarly, there should be processes in place for informing relevant contacts of deceased donors as appropriate.»**

~~For living donors this should be at a local level where the donor was recruited.~~ Confidentiality must be ensured, and **«for living donors,»** the donor's permission sought prior to referral for further medical follow-up and assessment. **«If the donor is still in hospital, the results may be given through the medical team, provided that this is covered by the consent.»**

In the case of a deceased **«organ and tissue»** donor, the initial contact should be by the medical team who provided clinical care at the time of death, or **«in the case of a deceased tissue donor where»** if death occurred outside a healthcare facility by the Specialist Nurse Organ Donation or the Tissue Establishment. They should ensure that those close contacts of the deceased donor for whom results may have health implications are appropriately informed ~~and counselled. Appropriate specialist referral should be offered.~~

## 20.9: Autologous tissue donation

The designated clinician should decide the policy in relation to the provision of an autologous service. Autologous donors should be tested for the same microbiological markers as for an allogeneic living donor. **«Where the tissue is to be stored,»** microbiological testing must include bacteriological culture where tissue does not undergo a validated terminal antimicrobial treatment **«(for allogeneic tissues see Chapter 21)»**. The medical history may be less relevant than for allogeneic donation of tissues. The rationale for any exceptions must be documented. **«Testing requirements for allogeneic tissues are detailed in Chapter 21.»**

Separate storage must be used to avoid inappropriate issue. Autologous tissue must be securely segregated from allogeneic tissue at all stages from collection to issue. Autologous donations **«must not be issued for allogeneic use.»** ~~may not be transferred to the allogeneic bank.~~

A system must be in place to enable the hospital to recognise that the tissue is autologous. The autologous tissue must be labelled with the **«patient's»** ~~donor/recipient~~ name, hospital number and date of birth.

## 20.10: Archiving of donor samples

An archive blood sample should be kept for look-back investigations in the event of an adverse reaction. **«It is recommended that this should be for a minimum of 10 years from the date of donation.»** ~~This must be for a minimum of 11 years after the expiry date of the tissue with the longest storage life.~~

Tissues can be held for a number of years prior to issue. During this period in storage there may be changes to the mandatory microbiology test requirements and improvements in screening assays for mandatory or other markers. Consideration should be given for an additional blood sample archive for tissues with a long expiry for possible future testing that is not currently available.

~~A policy regarding the need for re-testing of the tissue inventory needs to be established. Any policy adopted must be operationally feasible and will depend on both the maximum storage period of the tissue and the probability of the tissue being issued.~~ When new, or significantly improved, mandatory tests are introduced consideration should be given to the re-testing of archive samples from the donors of tissue still in issuable stock. Where there is no archive sample available to test, a risk assessment must be performed. It should include factors such as the seriousness of the infection, any viral inactivation procedures performed on the tissue, the effect on inventory of discarding such tissues and the severity of impact of possible tissue shortages on recipients.

## 20.11: Release criteria

For allogeneic donors the concluded result of all microbiological assays, with the exception of syphilis and anti-HBc, must be negative for a tissue to be released from quarantine for issue.<sup>7</sup> For donors who are found to be 'repeat reactive' in any screening assay but for whom subsequent testing confirms lack of infection, the initial reactivity in the screening assay is due to non-specific reactivity and any tissue products from this donation may be safely released for clinical use **«(see Chapter 9). In the case of allogeneic donors, the completed donor records must be reviewed and assessed for suitability and signed by a registered healthcare professional»**.

In the case of a deceased infant donor where a maternal sample is found to be positive for any mandatory marker of infection, the donation must not be used irrespective of the test result for the infant.

~~Donors with a positive anti-HBc may be considered as eligible provided an anti-HBs has been documented at more than 100 IU/L at some time.~~



Donors with reactive confirmatory tests for the presence of treponemal infection should be fully assessed, taking into account the results of confirmatory (reference) testing and medical history. The presence of current (active) infection will exclude the use of tissues from such donors. Where the assessment leads to the conclusion that the risk of active infection is remote, then non-cardiovascular tissues may be used. The presence of serological marker patterns of treponemal infections (e.g. IgM positivity) should not be used as a sole criterion to determine the presence of active infection (and therefore their eligibility). Any reactive results obtained on confirmatory testing should be discussed with staff experienced in interpreting treponemal test results, before a decision is made to use tissues.

For autologous donors positive test results will not necessarily prevent the tissues or cells or any product derived from them being stored, processed and reimplanted, if appropriate isolated storage facilities are available to ensure no risk of cross-contamination with other grafts and/or no risk of mix-ups at issue.

## 20.12: References

«

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[https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/876161/SaBT\\_O-microbiological-safety-guidelines.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/876161/SaBT_O-microbiological-safety-guidelines.pdf)
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[www.transfusionguidelines.org.uk](http://www.transfusionguidelines.org.uk)
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- ~~7. SaBTO (2011). Guidance on the Microbiological Safety of Organs, Tissues and Cells used in Transplantation. Available at [www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH\\_121497](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_121497)~~

The following changes apply to:

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## Chapter 21 Tissue banking: tissue retrieval and processing

### 21.1: General considerations

Tissue **«Establishments» banks** should have dedicated processing and storage facilities designed and **«be»** operated to prevent contamination, cross-contamination, mislabelling and deterioration of tissues.

All processes which affect the safety or quality of tissues must be validated.

#### 21.1.1: Equipment – retrieval/processing

All equipment which affects the safety or quality of tissues must be validated.

Where possible single-use instruments must be used.

If it is impractical or not possible to use single-use instruments and reusable equipment has to be used, then the use must be risk assessed to ensure that all required mitigating actions are considered. Tissue **«Establishment» bank** reusable instruments and other items which come into direct contact with donor tissue during retrieval and processing must be thoroughly washed and sterilised between uses. These must be fully traceable to the individual tissue donor/batch and allow tracking through decontamination, sterilisation and use. These instruments should be washed and sterilised according to NHS Estates Health Technical Memoranda (HTM) **«01-01, 1»2010;**<sup>2</sup> 2030<sup>2</sup> and 2031.<sup>3</sup> Instruments must not be allowed to dry out before washing prior to sterilisation. Prompt removal of residual blood and tissues is an important aspect of decontamination, particularly with regard to **«removal of prions»** ~~Creutzfeldt-Jakob Disease (CJD).~~

#### 21.1.2: Incoming materials and solutions

All purchased materials and solutions which affect the tissue quality and safety must be inspected on receipt to ensure compliance with specification.

#### 21.1.3: Use of third parties

UK Blood Transfusion Services **«Tissue Establishments» tissue-banks** may use third parties to perform tissue retrieval **«(including eye retrieval)»**, processing steps such as irradiation, tissue evaluation such as bacterial tests, quality control tasks such as environmental monitoring or tissue storage, transport and distribution. **«Tissue storage beyond 48 hours can only be undertaken at a premises directly licensed under the Q&S Regulations. Storage >48h cannot be undertaken at the premises of an unlicensed third party.»** Wherever such tasks are performed by or on behalf of a third party, this must be subject to a written agreement between the parties involved. This must specify the processes to be performed, the applicable standards and specifications, and the responsibilities of both parties in achieving the desired outcome. The processes should be performed, as a minimum, in accordance with the guidance **«referenced from Chapter 19.»** ~~given in HTA Direction 003/2010.~~<sup>4</sup>

#### 21.1.4: Tissue contamination

In the event of a healthcare worker sustaining an injury such that his/her blood comes into contact with the tissue, the tissue must be discarded.

### 21.2: Retrieval

#### 21.2.1: Retrieval times and preliminary storage

Tissue retrieval should be completed as soon after death as possible. For eye donation retrieval must be completed within 24 hours after death and the body should preferably be cooled or refrigerated. For all other tissues, if the body has not been cooled or refrigerated, procurement must be completed within 12 hours after death. If the body has been cooled or refrigerated within 6 hours of death, procurement should preferably start within 24 hours and must be completed within 48 hours of death. In this context, the term 'cooled' is used to reference situations where the body is not placed in an actively refrigerated location, but other attempts to reduce body temperature are employed. These may include for example application of sufficient amounts of wet ice to the body, use of a cooling blanket or (for neonatal donors) a cold cot, or the body being located in a cold location following death.

Tissues must be placed at a temperature of 0–10°C within 4 hours of retrieval. **«See tables 21.1 and 21.2.»**

### 21.2.2: General considerations for tissue retrieval

Every effort must be made to minimise contamination of tissue during procurement.

The procurement facility must be suitable for procurement of tissues and must be risk assessed prior to commencement of tissue retrieval.

A local sterile field must be created using sterile drapes. An appropriate antibacterial skin preparation agent must be used before commencing the retrieval.

All instruments used during the retrieval must be sterile and should be stored on a «**separate surface**» ~~back-table~~ which is covered with a sterile drape. Where possible, single-use equipment should be used.

Staff conducting the retrieval must be appropriately gowned in sterile clothing, and wear sterile gloves and protective masks.

Every effort should be made to minimise the number of people present during deceased tissue retrieval and to ensure that «**other activities, such as**» a post-mortem «**examinations are**» ~~is~~ not proceeding «**in the same location**» during the retrieval.

Where possible the retrieval should precede any post-mortem examination of the donor. In cases referred to the Coroner (or the Procurator Fiscal in Scotland), the Coroner's consent must be obtained to enable the retrieval of tissues.

### 21.2.3: Deceased donor reconstruction

It is integral to the maintenance of the dignity of the donor that the body is cleaned and reconstruction is carefully undertaken. Whenever long bones are removed they must be replaced with appropriate prostheses. All incisions should be neatly sutured.

For similar reasons, skin must not be procured from the neck, arms, face or other areas that may affect funeral viewing.

Every effort should be made to ensure that appropriate advice on the handling of deceased donors after retrieval should be made available for mortuary and funeral home staff.

### 21.2.4: Labelling of donations

At the time of donation, the container for each category of tissue (e.g. skin, bone or heart valves) must be labelled with the nature of the contained tissue and a barcoded tissue or donor identification (ID) label as appropriate.

The accompanying donation record must be labelled with the same tissue or donor identification number(s), key donor identifiers (name, date of birth etc.), and the date of collection prior to removal from the retrieval site. «**Blood samples, and where relevant,**» bacteriology ~~and blood~~ samples, together with accompanying documentation where relevant, must be labelled according to agreed local procedures such that the results can be linked to the correct donor/tissue while still preserving anonymity where required.

A double container system is required for all tissues retrieved. The containers must not be opened until ready for use or further aseptic processing at a facility approved by the «**Tissue Establishment**» ~~tissue bank~~.

### 21.3: Transportation conditions from retrieval site to Tissue Establishment

Transportation systems must be validated to show maintenance of the required storage temperature.

«**Transport solutions must be validated to preserve the required characteristics of the tissue to be transported.**»

~~The requirement for transport solution needs to be validated with respect to the preservation and characteristics required of the tissue to be transported.~~

For viable tissue the grafts should be placed into a transport solution with due regard to its effects on the ability of cells to propagate or metabolise. There must be adequate control of buffering capacity, osmolarity and tissue oxygenation. External contamination and desiccation must be avoided.

The type, lot, manufacturer and the expiry date of the transport solution «**and components coming into contact with the tissue, such as the primary container,**» must be documented.



## 21.4: Bacteriostasis and disinfection

«Storage conditions and expiration periods must be supported by validation. Historical data, experience and documented literature are acceptable as evidence of validation. Any new processing or significant changes to existing processing are subject to pre-authorisation by the HTA.»

### 21.4.1: Tissue without terminal antimicrobial processing

Tissue must be subjected to one of the following treatments, as soon as possible and within 24 hours of retrieval:

- antibiotic disinfection
- an alternative disinfection method
- frozen storage at –20°C or lower.

In the case of tissue taken from heart-beating donors in the operating theatre at the time of organ retrieval, this period may be extended to 48 hours.

### 21.4.2: Tissue with terminal antimicrobial processing

~~Bone from living donors which is refrigerated within 4 hours of retrieval but not frozen until 24–48 hours after retrieval must be subjected to terminal antimicrobial processing.~~

Tissue with terminal antimicrobial processing must be subjected to one of the treatments detailed in the above section within 24 hours of retrieval with a maximum of 72 hours following death. A summary of the guidance regarding temperature/time relationships contained in these guidelines is given in Table 21.1 «and 21.2».

«Table 21.1 Temperature/time relationships for banked tissues from living donors

Retrieved tissue	Must be placed at an ambient temperature of 0–10°C within 4 hours of retrieval.
Bacteriostasis	Freezing tissue to at least –20°C within 24 hours of retrieval can be used as a bacteriostatic treatment. Bone from living donors which is not frozen until 24–48 hours after retrieval must be subjected to terminal antimicrobial processing.
Long-term storage	Bone from living donors may be stored at –20°C or lower for up to 6 months or at –40°C or lower for up to 5 years. Temporary storage of frozen living donor bone between –20°C and –40°C is limited to 6 months in total. Grafts stored at this temperature must then be transferred to –40°C or colder to give an expiry of up to a maximum of 5 years from donation. Amnion preserved in low-concentration (50%) glycerol may be stored below –40°C for up to 2 years.
Transportation and local storage	Must be transported and stored locally prior to clinical use, at –20°C or lower in order to have the designated expiry (specified above).»

**Table 21.2 Temperature/time relationships for banked tissues from deceased donors**

Retrieval	<p>For eyes, retrieval must be completed within 24 hours after death and the body should preferably be refrigerated</p> <p>For all other tissues, if the body has not been refrigerated, procurement of tissues must be completed within 12 hours after death.</p> <p>If the body has been refrigerated within 6 hours of death procurement should preferably start within 24 hours and must be completed within 48 hours of death.</p>
Retrieved tissue	Must be placed at an ambient temperature of 0–10°C within 4 hours of retrieval.
Bacteriostasis	Freezing tissue to at least –20°C within 24 hours of retrieval (or up to a maximum of 72 hours of death) can be used as a bacteriostatic treatment.
Long-term storage	<p><u>Frozen* non-viable tissue may be stored:</u></p> <ol style="list-style-type: none"> <li>1. At –20°C or lower for up to 6 months.</li> <li>2. At –40°C or lower for up to 5 years. Temporary storage of frozen musculoskeletal tissue between –20°C and –40°C is limited to 6 months in total. Grafts stored at this temperature must then be transferred to –40°C or colder to give an expiry of up to a maximum of 5 years from donation.</li> </ol> <p><u>Cryopreserved** viable tissue:</u></p> <p>At –135°C or lower to claim a 10-year expiry for all grafts to maintain a reasonable inventory of size-matched grafts (e.g. heart valves and menisci). Other cryopreserved tissues should have a 5-year expiry.</p> <p><u>Glycerol-preserved tissue:</u></p> <p>Skin preserved in high-concentration (&gt;90%) glycerol may be stored at 0–10°C for up to 2 years.</p> <p><u>Freeze dried tissue:</u></p> <p>Freeze-dried tissue may be stored at ambient temperature for up to 5 years. This includes freeze dried demineralised bone tissue mixed with a glycerol carrier</p> <p><u>Decellularised tissue:</u></p> <p>Decellularised dermis tissue that has been terminally sterilised may be stored at below –40oC for up to five years, or at below +40oC for up to two years.</p>
Transportation and local storage	<p><u>Frozen* tissues</u> must be transported and stored locally prior to clinical use, at –20°C or lower in order to have the designated expiry (specified above).</p> <p><u>Cryopreserved** tissues</u> may be transported in the vapour phase of liquid nitrogen (&lt;–135°C) or on dry ice (–79°C). If tissues are transported on dry ice they should continue to be stored locally at around –80°C for a maximum of 6 months.</p>
<p>For the purposes of this guidance, the following definitions apply:</p> <p>* Frozen tissue – tissue frozen and stored under conditions unlikely to be compatible with preservation of cells.</p> <p>** Cryopreserved tissue – tissue treated with a cryoprotectant and/or cooled at a controlled rate in order to preserve cells.»</p>	

**Table 21.1 Temperature/time relationships for banked tissues**

<b>Retrieval</b>	<p><del>If the body has not been refrigerated, procurement of tissues must be completed within 12 hours after death.</del></p> <p><del>If the body has been refrigerated within 6 hours of death procurement should preferably start within 24 hours and must be completed within 48 hours of death.</del></p>
<b>Retrieved tissue</b>	<p><del>Must be placed at an ambient temperature of 0–10°C within 4 hours of retrieval.</del></p>
<b>Bacteriostasis</b>	<p><del>Freezing tissue to at least –20°C within 24 hours of retrieval (or up to a maximum of 72 hours of death) can be used as a bacteriostatic treatment.</del></p> <p><del>Bone from living donors which is not frozen until 24–48 hours after retrieval must be subjected to terminal antimicrobial processing.</del></p>
<b>Long-term storage</b>	<p><del>Frozen* non-viable tissue may be stored:</del></p> <p><del>1. At –20°C or lower for up to 6 months.</del></p> <p><del>2. At –40°C or lower for up to 5 years. Temporary storage of frozen musculoskeletal tissue between –20°C and –40°C is limited to 6 months in total. Grafts stored at this temperature must then be transferred to –40°C or colder to give an expiry of up to a maximum of 5 years from donation.</del></p> <p><del>Cryopreserved** viable tissue should be stored:</del></p> <p><del>1. At –135°C or lower to claim a 10-year expiry for all grafts to maintain a reasonable inventory of size-matched grafts (e.g. heart valves and menisci). Other cryopreserved tissues should have a 5-year expiry.</del></p> <p><del>Glycerol-preserved tissue:</del></p> <p><del>1. Skin preserved in high-concentration (&gt;90%) glycerol may be stored at 0–10°C for up to 2 years.</del></p> <p><del>2. Amnion preserved in low-concentration (50%) glycerol may be stored below –40°C for up to 2 years.</del></p> <p><del>Freeze-dried tissue may be stored at ambient temperature for up to 5 years.</del></p>
<b>Transportation and local storage</b>	<p><del>Frozen* tissues must be transported and stored locally prior to clinical use, at –20°C or lower in order to have the designated expiry (specified above).</del></p> <p><del>Cryopreserved** tissues may be transported in the vapour phase of liquid nitrogen (&lt;–135°C) or on dry ice (–79°C). If tissues are transported on dry ice they should continue to be stored locally at around –80°C for a maximum of 6 months.</del></p>
<p><del>For the purposes of this guidance, the following definitions apply:</del></p> <p><del>* Frozen tissue—tissue frozen and stored under conditions unlikely to be compatible with preservation of cells.</del></p> <p><del>** Cryopreserved tissue—tissue treated with a cryoprotectant and/or cooled at a controlled rate in order to preserve cells.</del></p>	

### 21.4.3: Positive bacteriology or mycology

It is the responsibility of the designated medical officer or designated microbiologist to develop written policies regarding the selection and conduct of tests for bacterial and fungal contamination and the acceptance criteria for specific tissues.

Where tissues are shown to carry viable bacteria or fungi they may be suitable for clinical use (e.g. skin grafts) depending on microbial types and densities of growth on culture. For other tissues the material may be approved for use provided that a validated antimicrobial processing technique is used.

## 21.5: General guidelines for tissue processing

Processing must not change the physical properties of the tissue so as to make it unacceptable for clinical use. Processing steps must be validated to demonstrate that the final product does not have any clinically significant residual toxicity.

### 21.5.1: Aseptic processing facilities

Facilities for aseptic processing must comply with the Rules and Guidance for Pharmaceutical Manufacturers and Distributors «2015<sup>5</sup>,» 2007<sup>6</sup> and EC Guidelines to Good Manufacturing Practice<sup>6</sup> «and the Human Tissue (Quality and

**Safety for Human Application) Regulations 2007 (as amended)<sup>7</sup>** They must provide separate work areas with defined physical and microbiological parameters. Facilities must have:

- floors, walls and ceilings of non-porous smooth surfaces that are easily sanitised
- temperature control
- air filtered through high-efficiency particulate air (HEPA) filters with appropriate pressure differential between zones, which must be documented
- a documented system for monitoring temperature, air supply conditions, particle numbers and bacterial colony-forming units (environmental monitoring)
- a documented system for cleaning and disinfecting rooms and equipment
- a documented system for gowning and laundry
- adequate space for staff and storage of sterile garments
- access limited to authorised personnel
- documented system for general staff hygiene practices.

### 21.5.2: Tissue not destined for terminal microbial processing

Critical work areas are those where tissue is manipulated openly either following a disinfection or sterilisation step or in those cases where tissue has been procured aseptically and will not be further disinfected or sterilised. Critical work areas on which sterile containers, aseptically procured tissue or disinfected tissue are exposed to the environment, must have an air quality of Grade A and should have a Grade B background. (For further information see *Rules and Guidance for Pharmaceutical Manufacturers and Distributors «2015» 2007<sup>5</sup>* and the EC Guidelines to Good Manufacturing Practice.<sup>6</sup>) Any lowering to this standard in the background environment ~~(as long as it is compliant with EU requirements)~~ must be documented and it must be demonstrated that the chosen environment achieves the quality and safety required, at least taking into account the intended purpose, mode of application and immune status of the recipient.

Wherever possible, representative samples of tissue should be removed and tested for bacterial and fungal contamination using protocols authorised by the designated medical officer or designated microbiologist. Swabs or other validated non-destructive sampling methods should be used where it is impossible to remove tissue without damaging the graft. ~~Microbiological inclusion/exclusion criteria should be developed by the designated medical officer or designated microbiologist in accordance with national policy.~~

~~Where tissues are processed in batches,~~ Procedures must ensure that no cross-contamination between batches **«of tissue from different donors»** can occur. Key process parameters and acceptance limits must be identified and validated. A full record of each process applied to each tissue or batch must be retained.

### 21.5.3: Tissue destined for terminal microbial processing

Work areas in which tissue materials and containers are prepared should have an environment with air quality of at least Grade C in the vicinity of exposed tissue.

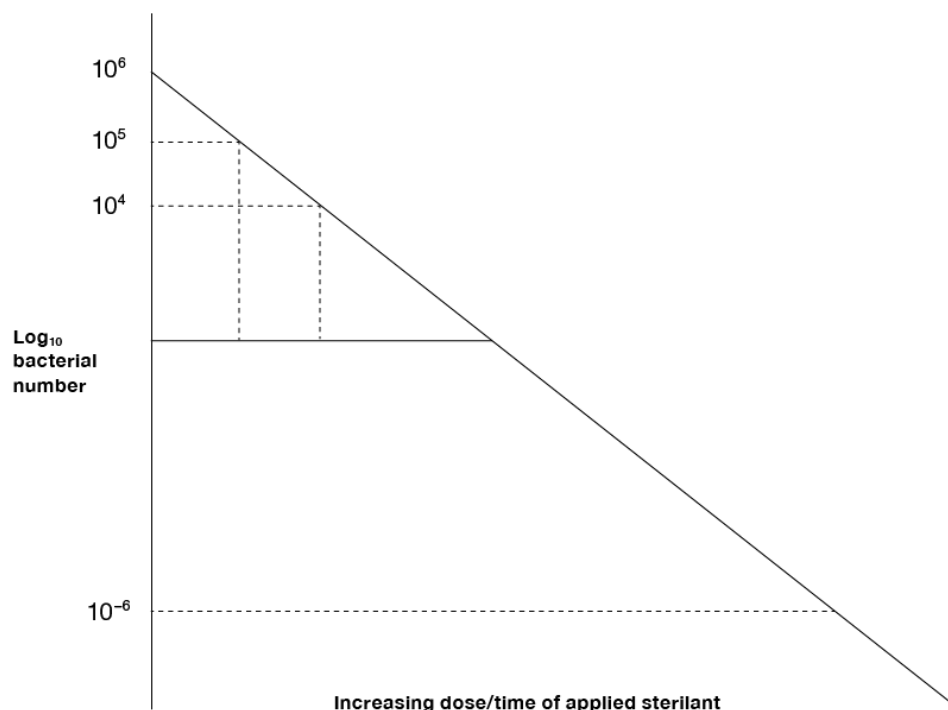
Terminal antimicrobial processing must follow the filling of the final container. The procurement, processing and filling environment must be of sufficient quality to minimise the microbial contamination of the tissue to ensure that the subsequent antimicrobial processing is effective.

The tissue in its final container must be subjected to a validated procedure utilising an agent such as gamma irradiation. ~~The processing method and dose of the sterilant should be validated as sufficient to bring about at least a six logarithms reduction in a recognised marker resistant organism (e.g. Clostridium sp. for irradiation).~~

#### 21.5.3.1: Terminal sterilisation

Sterilisation is a statistical phenomenon, expressed as the probability of microorganisms surviving the procedure. The sterility assurance level (SAL) is the probability of a microorganism on one item within a batch or within a defined population. The accepted level for considering medical devices to be 'sterile' is a SAL of  $10^{-6}$  (i.e. less than one item per million items will have a surviving microorganism on it). For medical devices, the microorganisms under consideration are contaminants (i.e. bacteria and fungi and their spores). Unless specifically stated, viruses are not routinely considered.

Because of the large numbers involved, demonstrating SAL of  $10^{-6}$  must use procedures that extrapolate from smaller batches. For sterilisation procedures that show a log10/linear decrease in microbial viability, extrapolation can be achieved using the D-value (decimal reduction value) concept.



**Figure 21.1 An example of increasing inactivation of bacteria related to increasing the dose of the sterilant**

In the example shown in Figure 21.1, each log reduction requires an additional unit of the sterilant to be applied, hence D-value = 1.0. Therefore moving from an initial bioburden of  $10^6$  bacteria to a SAL of  $10^{-6}$  would require  $12 \times$  D-value of the sterilant.

In practice, the processing that is applied to tissue grafts prior to application of the terminal sterilisation step often reduces the bioburden to close to zero. Therefore application of a sterilisation procedure sufficient to provide a 6-log reduction of bacteria is often satisfactory to achieve a SAL of  $10^{-6}$ .

Very often, validation studies will be carried out using the microorganism that is known to be most resistant to the sterilisation procedure (often bacterial spores). This is therefore a 'worst-case' validation. Achieving a SAL of  $10^{-6}$  for this microorganism will guarantee a significant overkill for more sensitive microbes.

### 21.5.3.2: Validation of terminal sterilisation

Whenever a novel terminal sterilisation step is introduced the following validations need to be addressed:

- That the sterilisation technique achieves a SAL of  $10^{-6}$  for the most resistant microorganisms.
- That the sterilisation technique can be applied to the tissue graft in its final packaging without subsequent exposure, and that the integrity of the packaging is not adversely affected by the process.
- That the sterilisation technique does not adversely affect the essential properties of the graft and does not leave toxic residuals.
- That the sterilisation technique inactivates all categories of microorganisms commonly found on tissue grafts including vegetative Gram positive and Gram negative bacteria, vegetative fungi, and bacterial and fungal spores. This must be demonstrated either by literature review or validation.

#### 21.5.4: Gamma irradiation

Gamma irradiation must be performed in a controlled manner to ensure that all tissue receives at least the minimum specified dose of radiation. This requires the use of standard packaging materials and irradiator load configuration and is usually validated using calibrated dosimeters placed throughout the load. The dose should never be less than 15 kGy, unless pre-irradiation processing has been validated to consistently yield a low microbial bioburden such that there is the required assurance, in accordance with medical device standards, that the dose will result in the tissue being sterile.

Tissue must be irradiated in its final packaging, which must bear a suitable indicator to demonstrate that it has been irradiated. This must be checked before release of the tissue.

If a dose in excess of 25 kGy is required, then consideration must be given to the possible detrimental effect on the biological and physical properties of the tissue.

Many viruses are resistant to irradiation and therefore any claim of viral inactivation must be supported by validation data obtained using appropriate marker viruses.

#### 21.5.5: Pooling

Pooling of tissues from different donors is not **«recommended and should only be considered if this is the only way in which clinical efficacy can be achieved.»** ~~permitted.~~

#### 21.5.6: Preservation methods

Where specific attributes of a tissue are claimed, the process should be validated to show these attributes are preserved.

##### 21.5.6.1: Freezing

For the purposes of this guidance this term applies to tissues that are frozen and stored under conditions that are unlikely to be compatible with preservation of cells. Frozen tissue must be stored below –20°C and the length of storage permitted depends on the temperature the tissues are stored at (see Table 21.1 **«and 21.2»**).

##### 21.5.6.2: Cryopreservation

For the purposes of this guidance this term applies to tissues that are treated with a cryoprotectant and/or cooled at a controlled rate in order to preserve cells. Cryopreserved tissue must be stored below –135°C. For storage at higher temperatures, validation must be performed to demonstrate that the required properties of the graft are maintained for the stated expiry.

##### 21.5.6.3: Freeze-drying

Where tissues are freeze-dried, a sample of each type of tissue from each freeze-drying run must be analysed for residual water which must be less than 5% (weight/weight) of the dry weight of the graft or equivalent residual water activity of between **«0»** ~~0-2~~ and 0.5 Aw.

##### 21.5.6.4: Glycerolisation

Where tissues are preserved by high concentrations of glycerol the procedure should be validated to demonstrate achievement of the specified glycerol concentration within the tissue or an acceptable range within the tissue.

#### 21.5.7: Solutions

Rinse solutions, antibiotic mixtures, nutrient media and cryopreservation solutions must be stored at a specified temperature and with a storage period consistent with functional requirements. They must be discarded if not used within 24 hours of opening. Any solutions coming into direct contact with tissues during retrieval or processing must be sterile **«and fully identified in the associated records»**.

#### 21.6: Tissue storage

Refrigeration devices containing tissue shall be suitable for the use intended and procedures for monitoring such devices shall be validated so that tissues are maintained at the required storage temperature. Continuous monitoring and recording of temperature, together with suitable alarm systems, shall be employed on all storage refrigerators, freezers and liquid nitrogen tanks.

Every effort should be made to avoid cross-contamination of material stored in liquid nitrogen vessels. **«Material should be stored in the vapour phase of liquid nitrogen, not immersed in the liquid phase. Liquid nitrogen storage vessels should be designed to incorporate automatic filling systems to avoid transfer of filling hoses between vessels. Thermocouple temperature probes should be placed in storage vessels, with at least one probe located in the warmest position, as determined by temperature mapping.»** ~~Wherever possible, there should be specifically designated pieces of equipment (e.g. nitrogen level rulers, portable thermometers) for each vessel. Where this is not possible (e.g. liquid nitrogen delivery hoses) and the item has to be used for more than one vessel, it should not come into contact with the liquid phase or the sides of the vessel.~~

Frozen and cryopreserved tissue should be double wrapped during storage. The seals and the material employed must be validated for their use at the designated storage temperature and the conditions of use, to demonstrate integrity of the packaging and labelling. This is crucially important for storage in liquid nitrogen vessels because of the high levels of accumulated microbial contaminants found within these vessels.

Quarantined and released tissue must be stored in physically segregated, clearly designated locations distinct from each other.

### 21.6.1: Tissue release

Prior to any tissue being cleared for issue, all relevant records including donor records, processing and storage records, and post-processing quality control test results must have been reviewed, approved and documented as acceptable by the individual(s) responsible according to the relevant local standard operating procedures. Responsibilities for setting policies for exceptional release of tissues reside with the **«authorised»** ~~designated~~ medical officer.

### 21.6.2: Tissue discard

There must be a documented policy for the discard of tissue unsuitable for clinical use. Records should include details of date and method of discard and reason for discard. Tissues for discard should be appropriately handled and disposed of in a manner compliant with local control of infection guidelines. **«Traceability records must be retained in the same way as for tissue used in human application.»**

### 21.6.3: Labelling and packaging of tissues for issue

Packaging must ensure integrity and maintain sterility of the contents of the final container and must also comply with current legislation.

The container must be labelled with the graft-specific identification (**«tissue type,»** batch and shipment number if applicable), expiry date and supplying **«Tissue Establishment»** ~~tissue bank~~, storage instructions and barcoded product description and instruction to see pack insert, as a minimum. In addition, more detailed information should be provided either on the label or package insert or both as follows:

- sizing information **«, if applicable»**
- antimicrobial processing procedure used (if applicable)
- preservative used and its concentration (if applicable)
- special instructions (e.g. 'Do not freeze'), thawing, dilution instructions
- presence of known sensitising substances
- type ~~and calculated quantity~~ of antibiotics added during processing (if applicable)
- any other potential residual processing agent
- RhD type (where appropriate)
- a statement that the tissue was prepared from a donor who was non-reactive for current mandatory markers of infection, with the added rider that all biological tissue carries some risk of disease transmission
- results and findings from clinically relevant bacteriological cultures performed on the tissue before final packaging
- storage instructions
- instructions for reconstitution (if appropriate)
- a warning on loss of package integrity



- instructions on dealing with queries, reporting adverse events/reactions and return or disposal of unsuitable or unused tissue
- a statement that tissue use must be authorised by a medical/dental practitioner
- a statement should accompany each tissue product stating that it may not be sterilised after leaving the «Tissue Establishment» ~~tissue bank~~
- a statement should accompany each package stipulating that each package is for single-patient use only
- if the package insert carries graft-specific information it must be labelled with the unique graft-specific identification code
- instructions to the user regarding the need for a documented system for the tracking and follow-up of the fate of the tissue
- when cells are known to be positive for a relevant infectious disease marker, it must be marked as a BIOLOGICAL HAZARD.
- in the case of autologous donations, the label must state 'for autologous use only'
- in the case of directed donations, the label must identify the intended recipient.

#### 21.6.4: External labelling of the shipping container

For transport, the primary container must be placed in a shipping container that must be labelled with at least the following information:

- identification of the originating Tissue Establishment, including an address and telephone number «and a contact person in the event of problems»
- identification of the organisation responsible for human application of destination, including address and telephone number «and the person to be contacted to take delivery of the container»
- a statement that the package contains human tissue/cells and HANDLE WITH CARE
- where living cells are required for the function of the graft, such as stem cells, gametes and embryos, the following must be added: 'DO NOT IRRADIATE'
- recommended transport conditions (e.g. keep cold, in upright position etc.)
- safety instructions/method of cooling (when applicable).
- the date and time that the product was prepared for transportation
- in the case of autologous donors, the following indication: 'FOR AUTOLOGOUS USE ONLY'
- specifications concerning storage conditions (such as DO NOT FREEZE).

#### 21.6.5: Distribution

All reasonable efforts must be made to ensure that tissues are sent to qualified individuals/organisations who have accepted responsibility for their proper handling and use. A written agreement must be in place between the Tissue Establishment and the organisation ordering the tissue.

Where tissue is transported in a refrigerated or frozen condition, adequate safeguards should be taken to ensure that the tissue remains at the designated temperature. Monitoring of temperature should be undertaken wherever practicable but if not, the method should at least have been validated to show that appropriate temperatures are maintained. «Consideration should be given to the potential for extremes of external temperature during transportation.»

#### 21.7: Tracking of tissues

Each Tissue Establishment shall ensure that it has the ability to locate and identify all tissues/cells during any step from procurement through to distribution to recipient or disposal and vice versa. This traceability shall also apply to all relevant data relating to products and materials coming into contact with these tissues and cells.

Tissue Establishments shall have effective and accurate systems to uniquely identify and label tissues/cells received and distributed.

Tissue Establishments shall keep the data necessary to ensure traceability at all stages. Data required for full traceability shall be kept for a minimum of 30 years after clinical use. Data storage may also be in electronic form. Data that must be kept are shown in Table «21.3» ~~21.2 (based on Annex VI, Directive 2006/86/EC).~~<sup>7</sup>

**Table «21.3» ~~21.2~~ Minimum donor/recipient data set to be kept**

<b>A. BY TISSUE ESTABLISHMENTS</b>
<p><b>Donor identification</b></p> <p><b>Donation identification that will include at least:</b></p> <ul style="list-style-type: none"> <li>• Identification of the procurement organisation or Tissue Establishment</li> <li>• Unique donation identification number</li> <li>• Date of procurement</li> <li>• Place of procurement</li> <li>• Type of donation (e.g. single or multi-tissue; autologous or allogeneic; living or deceased).</li> </ul> <p><b>Product identification that will include at least:</b></p> <ul style="list-style-type: none"> <li>• Identification of the Tissue Establishment</li> <li>• Type of tissue and cell/product (basic nomenclature)</li> <li>• «Batch» <del>Pool</del> number (if applicable)</li> <li>• Split number (if applicable)</li> <li>• Expiry date</li> <li>• Tissue/cell status (i.e. quarantined, suitable for use etc.)</li> <li>• Description and origin of the products, processing steps applied, materials and additives coming into contact with tissues and cells and having an effect on their quality and/or safety</li> <li>• Identification of the facility issuing the final label</li> </ul> <p><b>Human application identification that will include at least:</b></p> <ul style="list-style-type: none"> <li>• Date of distribution/disposal</li> <li>• Identification of the clinician or end user/facility.</li> </ul>
<b>B. BY ORGANISATIONS RESPONSIBLE FOR HUMAN APPLICATION</b>
<ul style="list-style-type: none"> <li>• Identification of the supplier Tissue Establishment</li> <li>• Identification of the clinician or end user/facility</li> <li>• Type of tissues and cells</li> <li>• Product identification</li> <li>• Identification of the recipient</li> <li>• Date of application</li> <li>• Where applicable, date and method of disposal</li> </ul>

## 21.8: Notification of serious adverse events and reactions

Tissue Establishments in the UK are required to report «serious» adverse events «and reactions» to the Human Tissue Authority (HTA) «, within 24 hours of the incident being identified,» through the Serious Adverse Events and Reactions system. For the purposes of reporting, a serious adverse reaction (SAR) is defined as an unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life-threatening, disabling or incapacitating or which results in, or prolongs, hospitalisation or morbidity. A serious adverse event (SAE) is defined as any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalisation or morbidity.

Tissue Establishments shall ensure that there is a system in place to report, investigate, register and transmit information about serious adverse events and reactions. A root cause analysis should be performed. Moreover, each Tissue Establishment shall ensure that an accurate, rapid and verifiable procedure is in place which will enable it to recall from distribution any product which may be related to an adverse event or reaction.

## **21.9: Additional guidelines for skeletal tissue retrieval and processing**

### **21.9.1: Procurement of surgically removed bone**

A system of documentation must be in place to ensure that theatre staff are clearly informed that a particular patient has or has not consented to bone donation. This may be by enclosing a copy of the consent form in the patient's notes, or some equivalent method.

Where bones are retrieved during surgery by theatre staff on behalf of the «**Tissue Establishment**» ~~tissue bank~~, these staff must follow a protocol provided by the «**Tissue Establishment**» ~~tissue bank~~ in accordance with third party agreements.

The removed bone should be placed, as quickly as possible, «**and whilst in the surgical field,**» in a sterile container and labelled in a manner to distinguish it from «**bone authorised for transplant**» ~~cleared-issued bone~~.

Documentation must be completed in theatre, detailing the time of bone retrieval and providing the identity of the staff members carrying out the retrieval and labelling. «**Details of consumables and reagents coming in direct contact with the procured bone must be recorded (this does not include any items used during the elective surgery).**»

If the donated bone is not destined for terminal antimicrobial processing, it must be cultured for microbial contamination at the time of collection, using a collection and transport system provided by, or approved by, the «**Tissue Establishment**» ~~tissue bank~~. Bone sampling must be carried out immediately prior to «**placing in the**» ~~closing the bone~~ container.

Tissue samples for culture should comprise of chips of bone from the cut end of the bone, which should be placed in appropriate transport or culture media. The bone should be finally packaged in a double sterile container.

A secure system utilising barcodes for the identification and linkage of the donation to the donor and samples must be in place.

The bone container, tissue samples and blood samples, if collected at this time, must each be clearly labelled with the barcoded donation numbers and stored at appropriate temperatures until collection.

Alternatively, protocols can be put in place to arrange for the hospital blood bank or other appropriate laboratory, to separate serum from the blood samples and to store it and the donation at –20°C or lower, for collection at a later date. Testing should be performed within 1 month of sampling «**and any handling or storage of the sample prior to testing must be aligned with the test kit manufacturer's recommendations or suitably validated. Please see Chapters 9 and 20 for further details.**» Note: If tissues are stored by a hospital for more than 48 hours then the hospital requires to be licensed by the HTA, as storage cannot be covered by a 'third party agreement'.

Bone which is not subject to antimicrobial processing can only be released for use if cultures for aerobic and anaerobic bacteria, and fungi are negative.

Where environmental contaminants are detected on surgically retrieved bone, this bone may be further processed and subjected to terminal sterilisation, e.g. gamma irradiation (>1.5 megarads = >15 kGy) (see section 21.5.4).

### **21.9.2: Procurement of skeletal tissues from deceased donors**

If iliac crest is to be retrieved, it should be taken last in case the bowel is perforated and should be stored in a separate container. Where osteochondral allografts are to be retrieved, care should be taken to avoid drying of articular surfaces. It is best to retrieve the joint entirely and to dissect it later in the laboratory.

### **21.9.3: Processing of skeletal tissues**

Cycles of thawing and freezing must be minimised. Skeletal tissues should not be heated above 60°C and tendons and costal cartilage should not be warmed above 30°C.

~~Osteochondral allografts, such as proximal or distal femur or femoral hemicondyles, are cryopreserved with a cryoprotectant (such as DMSO) on the articular surfaces and cooled following appropriate cryopreservation protocols.~~ Cryopreservation of allografts must begin within 48 hours of procurement. These allografts must not be exposed to gamma irradiation and must therefore be procured and processed aseptically.

## **21.10: Cardiovascular tissue retrieval and processing**

### **21.10.1: General**

This section predominantly relates to the banking of heart valves.

### 21.10.2: Sizing and evaluation of cardiovascular tissue

Aortic and pulmonary valves should be sized at the annulus and the internal diameter recorded in millimetres. **«The competency of the valves should be evaluated.»**

The length of the aortic conduit, main pulmonary artery and right and left pulmonary artery remnants should be recorded.

**«For pulmonary patch allografts, the length and width of the graft should be recorded.»**

Detailed description of the condition of the valve must be recorded in the donor processing records, which should include a grading system or schematic representation. **«It may also be helpful to take a retain photographic records of the grafts.»**

Valve descriptions and evaluation must accompany the allograft distribution and be made available to the surgeon on request.

Heart valves and vessels should be processed using a disinfection process which has been shown to produce decontaminated tissues.

Disinfection time must not exceed that specified in a validated disinfection regime.

### 21.10.3: Bacteriological testing of tissue

Where tissues are exposed to a decontamination step an assessment of the bacteriological status prior to decontamination must be performed.

Processed tissue must be subjected to bacterial (including Mycobacterium tuberculosis) and fungal testing using validated techniques. Each **«Tissue Establishment» bank** should develop a list of exclusion criteria based on type and number of contaminating organisms prior to and following decontamination.

### 21.10.4: Cryopreservation

Currently accepted optimal procedures involve controlled rate cooling of cardiovascular tissues in the presence of cryoprotectant.

### 21.10.5: Storage and warming of cardiovascular tissues

For material stored at –135°C or below, if during warming the tissue is warmed too rapidly between the storage temperature and –100°C, fractures can occur. A validated method of warming (e.g. on dry ice) must be used to minimise the risk. This must ensure that the valve has reached a temperature above –100°C before thawing in a 37°C water bath.

Material stored at –135°C, which is subsequently transported with solid carbon dioxide (–79°C), should be maintained in a mechanical freezer (at –80°C) if not used immediately. Thereafter, a maximum storage time of 6 months will pertain.

### 21.10.6: Distribution

Cryopreserved valves and vessels must be transported either in solid carbon dioxide at –79°C or in a container maintaining a temperature of –135°C or lower. Cardiovascular tissue must not be submerged in liquid nitrogen during transport.

## 21.11: Skin retrieval and processing

### 21.11.1: Skin retrieval

Skin sites should be shaved if necessary and treated with an antimicrobial agent such as chlorhexidine.

~~**Samples of skin must be cultured for aerobic and anaerobic bacteria and fungi prior to and following decontamination.**~~

### 21.11.2: Skin processing

Skin can be processed to provide an acceptable graft in a number of ways. These include cryopreservation, high-concentration glycerolisation and other methods. The specification for any skin product should clarify the required properties.

**«Samples of skin must be cultured for aerobic and anaerobic bacteria and fungi prior to and following decontamination. The Tissue Establishment's microbiology policy should specify how these tests impact on suitability for clinical application.»**

## 21.12: Ocular tissue retrieval, processing and storage

### 21.12.1: Eye retrieval

«All required documentation must be fully completed by the eye retriever, including information related to the tissue donor and body map.

Approved SOPs must be followed.

The final cosmetic appearance is of critical importance as family or friends may wish to view the body. Any bleeding or bruising resulting from the enucleation must be documented, and this documentation transferred to the tissue establishment.»

*An 'NHSBT Tissue Retrieval Site Risk Assessment' form must be completed by the eye retriever to ensure the suitability of the retrieval site. This must be done for every eye retrieval as circumstances may change even within the same premises.*

*Eye retrieval must be carried out by a person who is trained and competent in enucleation. Either this individual must be employed by an HTA-licensed eye bank or there must be a third party agreement in place between the eye bank and the individual's employing authority.*

*Enucleation should be carried out as soon as possible, but no longer than 24 hours after death. The eye retriever must be satisfied that lawful consent/authorisation has been obtained and that at the time of retrieval there is no known medical reason to suggest that the eyes should not be retrieved. Sterile, single-use instruments must be used and disposed of safely after the retrieval. The NHS Blood and Transplant (NHSBT) Human Tissue Transport Box contains all the required documentation, including an enucleation protocol, and a set of sterile, single-use instruments. All required documentation must be fully completed by the eye retriever, including the NHSBT Ocular Tissue Donor Information form and body map.*

*The NHSBT enucleation protocol must be followed. 8 After enucleation a stump of optic nerve at least 5 mm long must remain attached to the eye, which is then secured in a plastic eye stand. The eye stand and eye (cornea uppermost) are placed on top of a moist cotton wool ball or gauze swab and placed in a sterile pot (moist chamber). The eye must not be immersed in any liquid in the moist chamber. The moist chambers are then packed in an NHSBT Human Tissue Transport box together with a plastic bag containing melting ice. At least 1 kg of ice is needed to keep the contents of the transport box below 5°C for up to 24 hours during transportation to the eye bank. The donor's eye sockets should be packed with cotton wool and lids closed over plastic eye caps to restore the original profile of the lids. The final cosmetic appearance is of critical importance as family or friends may wish to view the body. Any bleeding or bruising resulting from the enucleation must be noted on the body map.*

### 21.12.2: Ocular tissue processing and storage

Corneas should be excised and placed in an appropriate storage solution as soon as possible, but no longer than 24 hours after enucleation. Corneas may be stored for up to 2 weeks at 4°C in an appropriate hypothermic storage solution. Alternatively, the great majority of corneas in the UK are stored for up to 4 weeks in organ culture at 34°C. The corneal endothelium is examined by light microscopy a few days before use to ensure its suitability for transplantation in patients with corneal endothelial disease/deficiency. Organ-cultured corneas are delivered to hospitals in medium containing 5% dextran to reverse the stromal oedema that occurs during storage. Corneas with an inadequate endothelium may still be suitable for anterior lamellar grafts. These corneas may also be transferred to 70% ethanol and stored at room temperature for up to 12 months for use in glaucoma surgery. Sclera, which is also stored in 70% ethanol for up to 12 months, is used for glaucoma or other reconstructive surgery. Ocular surface stem cells may be isolated from the limbus and expanded in ex vivo culture for treating limbal stem cell deficiency.

## 21.13 References

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- ~~8. NHS Blood and Transplant Organ Donation & Transplantation Directorate Ocular Tissue Advisory Group OTAG(09)29 'Optimisation of Eye Retrieval'.~~



The following is a new addition to the Guidelines:

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## **Annex 6**      Advanced therapy medicinal products (ATMPs)

«An Advanced Therapy Medicinal Product (ATMP) is a medicinal product which is either:

- a gene therapy medicinal product
- a somatic cell therapy medicinal product
- a tissue engineered product

ATMPs are governed by UK medicines legislation. ATMPs are currently available under four routes: via marketing authorisation; via clinical trial authorisation; via unlicensed use either through hospital exemption or on a non-routine basis for an individual patient with a special clinical need under the 'specials' scheme.

Legislation around ATMPs include: the Human Medicines Regulations 2012 SI 2012/1916, setting the rules for marketing authorisation and pharmacovigilance, hospital exemption use and the specials regime; and the Clinical trials Regulations Medicines for Human Use (Clinical Trials) Regulations 2004 SI 2004 / 1031, regarding good clinical practice in the conduct of clinical trials on medicinal products for human use. For unlicensed use in the UK, manufacture is expected to be performed either under a Manufacturer's Licence for Exempt Advanced Therapy medicinal Products (MeAT) or in the case of special clinical need under a Manufacturer's Specials licence. In addition, depending on the starting materials and nature of the product, additional specific legislation may need to be considered e.g. The Human Tissue (Quality and Safety for Human Application) Regulations, 2007 (as amended) for the donation, procurement and testing of the human tissue or cells. It is important to ensure that other authorisations and licences are in place, for instance, consideration may need to be given to Health & Safety Executive (HSE) for contained use of Genetically Modified Organisms, Human Fertilisation and Embryology Authority (HFEA) for Embryonic considerations and Department for Rural Affairs (DEFRA) for materials that may include animal pathogens.

To this effect early engagement with regulators is recommended, for example via the MHRA Innovation office at <https://www.gov.uk/government/groups/mhra-innovation-office>. The Innovation Office and Regulatory Advice Service for Regenerative Medicines (RASRM) advice services offer research and development professionals across academia, industry and the NHS (including clinicians) a single point of access to free, joined-up regulatory information, advice and guidance. Through RASRM, this includes advice from the Health Research Authority (HRA), HFEA, Human Tissue Authority (HTA), and MHRA (Medicines and Healthcare products Regulatory Agency). Where needed, the advice service can also link up to other specialist bodies such as the HSE and DEFRA. Detailed scientific advice can be obtained from the MHRA at <https://www.gov.uk/guidance/medicines-get-scientific-advice-from-mhra>. MHRA has a new pathway to support innovative approaches to the safe, timely and efficient development of medicines to improve patient access through the Innovative Licensing and Access Pathway (ILAP) and further details are at <https://www.gov.uk/guidance/innovative-licensing-and-access-pathway>.

ATMPs are defined in Regulation 2A of the Human Medicines Regulations 2012. In relation to sale or supply in Great Britain only:

A "gene therapy medicinal product" is a biological medicinal product which has the following characteristics

- a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence; and
- b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

A "somatic cell medicinal product" is a medicinal product which has the following characteristics

- a) it contains or consists of cells or tissues that
  - i. have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or
  - ii. are not intended to be used for the same essential function in the recipient as in the donor; and
- b) it is presented as having properties for, or is used in or administered to human beings with a view to, treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.

A "tissue engineered product" is a medicinal product which

- a) contains or consists of engineered cells or tissues; and
- b) is presented as having properties for, or is used in or administered to human beings with a view to, regenerating, repairing or replacing a human tissue.



See Appendix A for further details.

Information on ATMPs can be found on the following links:

1. This link directs to the MHRA site for information on how to get a marketing authorisation for a regenerative medicine so it can be sold and supplied in the UK and Europe.  
<https://www.gov.uk/guidance/advanced-therapy-medicinal-products-regulation-and-licensing>
2. This link directs to the MHRA site for information on clinical trials and investigations  
<http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/index.htm>
3. This link directs to the MHRA site relating to the human medicines regulations 2012  
<http://www.legislation.gov.uk/ukxi/2012/1916/contents/made>

Information relating to the EU.

This link opens a pdf of Directive 2004/23/EC of the European parliament and of the council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells

<http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:102:0048:0058:EN:PDF>

This link opens a pdf of Directive 2002/98/EC of the European parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components, and amending directive 2001/83/ec

<http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:033:0030:0040:EN:PDF>

This link opens a pdf of Regulation (EC) no. 1394/2007 of the European parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending directive 2001/83/EC and regulation (EC) no. 726/2004

<http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:en:PDF>

This link opens a pdf of regulation (EC) no. 726/2004 of the European parliament and of the Council of 31 March 2004, laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

<http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0001:0033:EN:PDF>

This link directs to the European Medicines Agency site relating to Advanced Therapy Medicinal Products.

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**Appendix A – Guidance on Definitions, drawn from Regulation 2A of the Human Medicines Regulations 2012**

1. In these Regulations, in their application to products for sale or supply in Great Britain only, “advanced therapy medicinal product” means any of the following products
  - a. a gene therapy medicinal product;
  - b. a somatic cell therapy medicinal product; or
  - c. a tissue engineered product.
2. A “gene therapy medicinal product” is a biological medicinal product which has the following characteristics
  - a. it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence; and
  - b. its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.
3. A vaccine against infectious diseases is not to be treated as a gene therapy medicinal product.
4. A “somatic cell medicinal product” is a medicinal product which has the following characteristics
  - a. it contains or consists of cell or tissues that
    - i. have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or

- ii. are not intended to be used for the same essential function in the recipient as in the donor; and
  - b. it is presented as having properties for, or is used in or administered to human beings with a view to, treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.
- 5. A “tissue engineered product” is a medicinal product which
  - a. contains or consists of engineered cells or tissues; and
  - b. is presented as having properties for, or is used in or administered to human beings with a view to, regenerating, repairing or replacing a human tissue.
- 6. A tissue engineered product may contain
  - a. cells or tissues of human or animal origin;
  - b. viable or non-viable cells or tissues; and
  - c. additional substances, including cellular products, bio-molecules, biomaterials, chemical substances, scaffolds or matrices.
- 7. A product is not a tissue engineered product if it
  - a. contains or consists exclusively of non-viable human or animal cells or tissues;
  - b. does not contain any viable cells or tissues; and
  - c. does not act principally by pharmacological, immunological or metabolic action.
- 8. Cells or tissues are engineered if they
  - a. have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved; or
  - b. are not intended to be used for the same essential function in the recipient as in the donor.
- 9. The following manipulations are not substantial manipulations for the purposes of paragraphs (4)(a) and (8)(a)
  - a. cutting;
  - b. grinding;
  - c. shaping;
  - d. centrifugation;
  - e. soaking in antibiotic or antimicrobial solutions;
  - f. sterilisation;
  - g. irradiation;
  - h. cell separation, concentration or purification;
  - i. filtering;
  - j. lyophilisation;
  - k. freezing;
  - l. cryopreservation; and
  - m. vitrification.
- 10. In these Regulations, in their application to products for sale or supply in Great Britain only, “combined advanced therapy medicinal product” means an advanced therapy medicinal product
  - a. which incorporates, as an integral part of the product, one or more medical devices or one or more active implantable medical devices; and
  - b. the cellular part of which
    - i. contains viable cells or tissues; or
    - ii. contains non-viable cells or tissues which are liable to act upon the human body with action that can be considered as primary to that of the medical devices.
- 11. Where an advanced therapy medicinal product contains viable cells or tissues, the pharmacological, immunological or metabolic action of those cells or tissues is to be treated as the principal mode of action of the product.
- 12. An advanced therapy medicinal product containing both autologous and allogeneic cells or tissues is to be treated as being for allogeneic use.

13. A product which falls within the definition of a tissue engineered product and within the definition of a somatic cell therapy medicinal product is to be treated as a tissue engineered product.

14. A product which falls within the definition

- a. a somatic cell therapy medicinal product or a tissue engineered product; and
- b. a gene therapy medicinal product, is to be treated as a gene therapy medicinal product.»



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