FACILITATING THE AUTHORISATION OF

PREPARATION PROCESS FOR BLOOD, TISSUES AND CELLS

GOOD PRACTICE GUIDELINE TO AUTHORISATION ON PREPARATION PROCESSES IN BLOOD, TISSUES AND CELLS ESTABLISHMENTS

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Introduction

In conjunction with this guideline, a number of technical annexes have been developed to facilitate the development of a common approach to assess and authorise preparation processes in blood tissues and cells establishments (BE/TE). Links to the documents can be found in Appendix 7of this document, the Competent Authority (CA)should use these annexes to assist in the review of the applications received.

- Annex 1: Authorisation of changes in donation, procurement and collection, processing, preservation, storage and distribution (including labelling and packaging)
- Annex 2: Assessing the quality and safety of donor testing, pathogen reduction and sterilisation steps as part of preparation process authorisation (PPA)
- Annex 3: Assessing clinical data as part of PPA

A survey conducted as part of GAPP work package 5, was used to determine if any CAs had existing processes in place in relation to the management of changes to existing authorisations. The majority of CAs who responded indicated that a system was in place. Specific examples of changes were provided, some of the examples provided, e.g. change in responsible person, change in company name; may not fit in with the assessment and authorisation of preparation processes defined in this guideline. As such, these changes should continue to be managed through the CAs existing variation process or other existing change management process in place in the Member State (MS).

The survey conducted indicated that 75% (15/20) of CAs who responded specified that there was no risk categorisation system in place for application of changes to existing applications / or applications for authorisation of new or novel activities, products, processes or clinical indications.

Based on the feedback received from the survey, it was evident that there was no current widespread use of risk categorisation at CA level. As such, in order to harmonise the PPA process, and to ensure the use of risk categorization, this guideline recommends the use of the already approved EuroGTPII tool for risk assessment.

Scope of Guideline

This Guideline will only cover PPAs that are under the scope of the European Directive for blood and blood components (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); and the European Directives for tissues and cells (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).

The main scope of the guideline is to define how a PPA programme should or could be organised. This document provides recommendations to CA to have a common approach for a PPA. For that, different steps will be described throughout the guideline to assess the PPA.

As it was proved due to the survey results conducted at the beginning of the Joint Action, there was no risk categorisation system in place for application of changes to existing authorisations / or applications for authorisation of new or novel activities, products, processes or clinical indications. For that reason, this Guideline will use the tool included in the EuroGTP II project. With the use of this tool, there will be a harmonization approach in the PPA.

Throughout this guideline, there will be referrals to activities in the preparation process. These activities are the different steps of the process where the novelty might be implemented. These steps are donation selection; donation/collection/procurement; testing; processing; storage; transport and delivery; distribution/issue; exportation/importation; new application/infusion method; new anatomical site; new clinical indication.

This guideline will apply to any change in process, or change in blood tissue and cell (BTC), considered to display novelty and/or a significant change. For the purpose of this guideline, novelty and significant change are defined as follows:

- A **novelty** is 'any change that might affect the quality and/or the safety of the blood, tissues and cells and/or the safety of recipients'. This change includes a new BTC, a new procedure designed by the BE/TE, a new procedure adopted from another centre that has shown scientific evidence or the application of the BTC to treat a new clinical indication.
- A **significant change** is a 'change that could significantly affect the quality and/or the safety of the BTC/or the safety of recipients and that is assessed as a moderate or high risk. A significant change will have been identified through initial identification as a novelty and the subsequent risk assessment process described in EuroGTPII.

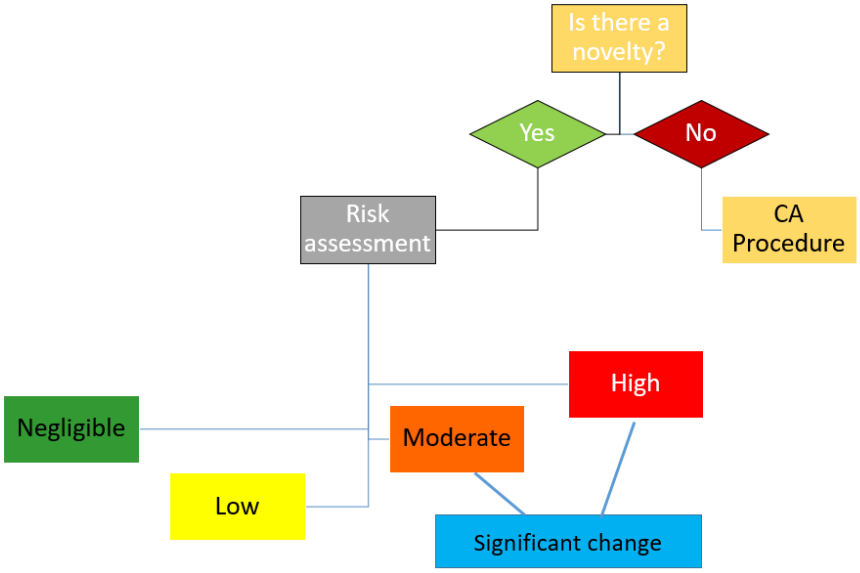

Figure 1: Novelty and Significant change flow-scheme.

In order to prevent confusion throughout the guideline, the term novelty will be used throughout, rather than referring to novelty and significant change, as significant change is also a novelty with a moderate or high risk. A novelty will refer to negligible (N), low (L), moderate (M) and high (H) risks.

Before beginning the PPA, applicants and CA should prove that the novelty would be under the scope of the EUBTCDs. This guideline will not apply to medical devices, medical products or advanced therapy medicinal product (ATMPs).

In the case of tissues and cells (TC)this guideline will only apply when the manipulations that will be performed are not considered substantial according to the Regulation (EC) No 1394/2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. These non-substantial manipulations are: cutting; grinding; shaping; centrifugation; soaking in antibiotic or antimicrobial solutions; sterilisation; irradiation; cell separation, concentration or purification; filtering; lyophilisation; freezing; cryopreservation and vitrification.

Also, if the TC are not intended to be used for the same essential function or functions in the recipient as in the donor (non-homologous), the novelty will not be evaluated under this guideline as it will be considered an ATMP.

This guideline will discuss the steps in relation to the PPA in detail and is divided into four sections.

- Application process:
    - A proposed PPD template has been developed and CAs can create their own guidelines for applicants in relation to this.
- Technical annexes
- Review and evaluation
    - A proposed template to aid CAs in the review and evaluation of PPDs has been developed and can be found in appendix 3.
- Framework for competent authority

The process flow below provides an overview of the PPA application from receipt to authorisation / refusal / withdrawal, which will be discussed in this guideline.

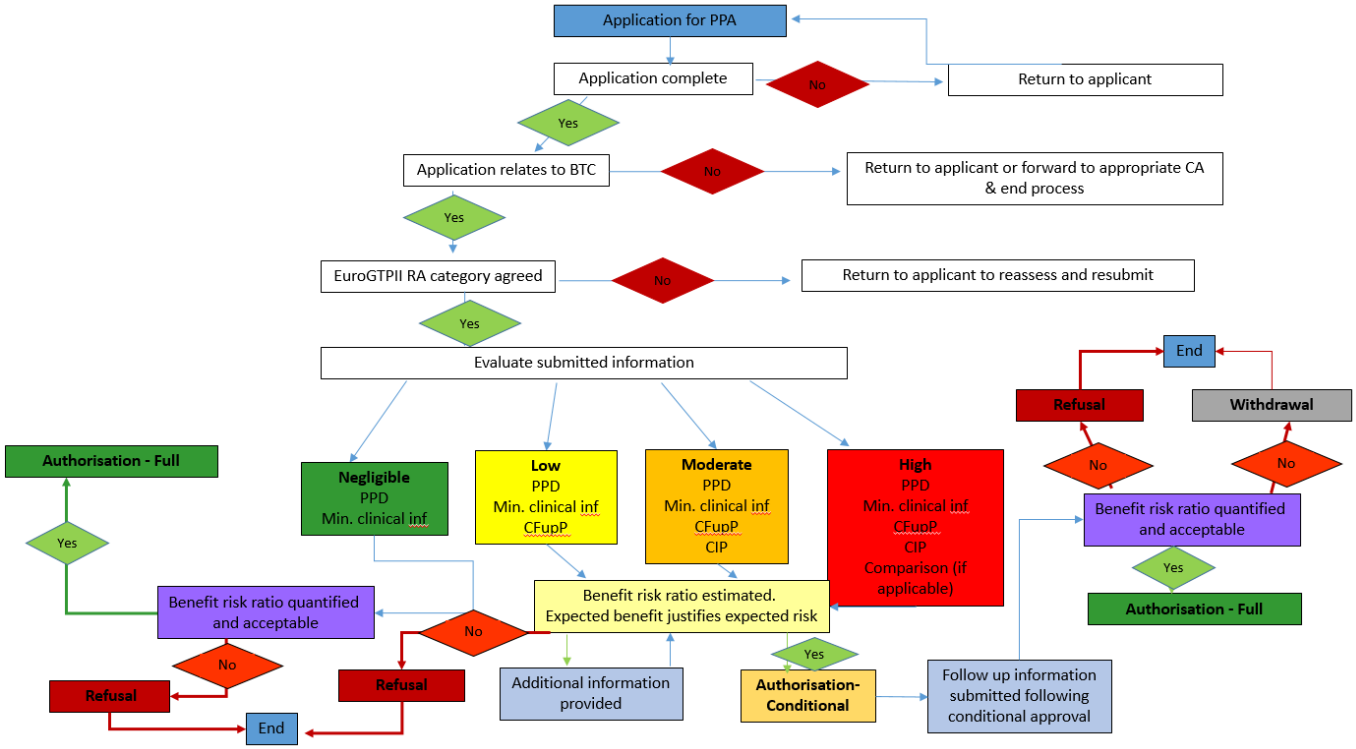

Figure 2: Process flow of the PPA application from receipt to authorisation / refusal / withdrawal.

This guideline will not apply to new facilities that are not previously authorised, as the CA shall follow their own authorisation procedure.

1. Application process

Preparation Process Dossier (PPD)

A proposed application process has been recommended and the required details are described below, with additional technical information provided for the CAs in the accompanying technical annexes to this guideline. Section 2 'Technical Annexes' highlights the technical issues to best assist with the review of each module.

This section will provide a brief overview of the application process, with further detail on the CAs activity provided in Section 3 'Review and Evaluation'.

A CA will receive a PPD when a change is proposed to a BTC, which indicates novelty (as per EuroGTPII).

For applications submitted where a degree of novelty has been identified, the CA will receive the applicant data as detailed below. The information related to the specific change will be completed within the relevant sections of the preparation process dossier (PPD).Sections of the PPD do not have to be completed for areas that the change does not affect, as the CA will have previously assessed these.

The PPD as described within this guideline is considered the PPD, consisting of a number of modules. An example template for the PPD can be found in appendix 2. The CA can create their own guidance for applicants in relation to completion of the PPD. It should be noted that the clinical module within the PPD is more detailed than the other modules, as this will be a new area to most. This module is aligned with GAPP WP8 (technical annex 3).

The proposed modules for the PPD are as follows:

Module 1: Applicant information	Modules 2 and 3: Novelty and risk assessment
• BE/TE data. • Data of the responsible person for the PPD.	• Description of BTC. • Novelty Questions. • Activity information. • Risk Assessment.

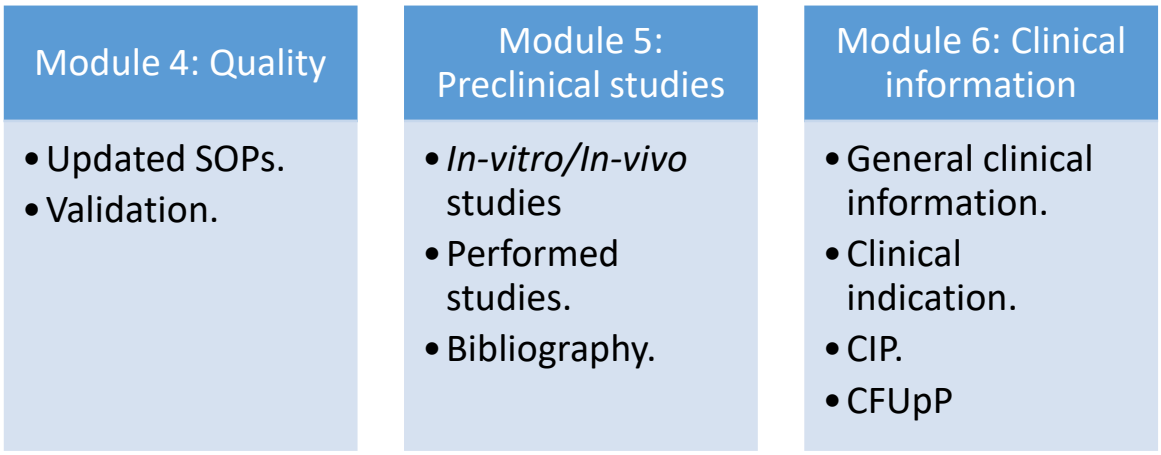

Figure 3: Summary of the information contained in each module.

Module 1: Applicant information

In this Module the CA will receive general applicant information.

- Full name of the BE/TE.
- The postal address of the BE/TE.
- The name of the responsible person of the BE/TE.
- The name of the person responsible for the dossier.
- The e-mail address of the person responsible for the dossier.
- The telephone number of the person responsible for the dossier.
- The submission date.
- Signature of the responsible person.

Module 2 and Module 3: BTC Novelty and Risk Assessment

In module 2, the applicant will provide information on the type of BTC where they request to implement the novelty.

On the PPD, the following chart will be included.

Description of the BTC to which this preparation process is applied	*In appendix I you can find the list of BTCs according to the COE EDQM Guide, TC Compendium* *Provide the relevant detail:*	
Blood and blood components □	**Blood Component:**	
	Preparation Characteristic:	
Tissues □	**Tissue Component:**	
	Preparation Characteristic:	
Cells □	**Cell Component:**	
	Preparation Characteristic:	
MAR □	**Cell Component:**	
	Preparation Characteristic:	

Table 1. List of BTC and type of component and preparation characteristic.

After defining the type of BTC the applicant has to perform the risk assessment using the EuroGTPII tool. The tool will provide a template with multiple parts that shall be provided to the CA:

- The novelty questions have the objective to identify which stage or stages the novelty will be implemented.
- The second part is a justification provided for the evaluation of the novelty questions.
- The third part is a chart with the detected risk factors for each of the activities where the novelty will be implemented, the detection of the risk consequences and its evaluation. In order to evaluate the risk, probability, severity and detectability need to be considered to obtain a potential risk value.
- The following step is the assessment of the risk reduction. This step has the objective to adjust the risk score by taking into account other external sources of information. These sources can be published data in peer reviewed literature, unpublished data from external sources, advice and information from external experts, clinical outcome data form external sources, etc.
- A final risk score will be provided, and this number will be linked to a level of risk. The levels of risks provided in the EuroGTP II tool are negligible (N), low (L), moderate (M) and high (H). If the risk is low, moderate or high, different risk reduction strategies and extent of clinical evaluation are needed.

Select the risk level assigned after performing the EuroGTPII risk assessment and provide the completed EuroGTPII tool template	**The information below is required based on the indicated risk. To submit the required information proceed to module 4, 5 and 6 as appropriate.**
Negligible □	Quality SARE reporting*
Low □	Quality Preclinical information SARE reporting* CFUpP
Moderate □	Quality Preclinical information SARE reporting* CFUpP CIP
High □	Quality SARE reporting* Preclinical information CFUpP CIP Comparison Study

Table 2: risk level assigned after performing EuroGTPII risk assessment and the corresponding required information.

** SARE reporting refers to the SARE SOP initially. SARE reports can be submitted as part of any interim reports and should be submitted to the CA as required by legislation.*

In order to facilitate the review and evaluation by the CA, the PPD also contains the novelty questions. The third column details the section that must be fulfilled for those questions that have a NO answer.

Novelty questions	Yes	No	See section
Has this type of BTC previously been prepared and issued for clinical use by your establishment?			All sections as applicable
Will the starting material used to prepare this BTC be obtained from the same donor population previously used by your establishment for this type of BTC?			1 and 3 as applicable
Will the starting material for this BTC be procured/collected using a procedure used previously by your establishment for this type of BTC?			2 and 3 as applicable
Will this BTC be prepared by a procedure (processing/preparation, decontamination and preservation) used previously in your establishment for this type of BTC?			4
Will this BTC be packaged and stored using a protocol and materials used previously in your establishment for this type of BTC?			5
Will this type of BTC provided by your establishment be applied/ infused clinically using an application/infusion method used previously?			6, 7, 8 and 9 as applicable
Has your establishment provided this type of BTC for a same clinical indication or applied/infused into a same anatomical site?			10 and 11 as applicable

Table3: EuroGTPII questions and information and sections to be checked to provide the related information.

The activities where the novelty can be implemented:

1. Donor Selection
2. Donation/Collection/ Procurement
3. Testing
4. Processing
5. Storage
6. Transport and delivery
7. Distribution/issue
8. Exportation/importation
9. New application/infusion method
10. New clinical indication
11. New anatomical site

The applicant, as is requested on the PPD, will submit a short summary of the novelty that will be implemented. They will also submit the information detailed for each of the activities that will be modified and that are identified in the novelty questions chart.

Module 4: Quality

The quality module contains the information regarding the SOPs and the validation according to the activities where the novelty will be implemented.

Module 5: Preclinical Studies

The applicant will provide the CA with details of any *in-vitro / in-vivo* studies performed. If any studies have been performed, the applicant has to provide a summary as well as relevant bibliography.

Module 6: Clinical Information

This module has several parts, each one with different sub points.

The main parts are:

- Minimum information of the clinical component of the PPD
- Clinical Follow-Up Plan (CFUpP)
- Clinical Investigation Plan (CIP)
- Control treatments for BTC identified as high risk level

The CA shall check if this information is provided relevant to the degree of the risk identified.

2. Technical annexes

Several technical annexes have been developed to provide guidance to the CA on authorisation of changes in the different activities, including donor testing, pathogen reduction and sterilisation and the review of clinical data. Further information can be found in tables 4, 5 and 6.

Technical Annex 1 to overall guidance: authorisation of changes in donation, procurement and collection, processing, preservation, storage and distribution		
Chapter	Title	Use to help assess the following module of PPD
Chapter 1	Introduction	
Chapter 2	Blood- Specific aspects of preparation process authorisation	Module 2, 3 and 4
Chapter 3	Haematopoietic Progenitor/ Stem Cells- Specific aspects of preparation process authorisation	
Chapter 4	Tissues and Cells- Specific aspects of preparation process authorisation	
Chapter 4	Medically Assisted Reproduction-Specific aspects of preparation process authorisation	
Appendix 1	Critical Quality Attributes (CQA) and Critical Processing Parameters (CPP) Tables	
Appendix 2	Organisation of the work, methods and sources	

Table 4: Technical Annex 1.

Technical annex 2 to overall guidance: assessing the quality and safety of donor testing, pathogen reduction and sterilisation steps as part of Preparation Process Authorisation (PPA)		
Chapter	Title	Use to help assess the following module of PPD
Chapter 1	General validation requirements	Module 2, 3 and 4
Chapter 2	Requirements and criteria for laboratories performing donor/donation infectious disease testing and microbiological testing of BTC	
Chapter 3	Requirements for selection, validation and performance of donor/donation infectious disease marker test kits	
Chapter 4	Criteria for validation of pathogen reduction steps	
Chapter 5	Criteria for validation of sterilisation methods	
Chapter 6	Requirements for assessing microbiological safety of the final BTC product	

Table 5: Technical Annex 2.

Technical Annex 3 to overall guidance: assessing clinical data as part of Preparation Process Authorisation (PPA)		
Chapter	Title	Use to help assess the following module of PPD
Chapter 1	Introduction	Module 2, 3, 5 and 6
Chapter 2	The extent of the plan for collecting clinical data should be based on risk assessment	
Chapter 3	Clinical data sources and types	
Chapter 4	Minimum information of the clinical component of the PPD	
Chapter 5	Assessment of Clinical Follow-Up Plan (CFUpP)	
Chapter 6	Assessment of Clinical Investigation Plan (CIP)	
Chapter 7	Control treatments for BTC with high risk level	
Chapter 8	Updates and amendments	
Appendix 1	Good practices of clinical setting for BTC	

Table 6: Technical Annex 3.

3. Review and evaluation

A proposed template to aid CAs in the review and evaluation of PPDs has been developed and can be found in appendix 3.

A. Review:

The CA should firstly assess the admissibility of the application by verifying that all appropriate information has been provided, followed by a technical review relating to quality, safety and efficacy.

The application received by the CA may consist of some or all of the six modules previously discussed in the 'application process' section and these are:

- Module 1: Applicant information
- Module 2 and 3: BTC novelty and risk assessment
- Module 4: Quality
- Module 5: Preclinical studies
- Module 6: Clinical information

Further details on the information to be submitted will be described on the following page.

Step 1: CA reviews applicant information

Module 1: Applicant Information

The CA should review module 1 of the application and ensure that the applicant information has been completed and that is has been signed by the responsible person.

Step 2: CA reviews and performs novelty questions and risk assessment

Module 2: BTC Novelty and module 3: BTC Risk Assessment

After reviewing the applicant information, the CA shall go through the novelty questions. These questions identify at which stage or stages the novelty will be implemented, indicated by an answer of "NO"

The CA will confirm that this information has been provided. In cases where it has not been provided, and the reason has not been justified, the CA shall request the information from the applicant following their established procedures.

The evaluation of the novelty risk assessment will identify the residual risk that can only be address with clinical follow up or clinical evaluation. The final output along with all associated documentation and evidence, can be used to support submissions to the CA to seek approval to provide the BTC for clinical use, either in a routine or restricted setting as indicated by the level of residual risk.

The CA will review the novelty questions and EuroGTPII risk assessment completed and submitted by the BE/TE.

The CA will complete the novelty questions and EuroGTPII risk assessment themselves to ensure that they are in agreement with the risk level assigned to the novelty by the BE/TE. If not, the CA will contact the applicant and discuss the risk assessment and request that the application is reassessed and resubmitted with the appropriate risk assessment and supporting information.

The assigned risk assessment determines the information to be provided.

Information on the BTC to which the novelty applies:

The CA will check the BTC information provided by the BE/TE in the PPD. As it is described on Figure 4, according to the authorised activities of the BE/TE, the CA will know if the application is related to:

- A novelty related to an already authorised preparation process. This means that the BE/TE requests for a novelty in a specific activity of their PPA. For example, a TE that used to freeze amniotic membrane applies to their CA to lyophilise it. In this example, only the information regarding the novelty shall be provided. New clinical indications and new anatomical sites could also be included in this section.
- A new BTC :
    - A BTC that is already in the EUTC Compendium and/or the EDQM Guides but has not previously been authorised at the BE/TE applicant. For example, when a TC wants to begin to process heart vessels for the first time.
    - A BTC that is not included in the EUTC Compendium or EDQM Guides. For example, when a Blood Bank intends to process Convalescence Plasma to treat patients infected with COVID-19.

Figure 4. Information to be provided by the BE/TE according to novelty.

Whether the BE/TE applies for a change in an already authorised preparation process or for a new BTC to be authorised in their facilities, they have to go through the novelty questions to assess that what they apply for has a novelty. If no novelty is identified, the BE/TE must follow the procedures established by their own CA. (See figure 5).

Each CA shall provide a procedure for those changes that do not include a novelty: for example when the BE/TE changes responsible person of the establishment.

When there is a novelty, it is necessary to perform the risk assessment using the EuroGTP II tool and determine the level of risk that this change will mean.

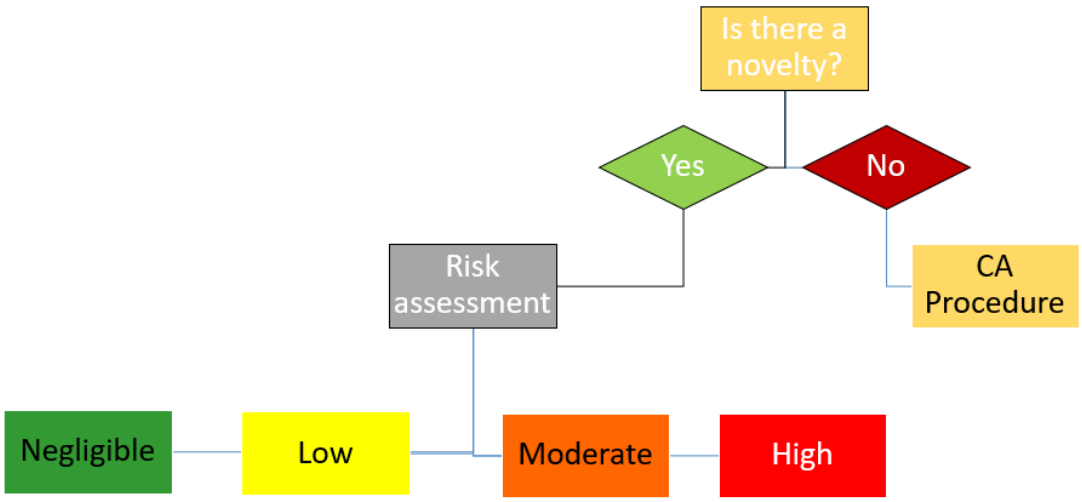

Figure 5: Novelty and Risk Assessment flow chart.

Evaluation of Novelty:

The applicant will have assessed the novelty of the change prior to submitting the PPD and a copy of the 'novelty questions' in Table 7 will be provided to the CA with the application.

This evaluation of novelty consists of answering questions related to all the different stages, from the donor selection to the application in a recipient. If the answer to all of the different questions is "yes", it means that there is no novelty, and this overall guideline should not be applied. A CA may apply their own variation process for these changes.

The question or questions answered with "no" identify the steps where the applicant would like to implement the change. This will provide the CA with awareness of the different procedures that may be changed by the BE/TE. The details of the changes will be provided by the applicant to the CA.

The questions used to determine novelty are found in EuroGTPII and are also detailed below in table 7. The last column indicates the sections of the PPD that need to be fulfilled according to the "no" answers selected.

Novelty questions	Yes	No	Sections to be fulfilled
Has this type of BTC previously been prepared and issued for clinical use by your establishment?			All sections as applicable
Will the starting material used to prepare this BTC be obtained from the same donor population previously used by your establishment for this type of BTC?			1 and 3 as applicable
Will the starting material for this BTC be procured/collected using a procedure used previously by your establishment for this type of BTC?			2 and 3 as applicable
Will this BTC be prepared by a procedure (processing/preparation, decontamination and preservation) used previously in your establishment for this type of BTC?			4
Will this BTC be packaged and stored using a protocol and materials used previously in your establishment for this type of BTC?			5
Will this type of BTC provided by your establishment be applied/ infused clinically using an application/infusion method used previously?			6, 7, 8 and 9 as applicable
Has your establishment provided this type of BTC for a same clinical indication or applied/infused into a same anatomical site?			10 and 11 as applicable

Table 7: Novelty questions. Adapted from EuroGTPII.

The novelty questions above form the first step in the risk assessment process detailed under the 'Risk assessment' section. The CA will also complete the novelty questions based on the application information received. The list of activities in the PPD can be used by the CA as an aid to determine the different activities where the novelty shall be implemented as well as the descriptions provided by the BE/TE.

As it has been described in the Scope of the Guideline, the activities where the novelty can be implemented are donor selection; donation/collection/procurement; testing; processing; storage; transport and delivery; distribution/issue; exportation/importation; new application/infusion method; new anatomical site; new clinical indication.

a) Activities

The applicant should provide information and answer the related questions for each of the activities where they intend to implement the novelty. The applicant should also provide the CA with relevant training records for each activity.

The definitions of the different activities can be found on the glossary included in appendix6 of this guideline.

1) Donor selection

The CA will confirm the type of donor selected (living, deceased, partner, non-partner, etc.) by the applicant is as they have indicated in the application.

The applicant will also provide information about the donation criteria, and if they are not included in the EUBTCDs or in the national/regional legislation, they should explain which criteria they would like to modify and the clinical justification for this.

Within the application, the BE/TE has to provide a summary of the donor selection criteria and a copy of the health and medical history questionnaire that is going to be used to evaluate the donor. The CA shall ensure that the procedure includes the medical history, the behaviour history, the physical examination and in the case of living donors, the psychological examination. Testing will be described below in activity section 3.

In addition to the clinical criteria to accept the donor, the CA shall review how the donors are recruited, the information provided in the consent form and if the donation is voluntary and unpaid.

2) Donation/Collection/Procurement

The CA shall assess if the applicant has provided a summary of the donation/collection/procurement process and the description of the equipment or materials that will be exposed to the BTC. If the novelty implies a new donation or retrieval technique, the CA shall assess that it meets the EUBTCDs and the national/regional legislations.

The CA shall assess if the data of the centre or centres where the change in the donation procedure shall be implemented has been provided. They shall also assess if the donation or retrieval shall be performed in a new area inside the facilities or if there will be a new labelling process applied to the BTC.

If the facilities are new and they are not authorised, the CA shall follow their own authorisation procedure.

The CA shall assess that the storage conditions of the BTC at the different stages (collection, procurement, packaging and transport) have been provided.

It is necessary also to assess the written agreements with any personnel, clinical team or third party procurement organisation that takes part in the procurement, and that this agreement has been signed by the relevant parties. The CA shall ensure that the method of collecting critical information used in the selection of donors has been provided.

If the BE/TE promotes donation, the CA shall review the material used and assess that it follows the ethical principles of consent, if required, un-paid donation, respect for public health and the donor criteria requested in the EUBTCDs.

3) Testing

Testing, as it is explained in Technical Annex 2 is used “to refer to the investigations performed on either donor or donation sample to determine any infectious disease risk associated with the donation”.

If the novelty is to be implemented at this stage, the CA shall assess a summary of all donor/donation testing for infectious diseases, ABO, blood count etc.

The CA shall review the information about the laboratory performing the testing and the test kits that shall be used. Confirm that the kits are CE-marked or otherwise meet the requirements defined in Technical Annex 2.

If the BE/TE outsources the testing, an agreement with the laboratory shall be provided, as well as a copy of their licence / authorisation or accreditation. The CA shall review the agreement and ensure it includes the roles and responsibilities of all parties and provides details of the testing procedures. The transport procedure to take the samples to the testing laboratory shall be also reviewed. The CA shall also assess to ensure that all the tests required by the EUBTCDs are carried out.

4) Processing

Processing encompasses all the operations involved in the preparation, manipulation, preservation, of BTCs intended for human application. In case the novelty is at this stage, the CA shall request a summary of the preparation process.

If any part of the processing is sub-contracted, the applicant shall detail which steps are sub-contracted. The applicant shall also provide the name and the contact details of the third party. The CA shall review if the agreement meets the EUBTCDs and that it describes the responsibilities for each party and clearly details the control-sampling points.

The CA shall review the summary/classification/certification of the environmental conditions under which the process will take place. The measures and steps taken by the BE/TE to minimise cross contamination should also be reviewed for suitability.

The CA shall check the list of tested parameters (CPPs), the methods used and the acceptance criteria (CQAs and KPIs) detailed.

The CA shall check the microbiological testing and the quality control SOP provided by the BE/TE. They shall also check if the testing kits are CE-marked or in-house ones. For the evaluation of the microbiological tests, the CA will follow Technical Annex 2.

The CA shall also assess the details on the equipment or material used to process the BTC including if there is an instruction manual available, the schedule for maintenance and if the equipment is CE-marked.

5) Storage

The applicant shall choose this option if the novelty relates to the protocols and the materials involved in the storage of the BTC. The conditions that might be changed are the storage process, the storage parameters and the shelf life. The BE/TE may also modify the equipment or the material used to store the BTC as well as the packaging.

The CA shall assess this novelty and shall ensure that the new storage process maintain the product under appropriate controlled conditions until it is distributed.

6) Transport and delivery

Applicants should provide the following information in case the novelty relates to the distribution conditions of the BTC. The BE/TE shall provide the CA with a summary of the proposed transport conditions and an explanation of the novelty to be implemented.

The description of the equipment and the material used to transport and deliver the BTC shall also be provided. The applicant shall provide a copy of the BTC labelling procedure.

The CA shall assess this novelty and shall ensure that the BTC will be transported under appropriate conditions.

7) Distribution/ issue

The BE/TE shall provide a summary of the release/issue criteria and provide a justification for the novelty that shall be implemented. The CA shall assess the appropriateness of the release/issue criteria.

8) Exportation/importation

This step is applied when the novelty to be implemented by the BE/TE implies the cross-border movement of a BTC: from a BE/TE outside the European Union (EU) to a BE/TE (importation) in the EU; or from a BE/TE inside the EU to another country outside the EU (exportation).

The CA shall assess the summary of the exportation or importation requirements submitted by the BE/TE to check that the novelty fulfils the current legislation.

9) New application/infusion method

If the novelty implies a new application or infusion method, the CA shall review the summary of the new application/infusion method. In case this novelty implies new equipment use, the CA shall assess that all the related information has been provided and that it meets the current legislative requirements.

10) New clinical indication

Although the clinical indication is out of the scope of the EUBTCDs, this guideline will provide recommendations for the CA in case a BTC is going to be used to treat a new clinical indication.

This guideline recommends the checks for a CA to perform where a BE/TE requests authorisation to provide a BTC to be used in a new clinical indication.

11) New anatomical site

As above with the 'new clinical indication', a new anatomical site is outside of the scope of the EUBTCDs, but this guideline will provide recommendations for a CA to perform in the case where a BE/TE requests authorisation to provide the BTC to be used in a new anatomical site.

When the novelty relates to a new anatomical site, this can be where there is insufficient scientific evidence relating to that site, or a site that has never been used before.

This new anatomical site is for applications that are not regulated under the Regulation 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.

b) Risk assessment:

After confirming that what the BE/TE intends to implement is a novelty, the risk assessment shall be performed.

The risk assessment is the identification of potential hazards with an estimation of the likelihood that they will cause harm and of the severity of the harm should it occur. The BE/TE will provide this assessment with their application, for the CA to review. The CA should perform their own risk assessment to ensure they agree with the risk level assigned by the applicant.

The risk assessment determination will decide what supporting information the CA should expect the applicant to submit with their application.

To perform this assessment, the CA shall use the EuroGTPII tool. The tool was designed initially for tissues and cells, but it has been extended to incorporate blood and blood components.

The CA using the EuroGTPII Guide and the interactive assessment tool will generate a short summary report detailing the risks identified and the risk scores, the summary produced by the applicant will be available for comparison. A summary of the EuroGTPII steps can be found below. The CA must review the EuroGTPII guide to obtain the full details on how to perform the risk assessment.

It is recommended that CA professionals and any external advisors used by the CA that will review the PPD should be competent in the use of the EuroGTPII tool.

In case the risk assessment performed by the CA does not meet the same risk level as the BE/TE applicant, the CA shall contact the BE/TE to inform them and to discuss the differences. If there is no consensus, the CA will decide which risk level to apply.

On the following flow chart in Figure 6 there is a summary of the risk assessment steps. Table 8 summarises the documents required based on the risk analysis level identified and assessment of risk reduction for BTC adapted from EuroGTPII. Table 9 lists the extent of studies needed based on the risk level identified.

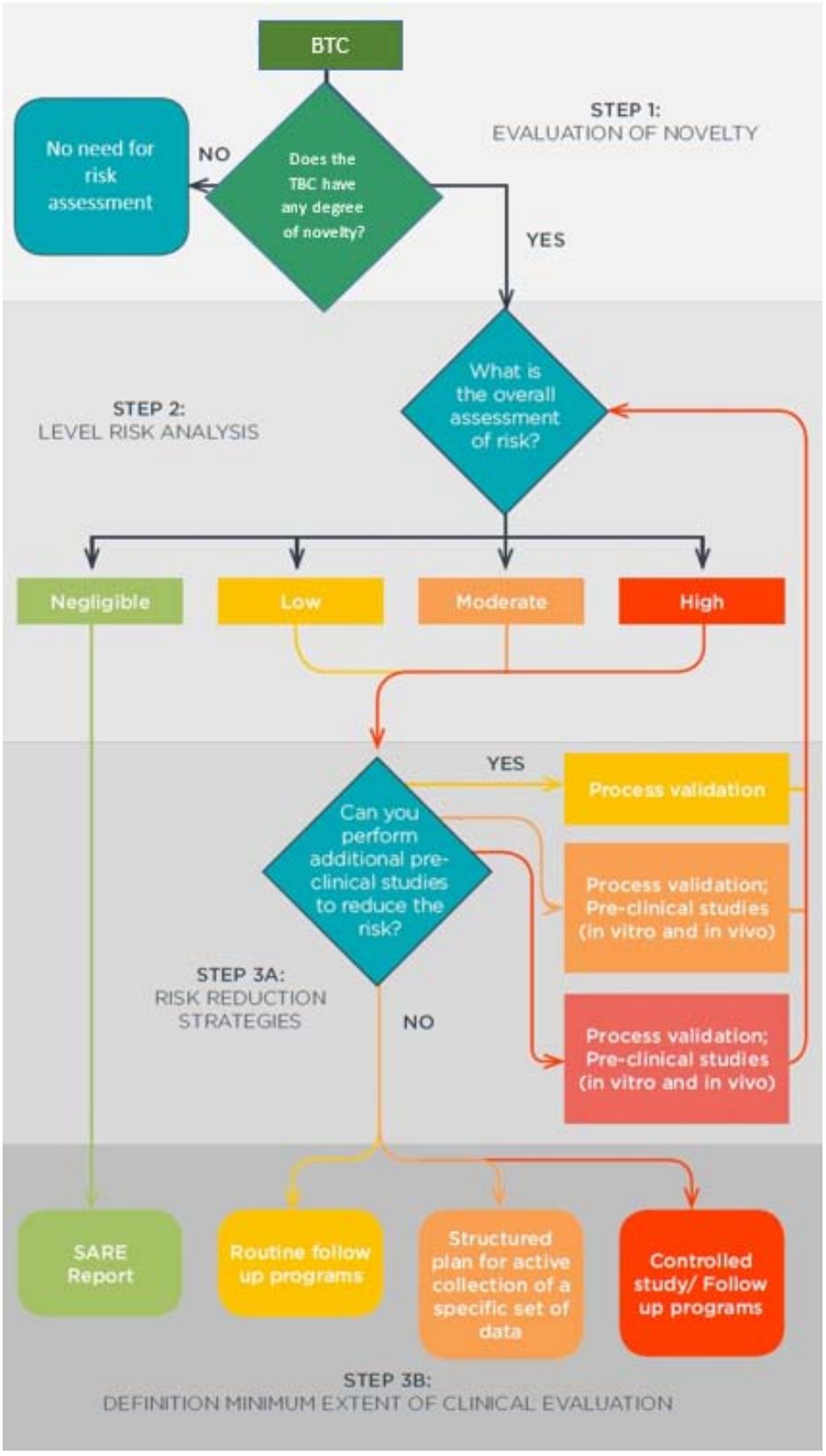

Figure 6. The risk reduction and determination of the extent of studies required. Adapted from EuroGTPII.

Tissues and Cells	Blood and Blood components
Identification of risk factors:	
Donor Characteristics Procurement process and environment Processing and environment Reagents Reliability of Microbiology Testing Storage Conditions Transport Conditions Presence of unwanted cellular material and/or graft vascularity Loss of viability and/or functionality Complexity of the immediate pre-implantation preparation and/or application method	Donor Characteristics Collection process and environment Processing and environment. Reagents / Added component Reliability of Testing Storage Conditions Transport Conditions Presence of unwanted residues Clinical indications
Identification of risk consequences	
Unexpected immunogenicity Implant failure / engraftment failure / pregnancy loss Disease transmission Toxicity / Carcinogenicity Other potential risks (can be associated with specific TC)	Unexpected immunogenicity Failure to perform clinically / Incremental failure Disease transmission Toxicity/Carcinogenicity Other
Quantification of risk	
The probability of the risk occurring. The severity of the consequences should the risk occur. The probability the source of the hazard for the risk consequences will be detected before the TC is applied.	The probability of the risk occurring. The severity of the consequences should the risk occur. The probability that the source of the harm for the risk consequences will be detected before the BC is transfused/applied. This does not refer to detection of the consequences of the risk post transfusion/application. Any existing evidence that can be used to mitigate the risk.

Tissues and Cells	Blood and Blood components
Assessment of risk reduction	
It may be possible to adjust the overall risk score taking into account external sources of information. The data that should be taken into account when assessing the risk reduction are: • Published data in peer reviewed literature. • Unpublished data from external sources. • Advice and information from external experts. • Clinical outcome data from external sources (e.g. registries).	For blood the assessment of the risk reduction is performed within the quantification of the risk step.

Table 8: Level risk analysis and assessment of risk reduction for BTC. Adapted from EuroGTPII.

The third step is the definition of the extent of studies needed based on the risks quantified. The objective of this step is to provide guidance on how to evaluate and mitigate the detected and quantified risks.

Further guidance on how to evaluate and mitigate the risks through an application of specific pre-clinical and clinical evaluations can be found in the GAPP deliverables:

- Technical Annex 1 to overall guidance: authorisation changes in donation, procurement and collection, processing, preservation, storage and distribution.

- Technical Annex 2 to overall guidance: assessing the quality and safety of donor testing, pathogen reduction and sterilisation steps as part of Preparation Process Authorisation (PPA).

- Technical Annex 3 to overall guidance: assessing clinical data as part of Preparation Process Authorisation (PPA).

Tissues and Cells	Blood and Blood components
Extent of studies needed based on the risks quantified	
Process validation Pre-clinical *in vitro* studies Pre-clinical *in vivo* studies Clinical Evaluation Protocols: – SARE Reporting – Routine follow up programs – Structured plan for active collection of a specific set of data – Controlled study/Follow up programs	

Table 9: Extent of studies needed based on the risks quantified. Adapted from EuroGTPII.

c) Final result of the risk assessment

After performing the risk assessment, there will be four risk levels, and further actions according to this should be taken.

Risk Level	Actions to be taken
Negligible Risk	- The assessment indicates that the BTC is safe and efficacious for clinical use and very unlikely to cause harm to recipients. The change does not seem to affect the quality of the BTC. - A validation of the process should be conducted, if not already done.
Low risk	- The assessment indicates that more evidence is needed to support safe and effective use of this BTC and mitigate risk. A clinical follow up plan should be designed and submitted to the CA. - A validation of the process and a quality verification of the BTC, if not already done, should be performed.
Moderate risk	- The assessment indicates that more evidence is needed to support safe and effective use of this BTC and mitigate risk. A clinical follow up plan and a clinical investigation plan to be designed and submitted to the CA. - Process validation should be performed. - Pre-clinical *in vitro* evaluation studies, specific to the identified risks, should be performed if not already done. - Pre-clinical *in vivo* evaluation, specific to the identified risks, using an animal model should be done, if applicable and if not already completed.
High risk	- The assessment indicates that significantly more evidence is needed to support safe and effective use of this BTC and mitigate the risks. The BTC or the clinical application may be new. - A clinical follow up plan, a clinical investigation plan and comparison to standard therapy to be designed and submitted to the CA. - Process validation should be performed. - Pre-clinical *in vitro* evaluation, specific to the identified risks, should be performed if not already done. - Pre-clinical *in vivo* evaluation, specific to the identified risks, using an animal model should be done, if applicable and if not already completed.

Table 10: Risks levels after the risk assessment. Adapted from EuroGTPII.

The risk assessment assigned to the application determines the amount of supporting information to be supplied with the application.

Step 3: CA confirm appropriate information received and application confirmed as admissible

Risk	Information to be supplied to CA	Further information available in:
Negligible	Application Information BTC Novelty Risk assessment Quality* SARE reporting Clinical Information - Minimum clinical information	Module 1 Module 2 Module 3 Module 4 & WP6 & WP 7 Module 5 & WP8
Low	Application Information BTC Novelty Risk assessment Quality* SARE reporting Clinical Information - Minimum clinical information - Clinical follow up plan	Module 1 Module 2 Module 3 Module 4 & WP6 & WP 7 Module 5 & WP8 Module 6 & WP8
Moderate	Application Information BTC Novelty Risk assessment Quality* SARE reporting Preclinical Studies Clinical Information - Minimum clinical information - Clinical follow up plan - Clinical investigation plan	Module 1 Module 2 Module 3 Module 4 & WP6 & WP 7 Module 5 & WP8 Module 6 & WP8 Module 6 & WP8
High	Application Information BTC Novelty Risk assessment Quality* SARE reporting Preclinical Studies Clinical Information - Minimum clinical information - Clinical follow up plan - Clinical investigation plan - Comparison to standard therapy	Module 1 Module 2 Module 3 Module 4 & WP6 & WP 7 Module 5 & WP8 Module 6 & WP8 Module 6 & WP8
*only procedures affected by novelty are required to be submitted to CA		

Table 11. Lists the information that the CA should receive with the application based on the risk assigned to the novelty by the CA, and the modules on evaluating this information.

For Modules 4 / 5 / 6, the CA should also ensure that the information provided in the quality module, the pre-clinical and the clinical ones are appropriate. This information will be reviewed in detail during the evaluation of the application.

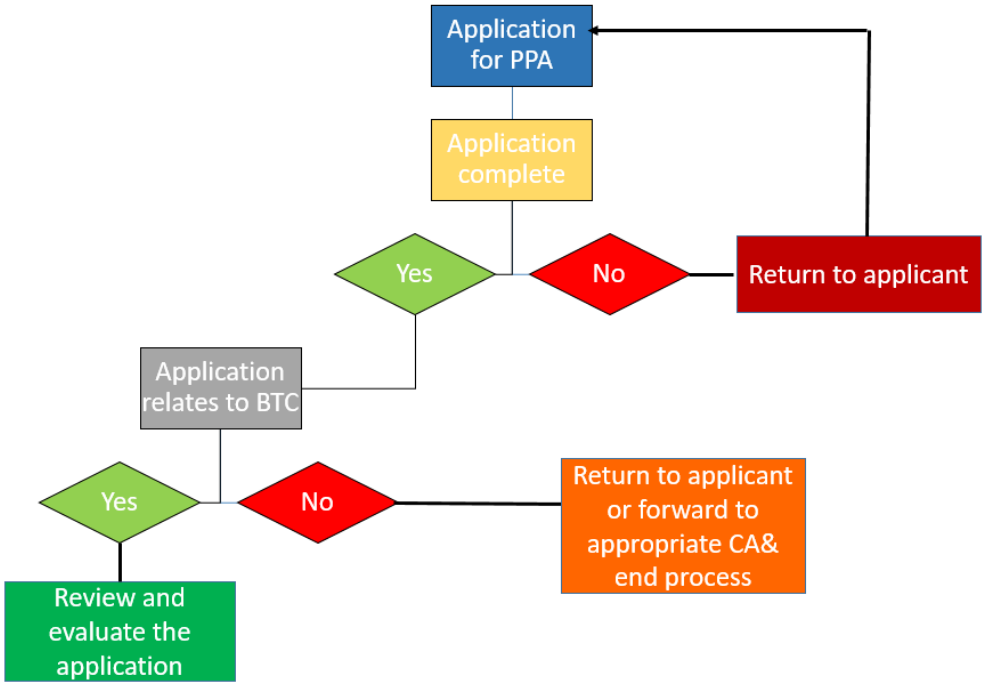

Figure 7. Flow chart to follow according the level of compliance of the PPA.

As it is described on figure, 7 if the file is incomplete, the applicant is informed and asked to send the missing documents / information and the technical / regulatory evaluation does not proceed until the application is complete. If during initial review of the PPD, the CA confirms that the application does not relate to a BTC which falls under the EUBTCDs, they will return the application to the applicant or forward to the appropriate CA, and the assessment process for the BTC CA will end.

Step 4: Flow of Evaluation of the Application according to the risk assessment:

As shown in table 11, the risk assigned to the novelty will indicate to the CA the information that should be submitted for them to evaluate. The following process flows indicate the flow for evaluation of the PPD based on the risk assigned to the novelty.

The following figures (8, 9, 10 and 11) describe the procedure to be followed by the CA taking into account the risk assessment. There is one figure for each risk level (negligible, low, moderate and high). Figures include a proposed time for the CA to review the application.

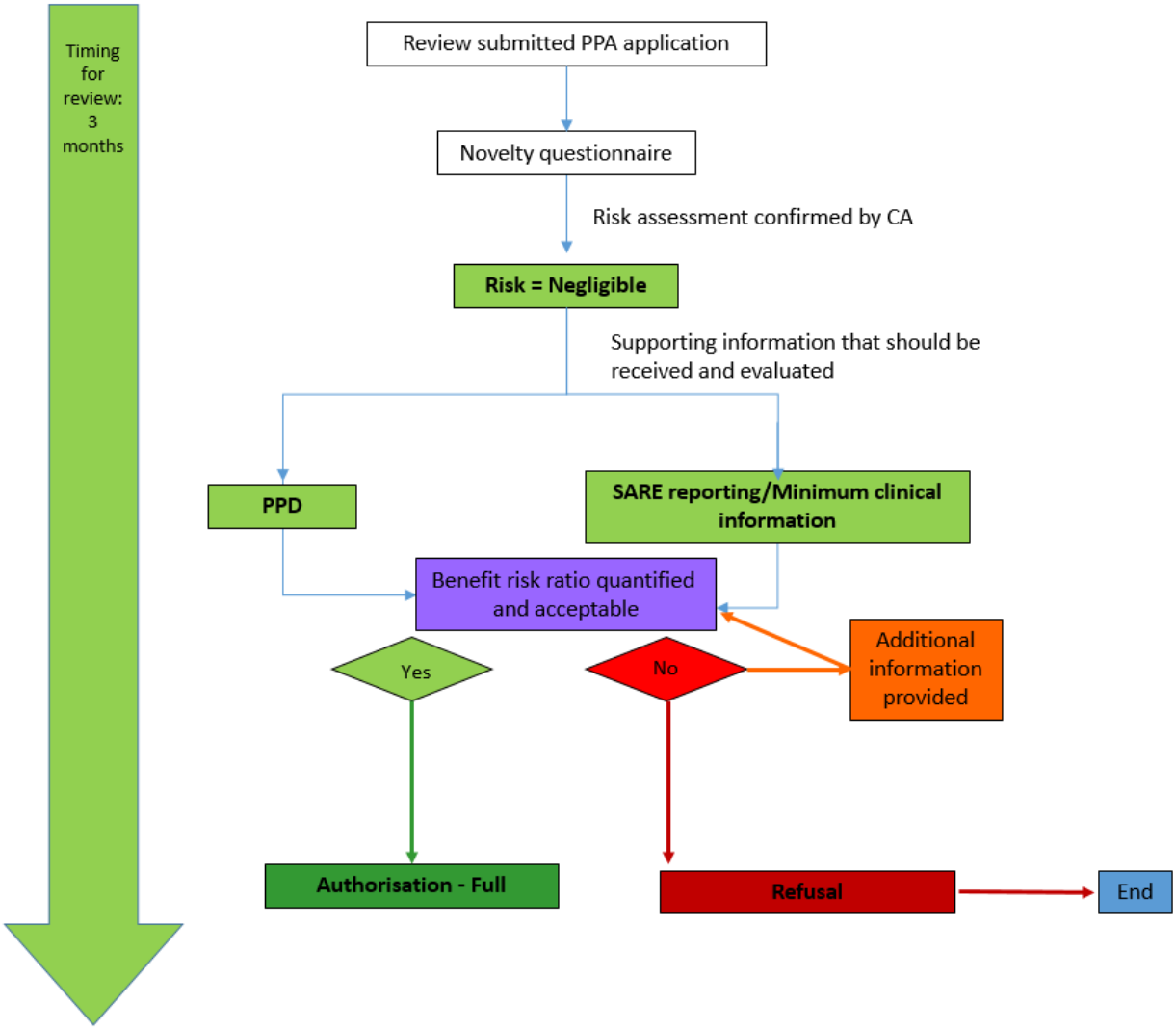

Figure 8. Evaluation process for negligible risk.

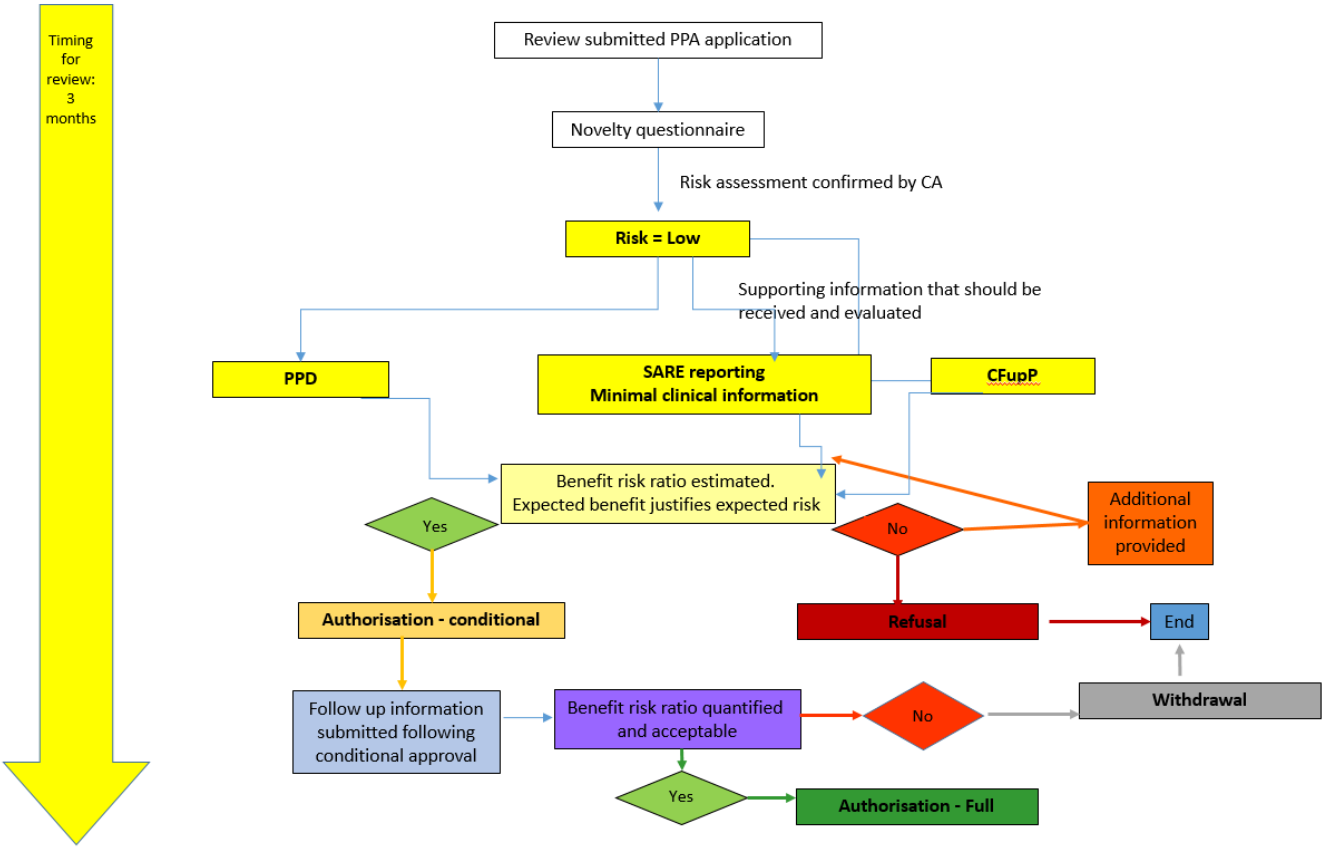

Figure 9. Evaluation process for low risk.

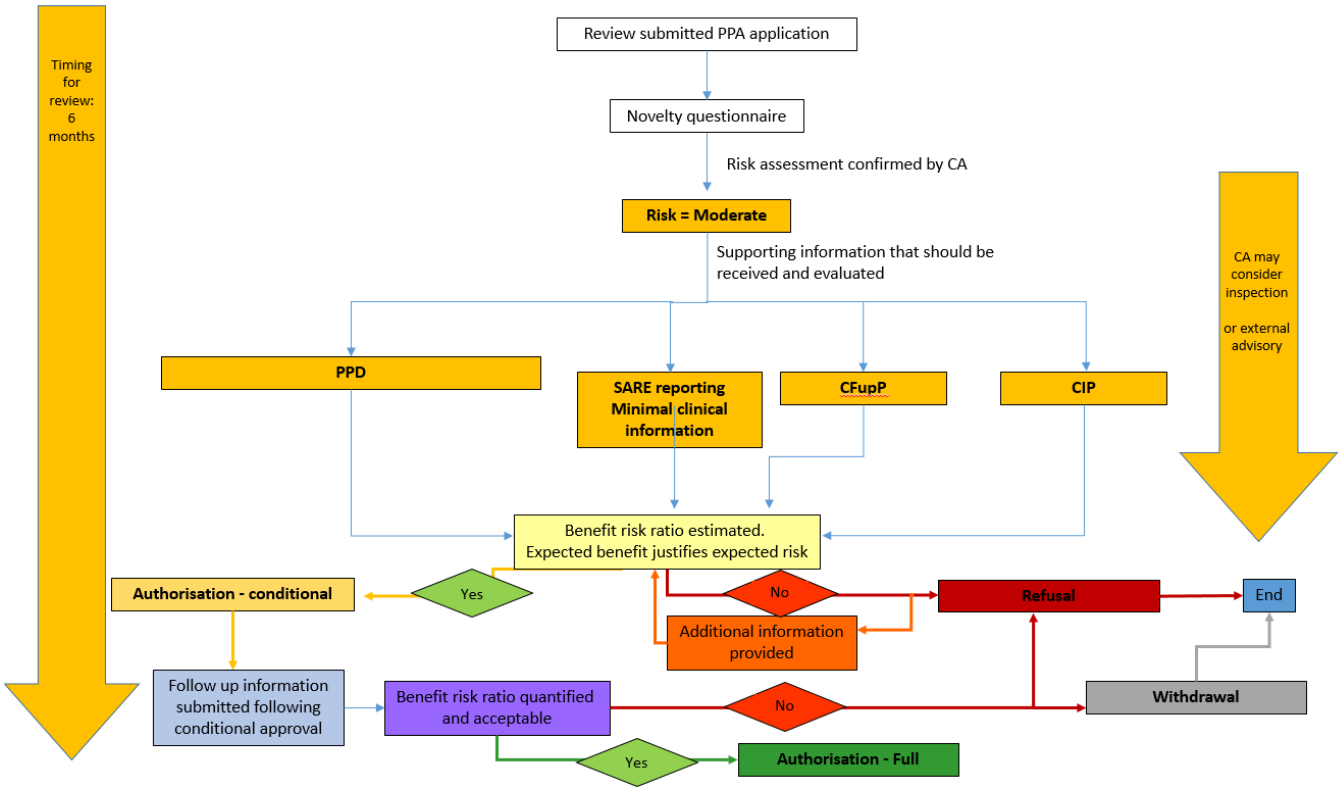

Figure 10. Evaluation process for moderate risk.

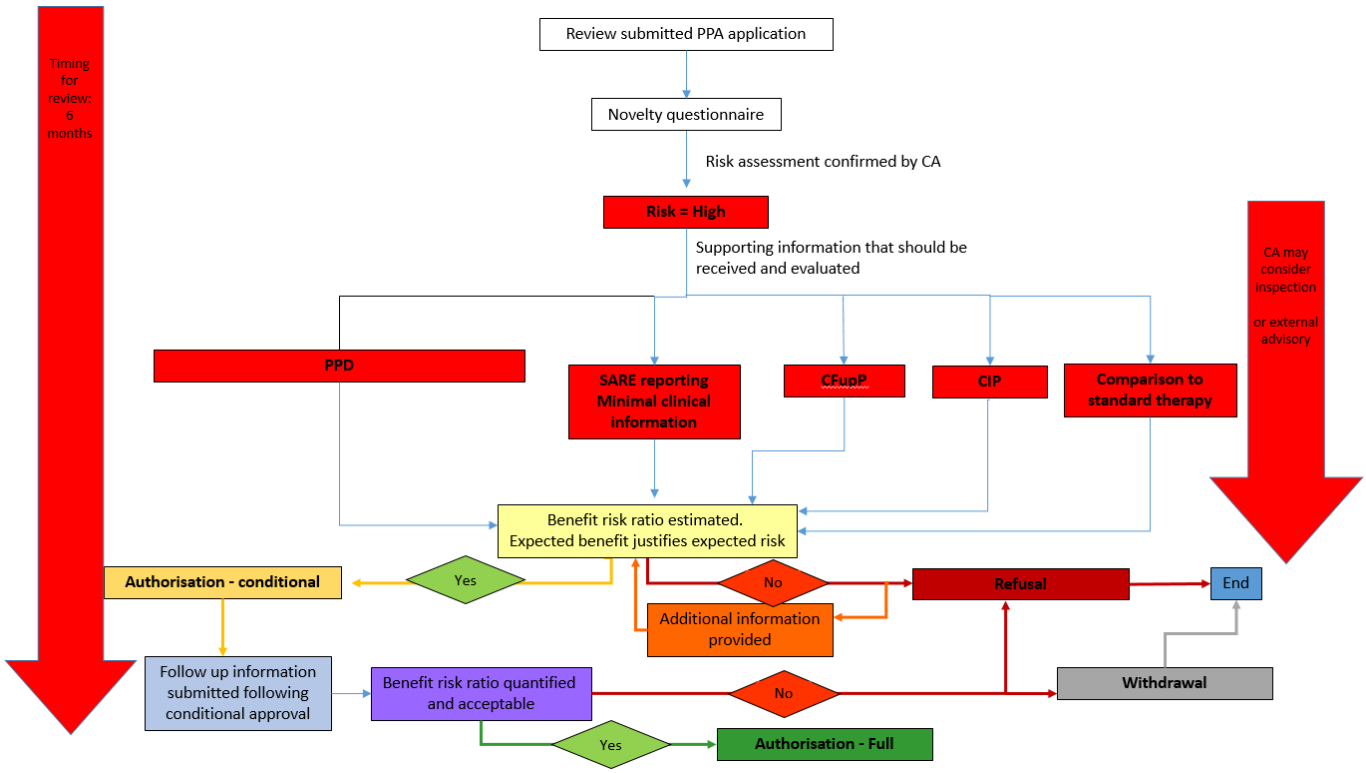

Figure 11. Evaluation process for high risk.

B. Evaluation:

Step 5: Evaluation of submitted information:

Module 4: Quality

At this stage of the process, the CA shall review the novelty steps and if the information according to each of them has been submitted following the information contained in the PPD.

Where an establishment is reliant on published data to support the planned work, they must be able to demonstrate that the methods they intend to follow directly mirror those in published reports and they must be able to demonstrate that they can reproduce the process (and results) in their own facility. In such situations the CA should look very closely at the equipment, reagents and protocols being employed, and the training that has been given to staff.

1) Donor selection

The CA shall review the updated SOP and ensure that it includes the selection criteria and the donor selection policy. If they do not meet the EUBTCDs or the national/regional legislation, the CA shall review the clinical justification provided by the BE/TE.

2) Donation/ Collection/ Procurement

The CA shall assess that the proposed SOP explains the novelty and provides clinical justification and appropriate validation.

The CA shall ensure that this novelty meets the EUBTCDs and the national/regional legislation.

If the material/equipment used for collection/procurement is not single-use, the CA shall also assess the sterilisation procedure.

3) Testing

The CA shall assess the SOP for donor or donation testing and the SOP for transporting the samples to the laboratory. The CA shall review the validation of the testing kit.

4) Processing

The CA shall check that the applicant has provided an updated process flow diagram, and that this includes the critical steps of the process.

The quality parameters should be reviewed and suitable for the intended novelty.

The CA shall check the applicant has submitted the validation process, the stability and the evaluation reports. The CA shall review how these processes have been performed.

The CA shall check the adapted SOP for processing and the SOP to minimise cross contamination. The SOP for assessing microbiological safety of the BTC shall be reviewed, and if sterilisation or pathogen reduction is used on the BTC, the validation report shall be assessed.

All the novelties in the processing shall be validated and the applicant shall provide the final validation reports. The CA shall ensure that the validation method meets the EUBTCDs and that it also considers the publications of the Council of Europe: the EDQM T&C Guide and the EDQM Blood Guide.

If any stages of processing are outsourced to a third party, the evaluation or audit report of the party(ies) shall be reviewed by the CA. If the audit shows deviations/ non-conformances, the CA shall request information on how they were resolved**.**

5) Storage

The CA shall assess the SOP for storage process, for storage conditions and shelf life and the evaluation or stability report.

The CA will assess the information provided, for example:

- If the storage novelty affects the quality of the BTC.
- The risks related to microbiological contamination.
- The package integrity over time.
- The expiry of storage solutions.
- The stability at the storage temperature.

6) Transport and delivery

The CA shall assess the SOP for transport, delivery, labelling and validation. The CA shall assess the stability report provided by the BE/TE.

The CA shall ensure that the conditions and the maximum time allowed for transport, preserve the biological and functional properties of the BTC. They shall also check that the container used to transport and deliver the BTC is safe and the CA shall also assess that the container and material used to transport the BTC is CE-marked, if required, and that there is an instruction manual. The maintenance schedule of the equipment should also be reviewed.

The validation of the transport procedure should also contain the validation of the containers.

If the distribution and the delivery is to be carried out by a third-party, the CA shall review the agreement between both parties and, also that the validation report verifies that the transport conditions are maintained.

7) Distribution/issue

The CA shall review the SOP and ensure that it details the specifications, circumstances, and the responsibilities and procedures for releasing the TC or issuing blood and blood components.

The CA shall review if the novelty in the release criteria implies a change in other steps of the process, such as donor selection, processing or storage. It is also necessary to assess if the new release criteria or the novelty in the distribution/issue meets the EUBTCDs and the national/regional legislation.

8) Exportation/Importation

If the novelty implies a change in the exportation or importation of the BTC, the CA shall assess that the SOP explains the novelty. The SOP also needs to be checked to ensure that the novelty meets the EUBTCDs and the national/regional legislation, particularly in the case of importing BTCs. In this situation, the CA shall assess if the third-country supplier fulfils the ethical principles of consent, non-remunerated donation, anonymity, respect for public health and the donor criteria required in the EUBTCDs.

9) New application/infusion method

If the BTC is going to be applied or infused using a new method, the CA shall review the SOP for this new application/ infusion method and the validation report for any new equipment required. This validation report should be approved by the person responsible for the activity

10) New Clinical indication

The CA shall assess the SOP for this new clinical indication.

The CA has to check the clinical report submitted by the BE/TE. This clinical report shall include the scientific reasons to use the BTC to treat patients with the new clinical indication, and the:

- Expected benefits.
- Expected risks.
- Consent form for recipient.

If this new clinical indications implies a change in the processing, the storage or the transport of the BTC, the CA shall also ensure that the BE/TE has provided the specific information regarding these changes.

11) New anatomical site

The CA shall assess the SOP for this new anatomical site.

The CA has to check the clinical report submitted by the BE/TE. This clinical report shall include the scientific reasons to use the BTC to treat patients at the new anatomical site, and the:

- Expected benefits.
- Expected risks.
- Consent form for recipient.

If this new anatomical site implies a change in the processing, the storage or the transport of the BTC, the CA shall also ensure that the BE/TE has provided the specific information regarding these changes.

Module 5: Preclinical studies

The EuroGTPII Guide provides information in relation the performance of *in vitro* and *in vivo* studies.
Generally, *in vitro* assessments should be performed prior to other pre-clinical (*in vivo*) studies. This category may also incorporate routine process validation studies. Where the overall risk is low, it is likely that it can be mitigated purely with *in vitro* assessments.
In vivo assessments will usually only be considered where the risk cannot be sufficiently mitigated with in vitro studies, for cost and ethical reasons. There may however be criteria that can only be accurately evaluated with *in vivo* models. The EuroGTPII Guide gives guidance on how to define which tests could be used for the different types of novel tissues and cells regarding specific risk consequences.

Non clinical studies: preferably there should be studies showing the experimental procedure is safe in animals.
Pre-clinical Studies: when experimental treatments encompass a laboratory phase, then at least the viability of cells should be looked at in detail, monitored and registered.

Module 6: Clinical information

The CA should review findings from clinical studies that affect, or could affect, the evaluation of safety in clinical use. This should be done through bibliography review and evaluation of the previous experience and existing knowledge of the risk provided by the applicant.

The CA should review SARE reports as per the existing CA process.

The CA should review the clinical information received in conjunction with technical annex 3.

The information provided will be dependent on the risk of the novelty and may include the following:

- Minimum clinical information.
- Clinical follow up plan
- Clinical investigation plan
- Comparison to standard therapy

Step 6: CA decision

The CA will evaluate the information received and authorise or refuse the application.

The types of authorisations can be broken down into: conditional, when there is limited data available, but the benefit justifies the risk; and a full authorisation, when all data is available; as well as the option to refuse an authorisation application.

The authorisations are based on principles devised by the VISTART joint action and are as follows:

- Quality and safety of the BTC has to be ensured by:
    - Assessment based on comprehensive data of BTC authorisation application.
    - Risk-based decision making on approval of the BTC application.
- When a full authorisation cannot be granted but the expected benefit justifies the residual risks, a conditional authorisation shall be granted.
- If the benefit does not justify the residual risk, the authorisation may be refused.

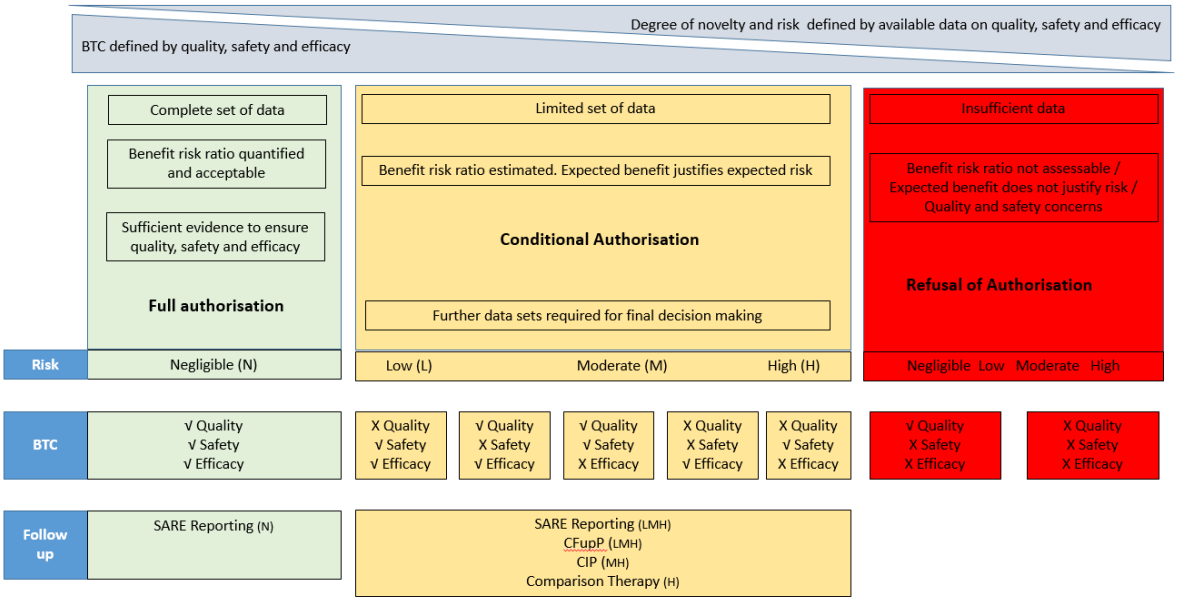

Figure 12: Algorithm for CA to decide according the novelty, risk, quality, safety and efficacy. Adapted from VISTART WP5B.

The above algorithm (figure 12) depicts the proposed authorisation options a CA should consider based on the benefit risk ratio; full, conditional, and refusal. The algorithm has been adapted from the VISTART WP5B algorithm, which previously defined how a CA may use it to decide on the authorisation of the novel BTC in consideration of the risk-benefit-ratio as a result of assessment of quality, safety and efficacy, based on available data and reflecting the maturity of the product and its degree of novelty, respectively.

Conditional authorisation:

Where regulatory requirements need to be balanced with the requirement of timely/urgent access of patients to novel BTCs, or a BTC prepared from a novel preparation process, a precautionary regulatory approach may be taken. In such cases, where the expected benefit justifies the expected risk and no alternative options are available, a conditional authorisation may be granted, defining the further data sets that are required for further assessment and for final decision-making (full authorisation or refusal).

It is recommended that this type of authorisation be issued for the preparation and clinical use of the novelty depending on the quantity and quality of results available at the time of submission of the PPA. The relevant information required following conditional authorisation, must be provided within the agreed timeframe of the CA. The CA should then assess and consider if a full authorisation should be granted or if the authorisation should be subsequently refused.

The conditional authorisation should detail the number of patients, the cohort of patients, and the centres that will manage the BTC. It is recommended that this authorisation is also linked to the CIP if possible.

Once a conditional authorisation has been granted, the CA must define the timelines within which the applicant must submit the clinical data.

Based on the correlation between risk level and type of follow upinformation the algorithm defines four main risk categories and these are linked to the four corresponding types of follow up:

- **Negligible risk:**
    - If the application of the BTC does not pose any risk for recipients (or offspring in the case of MAR), only SARE reporting that is mandatory for all BTC is required
    - SARE reporting should be immediate and as described in EUBTCDs.

- **Low risk:**
    - In addition to the mandatory continuous SARE reporting, a clinical follow-up plan should also be provided
    - SARE reporting should be immediate as described in EUBTCDs
    - A proposed timeline for receipt of the CFUpP for low risk is nine months to one year. The CA can receive interim updates if they wish.

- **Moderate risk:**
    - In addition to the SARE reporting and CFUpP, a clinical investigation plan should also be provided
    - SARE reporting should be immediate as described in EUBTCDs
    - A proposed timeline for receipt of the CFUpP and CIP for moderate risk is six to nine months. The CA can receive interim updates if they wish.

- **High risk:**
    - In the case of high risk, in addition to the SARE reporting and CFUpP, the CIP should be designed so as in order to compare the novel BTC to a standard/conventional therapy, if available.
    - SARE reporting should be immediate as described in EUBTCDs
    - A proposed timeline for receipt of the CFUpP and CIP (including reference to comparison therapy) for high risk is three to six months. The CA can receive interim updates if they wish.

If further appropriate additional follow up information has been received after granting a conditional authorisation, the CA may grant a full authorisation, see 'full authorisation' section.

In circumstances where additional follow up information has been received after granting a conditional authorisation, the CA may also withdraw the conditional authorisation and refuse to grant the full authorisation:

Withdrawal / Refusal

The CA will refuse an authorisation based on the results of the CFUpP/CIP and / or SARE reports and / or the quality, safety and efficacy of the novelty or change has not been proven. The CA may also refuse to grant the full authorisation.

Full authorisation

On evaluation of additional information following the granting of a conditional authorisation, the CA may grant a full authorisation, if the benefit justifies the risk and they have been appropriately satisfied that the quality, safety and efficacy of the novelty has been demonstrated. It is recommended that this authorisation for the preparation and clinical use of the novelty will be issued when there is sufficient evidence to assure the quality, safety and efficacy of the novelty. A full authorisation may also be granted for negligible risk BTCs / procedures, if all appropriate data is submitted with the application and is deemed appropriate by the CA. The benefit ratio should be quantifiable and acceptable in order for a full authorisation to be granted.

Refusal of authorisation

Competent Authorities shall refuse to issue an authorisation based on quality and safety concerns. If the expected benefit is not assessable, does not justify the risk, or if there are quality and safety concerns the authorisation should be refused.

Other decisions

In other circumstances a CA may be contacted by an applicant to discuss their conditional / full authorisation. This may occur in the following circumstances:

- **Extension**

  If a conditional authorisation has been granted, an extension should be requested when an applicant requires more time or an increase in the number of patients or addition of a site of human application to complete the clinical follow up / clinical investigation plan.

- **Renewals**

  For countries who have a process of issuing expiry dates on authorisation and where a conditional / full authorisation has been granted, the BE/TE must request a renewal before the current authorisation expires. This process should occur through the CA's regular authorisation renewal process.

- **Cessation**

  If the BE/TE is not in a position to continue with the authorisation, for example if they cannot meet the agreed criteria or recruit sufficient patients, they should request a cessation of the authorisation.

Additional considerations for CAs

Timing of Application for PPA

Although the timing of review depends on every Competent Authority, we recommend applying these two periods of timing to review the PPD. In case, a CA defines a different timing it should be made public and easily identifiable to applicants. It should be clearly communicated by the CA to the applicant that if a response is not received within the defined period of time, this does not mean that an authorisation has been granted. The applicant must receive an authorisation from the CA before implementing the novelty, particularly in relation to low, moderate and high risk applications.

Acceptable time of response for the different categories according to the level of risk:

Level of risk	**Recommended timing of review**	
Negligible risk	Three months	
Low risk		
Moderate risk		Six months
High risk		

Table 11. Recommended timing of review according to the level of risk.

External advisors

It is recommended that the professionals of the competent authority that will review the PPD have been trained in the EuroGTPII tool and in this GAPP Overall Guideline and its associated technical annexes. It is also recommended as per section 4 'Framework for Competent Authority', of this guideline that a CA have access to a panel of experts to help in the review of the PPD, if necessary.

Inspections

A CA may perform an onsite inspection based on their own national procedures, and may refer to VISTART 'Inspection Guidelines for EU Competent Authorities Responsible or the Inspection and Authorisation of Blood and Tissue Establishments'.

This decision can be made after the review of the information submitted with the application and can be based on the risk assessment performed according to the procedures in place by the CA itself.

Novel BTCs

On review of the information supplied in relation to a new BTC, it may become evident that the BTC requires classification from an expert group. It is advisable that the CA put in place some mechanisms and internal rules to get cooperation from experts/professional bodies providing specific knowledge and expertise in the concerning field.

It has been indicated in the revision of the BTC legislation that there is a proposal for an EU level mechanism to be set up to advise MS's on whether the BTC framework or other frameworks (in particular medicinal products and medical devices), should be applied for particular novel BTCs. If this is setup a CA should use this group for classification purposes.

A novel BTC may also require addition to the European Tissue and Cell Product Compendium or discussion with the EDQM for inclusion in the 'Guide to the quality and safety of tissues and cells for human application' or the 'Guide to the preparation, use and quality assurance of blood components'.

Insurance

Some CAs may need to ensure that there is adequate insurance cover for the recipients of novel BTCs in accordance with applicable regulatory requirements. Proof of insurance should be requested when this is stipulated by national legislation. Consideration may also be given to whether additional insurance coverage is required by the BE/TE/ORHA based on the regional or national legislation.

Ethical Committee

In some MSs a favourable decision/opinion from the Independent Ethics Committee (IEC) may be required in order to progress with authorisation. Refer to section 6.2 of Technical Annex 3.

4. Framework for Competent Authority

The evaluation of a PPD is based on the requirements set out in section 3, 'Review and Evaluation', of this guideline. In order to carry out an evaluation of a PPD a CA may rely on their own internal assessors, inspectors, or group of experts. The CA shall have access to personnel with relevant expertise and where possible such personnel shall be employed / retained by the CA itself and must meet the relevant qualification and training criteria. Such personnel shall be integrated throughout the CA assessment and decision-making process.

The VISTART 'Inspection Guidelines for EU Competent Authorities Responsible for the Inspection and Authorisation of Blood and Tissue Establishments' sets out a common framework for the conduction of inspections of BE/TE across MS's. Included in this is the general governance and quality management principles for CA's, such as: administrative structure; independence and impartiality; transparency; and training and development of staff. Aspects of this guideline could be adopted in the description of the framework for CA.

Qualifications and Training

The personnel responsible for carrying out technical reviews, including aspects such as clinical evaluation, biological safety, sterilisation etc., shall have the following proven qualifications relevant to the aspects of assessment for which they are responsible:

- Successful completion of a university or a technical college degree or equivalent qualification in relevant studies, e.g. medicine, biological science or other relevant sciences
- Professional experience in relevant aspects of the field of BTC related activities, or regulation of such activities
- Knowledge of BTC legislation, including the general quality and safety and efficacy requirements
- Appropriate knowledge and experience of relevant standards and guidance documents; e.g. EDQM Guides
- Appropriate knowledge and experience of risk management principles and processes, e.g. EuroGTP II
- Appropriate knowledge and experience of clinical evaluation
- Appropriate knowledge of the specific category of BTC which they are assessing;
- Appropriate knowledge and experience of the assessment procedures / software relevant to the CA
- The ability to maintain records and write reports demonstrating that the relevant assessment activities have been appropriately carried out

It is recommended that if the risk is identified as low, moderate or high, that the CA performs an inspection according to their own procedures. This may include a desk based, remote, or on-site inspection and further guidelines are available in the VISTART Inspection Guidelines.

The assessment of a PPD application is included in Deliverable 10.1 “Manual for training CA inspectors that assess and authorise preparation processes of tissue, cell, and blood products”. This should be included within each CA inspectors and assessors training programme.

It is evident that some CA’s may not have expertise available to assess all applications. For this reason, it may be beneficial to establish expert panels to assist in reviewing applications. The CA’s decision to authorise or reject the application should be the final decision. The VISTART inspection guideline discusses independence and impartiality and this includes external experts. If a CA chooses to use an external expert / expert panels, they should have a clear process for selection of the expert(s) and a clear defined policy on management of conflicts of interest.

Expert / Expert panels

Experts / expert panels may be required in the following circumstances:

- Review and scientifically challenge the clinical data /clinical investigations
- Be able to scientifically evaluate and, if necessary, challenge the clinical evaluation presented
- Be able to ascertain the comparability and consistency of the assessments of clinical evaluations conducted by clinical experts
- Be able to make an assessment of the clinical evaluation and a clinical judgement and make a recommendation to the CA's decision maker
- Be able to maintain records and write reports demonstrating that the relevant conformity assessment activities have been appropriately carried out

Criteria to join expert panels

- Professionals with plenty of experience in the specific field that the CA needs advice in
- If possible, they shall be appointed by the relevant Scientific Associations
- Assessments should be made by professionals without any political, professional, institutional or trade co-action, although their decisions will not be binding
- The appointment of the experts will be public and known by the applicants
- A written report explaining their opinion and recommendations should be sent to the CA
- Advisors should declare any potential conflicts of interest, if there are any

The availability of a European panel of experts from within CA’s would be beneficial, this would eliminate the need to engage the services of external experts who may have affiliations with BE/TE. The feasibility of establishing such a group, and possibility of sharing sensitive information between CA’s would need to be investigated and is outside the scope of this project.

Appendix 1BTC List

Active component	Preparation characteristics
Whole blood	Whole blood
	Whole blood, leucocyte-depleted
Red cells	Red cells
	Red cells, buffy coat removed
	Red cells, in additive solution
	Red cells, buffy coat removed, in additive solution
	Red cells, irradiated
	Red cells, leucocyte-depleted
	Red cells, leucocyte-depleted, in additive solution
	Red cells, apheresis
	Red cells, washed
	Red cells, cryopreserved
	Red cells, other
Platelets	Platelets, recovered, single unit
	Platelets, recovered, single unit, leucocyte-depleted
	Platelets, recovered, pooled
	Platelets, recovered, pooled, leucocyte-depleted
	Platelets, recovered, pooled, in additive solution
	Platelets, recovered, pooled, leucocyte-depleted, in additive solution
	Platelets, pooled, pathogen-reduced
	Platelets, apheresis
	Platelets, apheresis, leucocyte-depleted
	Platelets, apheresis, leucocyte-depleted, in additive solution
	Platelets, pathogen-reduced
	Platelets, cryopreserved
	Platelets, other
	Platelets, apheresis, in additive solution
Plasma and cryoprecipitate	Plasma, fresh frozen
	Plasma, fresh frozen, pathogen reduced
	Cryoprecipitate
	Cryoprecipitate, pathogen reduced
	Plasma, fresh frozen, cryoprecipitate-depleted
	Plasma, other
Granulocytes	Granulocytes, apheresis
	Granulocytes, pooled
Other	

Tissue/cell component	Preparation characteristics	
Adipose	Adipose tissue	
	Adipose cells	
Cardiovascular	Cardiovascular, valve	Cryopreserved heart valve allograft, antibiotic decontaminated
	Cardiovascular, vessel	Cryopreserved femoral artery allograft, antibiotic decontaminated
	Cardiac tissue	
	Cardiac cells	
Membrane	Membrane, amniotic	Amniotic membrane (AM) for biological dressing
	Membrane, dura mater	
	Membrane, fascia lata	
	Membrane, fascia rectus	
	Membrane, pericardium	
	Membrane, other	
Musculoskeletal	Musculoskeletal, bone	Cancellous bone chips
		Cortical bone struts
		Cryopreserved cortical bone
		Cryopreserved cancellous bone
		Dehydrated cancellous bone, viroinactivated, sterilised
		Demineralized bone matrix (DBM), viroinactivated, sterilised
	Musculoskeletal, cartilage	Cryopreserved cartilage meniscus
	Musculoskeletal, ligament	
	Musculoskeletal, tendon	Patellar tendon allograft
		Cryopreserved tendon
Neuronal	Neuronal, nerve	
Ocular	Ocular, conjunctival	
	Ocular, corneal	Organ-cultured corneal donor tissue for (deep) anterior lamellar keratoplasty (ALK/DALK)
		Cold-stored corneal tissue for (deep) anterior lamellar keratoplasty (ALK/DALK)
		Organ-cultured corneal tissue for Descemet membrane endothelial keratoplasty (DMEK)
		Cold-stored corneal tissue for Descemet membrane endothelial keratoplasty (DMEK)
		Organ-cultured corneal tissue for Descemet stripping automated endothelial keratoplasty (DSAEK)
		Cold-stored corneal tissue for Descemet stripping automated endothelial keratoplasty (DSAEK)
		Organ-cultured corneal tissue for penetrating keratoplasty (PK)
		Cold-stored corneal tissue for penetrating keratoplasty (PK)
	Ocular, sclera	
	Ocular, other	
Other Mature cells	Mature cells, hepatocytes	
	Mature cells, keratinocytes	
	Mature cells, mononuclear cells	Mononuclear cells from unstimulated peripheral blood apheresis – MNC(A)
	Mature cells, T-cells	
Pancreatic islets	Pancreatic islets	
	Pancreatic islet cells	
Parathyroid	Parathyroid	
Progenitor cells	Hematopoietic progenitor	Hematopoietic progenitor cells from bone marrow –

	cells, bone marrow	HPC(M)
	Hematopoietic progenitor cells, cord blood	Hematopoietic progenitor cells from umbilical cord blood – HPC(CB)
	Hematopoietic progenitor cells, peripheral blood	Hematopoietic progenitor cells from peripheral blood apheresis – HPC(A)
	Hematopoietic progenitor cells, other	
Reproductive	Ovarian	
	Testicular	
Skin	Skin, dermis	Acellular dermal matrix (ADM)
	Skin	Fresh skin allograft
		Deep-frozen skin allograft
		Glycerol-preserved skin allograft
		Cryopreserved skin allograft
		Lyophilized skin allograft
Umbilical cord	Umbilical cord tissue	
Reproductive	Reproductive cells and embryos	Sperm
		Oocytes
		Embryos
Other		

If it is a new BTC the subtype might not be available at the EDQM guide or the Compendium. In those cases the applicant shall take into account that this PPD will only apply if the BTC is under the EUBTCDs, and it is not considered an advanced therapy medicinal product or under another classification.

Appendix 2 Preparation Process Dossier

The PPD is organised in modules as follows:

- Module 1: Applicant information
- Module 2: BTC novelty
- Module 3: Risk assessment
- Module 4: Quality
- Module 5: Preclinical studies
- Module 6: Clinical information

For applications submitted where novelty has been identified, only the applicant data as detailed below, and specific sections related to the novelty should be submitted to the CA to review. The information related to the novelty should be completed within the PPD. The PPD does not have to be completed for areas that the novelty does not affect, as the CA will have previously assessed these.

For BE/TE that have not previously been authorised, information in relation to the establishment, preparation process, materials and equipment, quality control testing, process validation and labelling will not have been provided before, therefore the complete preparation process dossier and all information should be provided to the CA.

Please attach all the relevant information/data needed for a proper assessment including all relevant training records.

Note: information required can be provided in additional attachments

Module 1: Applicant Information	

Full name of BE/TE	
Postal address of BE/TE	
NameofResponsible Person of the BE/TE *(if new provide copy of cv)*	
Name of the person responsible for the dossier	
E-mail address	
Phone number	
Date of submission	
Signature of responsible person	

Module 2: BTC Novelty

Description of the BTC to which this preparation process is applied	*In appendix I, you can find the list of BTCs according to the CoE EDQM Guide, TC Compendium.* *Provide the relevant detail:*	
Blood and blood components □	**Blood Component:**	
	Preparation Characteristic:	
Tissues □	**Tissue Component:**	
	Preparation Characteristic:	
Cells □	**Cell Component:**	
	Preparation Characteristic:	
MAR □	**Cell Component:**	
	Preparation Characteristic:	

BTC Novelty

Evaluation of novelty:

Novelty questions	Yes	No	See section
Has this type of BTC previously been prepared and issued for clinical use by your establishment?			All sections
Will the starting material used to prepare this BTC be obtained from the same donor population previously used by your establishment for this type of BTC?			1 and 3
Will the starting material for this BTC be procured/collected using a procedure used previously by your establishment for this type of BTC?			2 and 3
Will this BTC be prepared by a procedure (processing/preparation, decontamination and preservation) used previously in your establishment for this type of BTC?			4
Will this BTC be packaged and stored using a protocol and materials used previously in your establishment for this type of BTC?			5
Will this type of BTC provided by your establishment be applied/ infused clinically using an application/infusion method used previously?			6, 7, 8 and 9
Has your establishment provided this type of BTC for a same clinical indication or applied/infused into a same anatomical site?			10 and 11

If the answer to any of the novelty questions above is 'NO'; the applicant must provide the information described in the corresponding section. For new applicants, who have not previously been authorised all details in the PPD must be completed as appropriate, as information will not have previously been assessed by the CA and all areas are considered a novelty.

Activities
For new applicants select all activities which apply to the BTC. For other applicants select the activities to which the novelty relates to: *1.* Donor Selection *2.* Donation/Collection/ Procurement *3.* Testing *4.* Processing *5.* Storage *6.* Transport and delivery *7.* Distribution /issue *8.* Exportation/Importation *9.* New application/infusion method 10.New anatomical site 11. New clinical indication
Provide a description of the novelty or new application to be implemented (include a description of the activity before the novelty is to be introduced):

1. Donor Selection:	
Type of Donation	*BTC*
	□ Autologous □ Allogeneic
	□ Living donation *□ Deceased donation* *□ Donation after brain death (DBD)* *□ Donation after circulatory death (DCD)*
	MAR
	□ non-partner □ partner
Provide a summary of the donor selection criteria	*□ Yes □ No* *If no, provide justification*
Does the donor criteria meet the EUBTCDs?	*□ Yes □ No* *If no, provide justification*
Copy of health and medical history questionnaire provided	*□ Yes □ No* *If no, provide justification*
Is the donation voluntary and unpaid	*Provide details:*
Provide a copy of the Informed consent form	
2. Donation / Collection / Procurement:	
Provide a summary of the donation / collection / procurement process, include the equipment / materials coming into contact with the BTC	*□ Yes □ No* *If no, provide justification*
Is the donation / collection / procurement center / organisation already authorised for the donation / collection / procurement of the BTC	*□ Yes □ No* *If yes, provide details:*
Are new facilities required for the donation / collection / procurement	*□ Yes □ No* *If yes, provide details:*
***Describe the storage conditions of the BTC at the collection / procurement facility and subsequent transport conditions to the* BE/TE**	*□ Yes □ No* *If no, provide justification*
Provide written agreements with any personnel, clinical team or third party procurement organisation involved in carrying out procurement as well as those collecting critical information used in donor selection	*□ Yes □ No* *If no, provide justification*
Material used to promote BTC donation	*Submit a copy of the material used to promote BTC donation (leaflets, web sites links…)*

3. ***Testing***	
Provide a summary of all donor / donation testing (e.g. infectious disease testing, ABO blood group)	*□ Yes □ No* *If no, provide justification*
Provide details on the laboratory performing the testing and the test kits used. Include a copy of the third party agreement with the laboratory, and the copy of the license/ accreditation of the laboratory	*□ Yes □ No* *If no, provide justification*
Provide a summary of the transport procedure to take the samples to the testing laboratory	*□ Yes □ No* *If no, provide justification*
Provide details on the type of tests used	*□ CE-marked □ In-house ones □Others* *Provide a copy of the authorisation if they are not CE-marked*
Are all the tests required by the EUBTCDs performed?	*□ Yes □ No* *If no, provide justification*
4. ***Processing***	
Provide a summary of the preparation process including those carried out by third parties, including control-sampling points	*□ Yes □ No*
Provide a summary / classification/ certification of environmental conditions under which the process will take place, including steps taken to minimise cross contamination	*If no, provide justification*
List tested parameters (CPPs), methods used and acceptance criteria (CQAs, KPIs)	*□ Yes □ No* *If no, provide justification*
If any part of the processing is sub-contracted, please provide details of the steps that are sub-contracted and the name and contact details of the third party	*□ Yes □ No* *If no, provide justification*
Provide a summary of the microbiological testing / QC testing	*□ Yes □ No* *If no, provide justification*
Provide details on the equipment or materials used to process the BTC	*□ Yes □ No* *If no, provide justification*
5. ***Storage***	
Provide a summary **of storage process / conditions / shelf life**	*□ Yes □ No* *If no, provide justification*
Provide details on the equipment/material used to store BTC	*□ Yes □ No* *If no, provide justification*
Provide a copy of the primary and secondary packaging	*□ Yes □ No* *If no, provide justification*

6. ***Transport and delivery***	
Provide a summary of the transport conditions	□ *Yes* □ *No* *If no, provide justification*
Describe the equipment/material used in the transport of the BTC	□ *Yes* □ *No* *If no, provide justification*
Provide a copy of the BTC labelling	□ *Yes* □ *No* *If no, provide justification*
7. ***Distribution / Issue***	
Provide a summary of the release / issue criteria.	□ *Yes* □ *No* *If no, provide justification*
Provide justification for release / issue criteria	□ *Yes* □ *No* *If no, provide justification*
8. ***Exportation/ Importation***	
Provide a summary of the exportation requirements	□ *Yes* □ *No* *If no, provide justification*
Provide a summary of* the importation *requirements	□ *Yes* □ *No* *If no, provide justification*
Does the importation novelty meet the EUBTCDs?	□ *Yes* □ *No* *If no, provide justification*
9. ***New application/infusion method***	
Provide a summary of the new application/infusion method	□ *Yes* □ *No* *If no, provide justification*
Provide details of new equipment requirements, if there are any	□ *Yes* □ *No* *If no, provide justification*
10. New Clinical Indication	
Describe the clinical indication	□ *Yes* □ *No* *If no, provide justification*
11. New Anatomical Site	
Describe the anatomical site	□ *Yes* □ *No* *If no, provide justification*

Module 3: Risk assessment

Select the risk level assigned after performing the EuroGTPII risk assessment and provide the completed EuroGTPII tool template	**The information below is required based on the indicated risk. To submit the required information proceed to module 4, 5 and 6 as appropriate.**
Negligible □	Quality SARE reporting Minimum clinical information
Low □	Quality Pre-clinical information SARE reporting Minimum clinical information CFUpP
Moderate □	Quality Pre-clinical information SARE reporting Minimum clinical information CFUpP CIP
High □	Quality Pre-clinical information SARE reporting Minimum clinical information CFUpP CIP Information on control treatment

Please, provide the name, qualification and institution/establishment/organisation of the people contributing to the risk assessment.

Name	**Qualification**	**Institution/establishment/organisation**

Module 4: Quality
Note: For BE/TE already authorised, only complete the section where the novelty is to be implemented. If this is a new application complete all sections

1.Donor selection	
Provide SOP for donor selection criteria	□ Yes □ No If no, justify
Provide donor selection policy	□ Yes □ No If no, justify
2.Donor/collection/procurement	
Provide SOP for collection / procurement	□ Yes □ No If no, justify
Provide validation report of the collection/procurement procedure	□ Yes □ No If no, justify
If any material/equipment used for collection/procurement is not single-use, provide the validation of the sterilisation procedure	□ Yes □ No If no, justify
3.Testing	
Provide SOP for donor/ donation testing	□ Yes □ No If no, justify
Provide SOP for transporting the samples to the lab	□ Yes □ No If no, justify
Provide validation of the testing kits	□ Yes □ No If no, justify
4.Processing	
Provide process flow diagram	□ Yes □ No If no, justify
Does the diagram point out the critical steps?	□ Yes □ No If no, justify
Has the validation, process validation, stability and evaluation reports been provided with the application?	□ Yes □ No If no, justify
Provide SOP for processing procedure	□ Yes □ No If no, justify
Provide SOP to minimise cross contamination	□ Yes □ No If no, justify
Provide SOP for assessing microbiological safety of the BTC	□ Yes □ No If no, justify
If sterilisation or pathogen reduction is used in the BTC, provide the validation information	□ Yes □ No If no, justify
Provide validation of the processing	□ Yes □ No If no, justify

Provide evaluation/ audit report of the third parties	□ Yes □ No If no, justify
5.Storage	
Provide SOP for storage process/ conditions/ shelf life	□ Yes □ No If no, justify
Provide evaluation / stability report	□ Yes □ No If no, justify
6.Transport and delivery	
Provide SOP for transport and delivery	□ Yes □ No If no, justify
Provide SOP for BTC labelling	□ Yes □ No If no, justify
Provide validation of the transport procedure	□ Yes □ No If no, justify
Provide stability report	□ Yes □ No If no, justify
7.Distribution/Issue	
Provide SOP for release/issue criteria	□ Yes □ No If no, justify
Provide validation of the new release/issue criteria	□ Yes □ No If no, justify
8.Exportation/Importation	
Provide SOP for exportation	□ Yes □ No If no, justify
Provide SOP for importation	□ Yes □ No If no, justify
9.New application/infusion method	
Provide SOP for new application/infusion method	□ Yes □ No If no, justify
If the new application/infusion method implies a new equipment, provide a validation report	□ Yes □ No If no, justify
10.New clinical indication	
Provide SOP for new clinical indication	□ Yes □ No If no, justify
11.New anatomical site	
Provide SOP for new anatomical site	□ Yes □ No If no, justify

Module 5: Pre-Clinical Studies

Provide the following Information	
In-vitro Studies	□ Yes □ No
In-vivo studies	□ Yes □ No If no, provide justification
Provide summary of study/studies performed **(Attach full study/studies report)**	
Relevant Bibliography	Description of literature search protocol provided: □ Yes □ No
	Literature search report provided: □ Yes □ No

Module 6: Clinical Information

Minimum Clinical Information to be provided	
BTC Characterisation	A clear characterisation and definition of the BTC under evaluation:
Key clinical benefits of the innovation, if applicable	
Alternative therapies or BTC, if any	
Clinical indications	Pathologies/conditions that can be treated or prevented with the BTC in question; Including code according to the International Classification of Diseases (ICD) (https://icd.who.int/en)
Novelty in clinical indication/target group	□ *Yes* □ *No*

The scientific rationale behind the proposition of a new clinical indication; and information on the earlier clinical indication	
Supplementary information – Clinical indications	
Potential contra-indications	
Level of risk as determined by EuroGTP II	Negligible, Low, Moderate, High
Risk assessment date	When was the risk assessment performed – Date (format example: DD/MM/YYYY)
Relevant Bibliography	(names of databases, search terms etc.), the literature search report, references
Other additional data	References to work of peers, technical reports, unpublished data etc.
Notify Library references	Relevant Notify Library Record ID(s)
Application/implantation methods	□ Infusion □ Application □ Surgery □ Laparoscopy □ Insemination □ Other(s)
Specific application/implantation methods	
Special skills or training required for application/ implantation of BTC	□ Yes □ No
Details of skills and training required	If yes, specify: ____ Training plan in place**:** □ Yes □ No
Application instructions, concentration(s) and dosage(s) of the BTC (as relevant)	
Immediate pre-application/ implantation preparation procedures	

Clinical Follow-Up Plan (CFUpP)	
Provide copy of CFUpP	
	Numerical value
Duration of clinical follow- up and justification for it	Numerical value (length of follow-up of each recipient in days, months or years)

Planned follow-up procedures	Description of e.g. tests, samples, imaging; including description of methodology for clinical data collection
Planned data consistency assessment and/or data analysis including biometrics, statistics	
Specific safety parameters defined for follow-up and data collection	□ Yes □ No
Detailed safety parameters	
Specific efficacy parameters defined for follow-up and data collection	□ Yes □ No
Detailed efficacy parameters	
Clinical follow-up results and conclusions	

Clinical Investigation Plan (CIP)	
Provide a copy of the CIP	
Objectives and purpose of the clinical investigation	
Number of BTC applications/recipients planned to be included in the clinical investigation; statistical methods and rationale used to determine the number of applications/ recipients needed	Numerical value:
Multicenter investigation	□ Yes □ No
List of centers and countries involved in the clinical investigation	
Inclusion criteria	
Exclusion criteria	
Control Treatment(Recommended particularly when risk level is high)	Control treatment used: □ Yes □ No
Details of control treatment (incl. randomisation, if applicable); Rationale of not using control treatment, if applicable	
Recruitment procedures and informed consent protocol for the recipients	Optional attachment (informed consent form)
Planned follow-up visits and procedures	Description of the sequence and details of all investigative procedures, including tests, samples, imaging etc.

Duration of the recipient participation	Numerical value (length of participation of each recipient in days, months or years)
Specific safety parameters defined for clinical investigation	□ Yes □ No
Detailed safety parameters	
Specific efficacy parameters defined for clinical investigation	□ Yes □ No
Detailed efficacy parameters	
Endpoints of the clinical investigation	
Methods for data collecting	E.g. review of medical records, registries, investigation report forms, patient reported outcome measures (e.g. questionnaires, diaries), samples, imaging; please specify
Statistical protocols, data handling, record keeping and methodology for data analysis	
Discontinuation/ termination criteria specified	□ Yes □ No
Specific discontinuation/termination criteria	
Good practices of clinical setting for BTC (adapted from GCP principles) will be followed in conducting the clinical investigation	□ Yes □ No
Independent Ethics Committee (IEC) decisions/opinions	Attachment
Patient insurance has been acquired or already exists for this clinical investigation	□ Yes □ No Optional attachment (proof of insurance)
Appendices e.g. **agreement between BE/TE and clinicians/institutions** • **CVs of Principal Investigators**	Attachment(s)
Expected date for final report of the clinical investigation	DD/MM/YYYY
Clinical investigation results and conclusions	Attachment

Appendix3 Template for PPD Assessment

Module 1: Applicant Information	
Applicant Information section completed appropriately	□ Yes □ No Date: DD/MM/YYYY
If applicant information completed appropriately continue to Module 2 BTC Novelty	
If the applicant information is not completed appropriately, contact applicant and request information is resubmitted.	
Resubmitted general information completed appropriately	□ Yes □ N/A Date: DD/MM/YYYY

<table>
<tr><th colspan="3">Module 2: BTC Novelty:</th></tr>
<tr><td colspan="3">Description of the BTC to which this preparation process relates</td></tr>
<tr><td rowspan="2">□ Blood and blood components
□ Tissues
□ Cells
□ MAR</td><td>Active Component:</td><td></td></tr>
<tr><td>Preparation Characteristic:</td><td></td></tr>
<tr><td>Has the BTC to which the novelty applies been clearly indicated?</td><td colspan="2">□ Yes □ No</td></tr>
<tr><td colspan="3">If the BTC information has not been appropriately indicated, contact applicant and request information is resubmitted.</td></tr>
<tr><td>Resubmitted information clearly indicates the BTC to which the novelty applies?</td><td colspan="2">□ Yes □ N/A</td></tr>
<tr><td>BTC information submitted:</td><td colspan="2"></td></tr>
<tr><td>Does the BTC require classification from an expert group?</td><td colspan="2">□ Yes □ No</td></tr>
<tr><td colspan="3">If yes, record result of classification details of expert group involved:
Assessors comments:</td></tr>
<tr><td colspan="3">If classification indicates that this BTC is considered to be under the remit of other legislation, inform the applicant and cease the PPA review.</td></tr>
<tr><td>Does this BTC support a new entry on the European Tissue and Cell Product Compendium / EDQM ‘Guide to the preparation, use and quality assurance of blood components’</td><td colspan="2">□ Yes □ No</td></tr>
<tr><td>If yes, confirm contact with Compendium / EDQM when assessment is complete</td><td colspan="2">Record date of contact</td></tr>
</table>

Evaluation of novelty as provided by applicant:

	Yes	No	N/A
A. Has this type of BTC previously been prepared and issued for clinical use by your establishment?			
	Yes	**No**	**N/A**
B. Will the starting material used to prepare this BTC be obtained from the same donor population previously used by your establishment for this type of BTC?			
	Yes	**No**	**N/A**
C. Will the starting material for this BTC be procured/collected using a procedure used previously by your establishment for this type of BTC?			
	Yes	**No**	**N/A**
D. Will this BTC be prepared by a procedure (processing/preparation, decontamination and preservation) used previously in your establishment for this type of BTC?			
	Yes	**No**	**N/A**
E. Will this BC be packaged and stored using a protocol and materials used previously in your establishment for this type of BTC?			
	Yes	**No**	**N/A**
F. Will this type of BTC provided by your establishment be applied/infused clinically using an application/infusion method used previously?			
	Yes	**No**	**N/A**
G. Has your establishment provided this type of BTC for a same clinical indication or applied/infused into a same anatomical site?			

Use the questions above to highlight areas that procedures may be changed as a result of novelty:
Assessors comments:

Are the activities selected by applicant to which novelty relates correct: □ Yes □ No

1. Donor Selection
2. Donation/Collection/ Procurement
3. Testing
4. Processing
5. Storage
6. Transport and delivery
7. Distribution /issue
8. Exportation/Importation
9. New application/infusion method
10. New anatomical site
11. New clinical indication

Description provided by applicant of novelty or new application (including description of the activity before the novelty is to be introduced:	
1. Donor Selection	
Type of Donation	**BTC**
	□ Autologous □ Allogeneic
	□ Living donation □ Deceased donation □ Donation after brain death (DBD) □ Donation after circulatory death (DCD)
	MAR
	□ non-partner □ partner
	Assessors Comments:
Donor selection criteria provided	□ Yes □ No Assessors Comments:
Does the donor selection criteria meet the EUBTCDs?	□ Yes □ No Assessors Comments:
Copy of health and medical history questionnaire provided	□ Yes □ No Assessors Comments:
Is the donation voluntary and unpaid	Assessors Comments:
Informed consent form provided	□ Yes □ No Assessors Comments:

2. Donation / Collection / Procurement	
	Assessors Comments:
Summary of the donation / collection / procurement process, including the equipment / materials coming into contact with the BTC, provided	□ Yes □ No Assessors Comments:
Information on whether the donation / collection / procurement center / organisation is already authorised for the donation / collection / procurement of the BTC, provided	□ Yes □ No Assessors Comments:
Are new facilities required for the donation / collection / procurement	□ Yes □ No Assessors Comments:
Storage conditions of the BTC at the collection / procurement facility and subsequent transport conditions to the BE/TE detailed	□ Yes □ No Assessors Comments:
Written agreements with any personnel, clinical team or third party procurement organisation involved in carrying out procurement as well as those collecting critical information used in donor selection provided	Provided: □ Yes □ No Assessors Comments:
Material used to promote BTC donation provided	□ Yes □ No Assessors Comments:
3. Testing	
	Assessors Comments:
Summary of all donor / donation testing (e.g. infectious disease testing, ABO blood count)	□ Yes □ No Assessors Comments:
Details on the laboratory performing the testing and the test kits used provided	□ Yes □ No Assessors Comments:
Copy of the third party agreement with the laboratory, and the copy of the license/ accreditation of the laboratory provided	□ Yes □ No Assessors Comments:

Summary of the transport procedure to take the samples to the testing laboratory provided	□ Yes □ No Assessors Comments:
Tests: CE-marked or in-house ones	Assessors Comments:
Are all tests required by the EUBTCDs performed?	□ Yes □ No Assessors Comments:

4. Processing	
	Assessors Comments:
Summary of the preparation process including those carried out by third parties, (control-sampling points) provided	□ Yes □ No Assessors Comments:
Summary / classification/ certification of environmental conditions under which the process will take place, including steps taken to minimise cross contamination provided	□ Yes □ No Assessors Comments:
Tested parameters (CPPs), methods used and acceptance criteria (CQAs, KPIs) listed	□ Yes □ No Assessors Comments:
Details of any processing that is sub-contracted, provided, including details of the steps that are sub-contracted and the name and contact details of the third party	□ Yes □ No Assessors Comments:
Summary of the microbiological testing / QC testing provided	□ Yes □ No Assessors Comments:
Details of the equipment or materials used to process the BTC provided	□ Yes □ No Assessors Comments:

5. Storage	
	Assessors Comments:
Summary of storage process / conditions / shelf life provided	□ Yes □ No Assessors Comments:
Details on the equipment/material used to store BTC provided	□ Yes □ No Assessors Comments:
Copy of the primary and secondary packaging provided	□ Yes □ No Assessors Comments:
6. Transport and Delivery	
	Assessors Comments:
Summary of the transport conditions provided	□ Yes □ No Assessors Comments:
Equipment/material used in the transport of the BTC described	□ Yes □ No Assessors Comments:
Copy of the BTC labelling provided	□ Yes □ No Assessors Comments:
7. Distribution / Issue	
	Assessors Comments:
Summary of the release / issue criteria provided	□ Yes □ No Assessors Comments:
Justification for release / issue criteria provided	□ Yes □ No Assessors Comments:

8. Exportation / Importation	
	Assessors Comments:
Summary of the exportation requirements provided	□ Yes □ No Assessors Comments:
Summary of the importation requirements provided	□ Yes □ No Assessors Comments:
Does the importation novelty meet the EUBTCDs	□ Yes □ No Assessors Comments:
9. New Application / Infusion Method	
	Assessors Comments:
Summary of the new application/infusion method	□ Yes □ No Assessors Comments:
Details of the new equipment used provided (if applicable)	□ Yes □ No Assessors Comments:
10. Clinical Indication	
	Assessors Comments:
Clinical indication description provided	□ Yes □ No Assessors Comments:
11. Anatomical Site	
	Assessors Comments:
Anatomical site description provided	□ Yes □ No Assessors Comments:

Module 3: Risk Assessment	
Risk Category Assigned by Applicant	□ High □ Moderate □ Low □ Negligible
Has a copy of the completed risk assessment template from EuroGTPII been provided?	□ Yes □ No
If no request a copy of the risk assessment before proceeding	
Is the CA in agreement with the risk category assigned by applicant	□ Yes □ No
Assessors comments in relation to final risk categorisation if not in agreement with applicant:	

If yes, continue with the assessment, if no, request applicant to reassess and resubmit the application with a revised appropriate risk assessment and the required associated information and documentation.

EuroGTPII	By the BE/TEp	Received
Negligible □	Application Information	□ Yes □ No
	BTC Novelty	□ Yes □ No
	Risk assessment	□ Yes □ No
	Quality*	□ Yes □ No
	SARE reporting	□ Yes □ No
	Clinical Information	
	- Minimal clinical information	□ Yes □ No
Low □	Application Information	□ Yes □ No
	BTC Novelty	□ Yes □ No
	Risk assessment	□ Yes □ No
	Quality*	□ Yes □ No
	SARE reporting	□ Yes □ No
	Clinical Information	
	- Minimal clinical information	□ Yes □ No
	- Clinical follow up plan	□ Yes □ No
Moderate □	Application Information	□ Yes □ No
	BTC Novelty	□ Yes □ No
	Risk assessment	□ Yes □ No
	Quality*	□ Yes □ No
	SARE reporting	□ Yes □ No
	Preclinical Studies	□ Yes □ No
	Clinical Information	
	- Minimal clinical information	□ Yes □ No
	- Clinical follow up plan	□ Yes □ No
	- Clinical investigation plan	□ Yes □ No

High □	Application Information	□ Yes □ No
	BTC Novelty	□ Yes □ No
	Risk assessment	□ Yes □ No
	Quality*	□ Yes □ No
	SARE reporting	□ Yes □ No
	Preclinical Studies	□ Yes □ No
	Clinical Information	
	- Minimal clinical information	□ Yes □ No
	- Clinical follow up plan	□ Yes □ No
	- Clinical investigation plan	□ Yes □ No
	- Comparison to standard therapy	□ Yes □ No

*relevant to the procedures that will be modified

Has the name, qualification and institution/establishment/organisation of the people contributing to the risk assessment been provided

□ Yes □ No

Module 4: Quality Management System	
1. **Donor Selection**	
	Assessors Comments:
SOP for donor selection criteria and donor selection policy provided	□ Yes □ No Assessors Comments:
2. **Donor/collection/procurement**	
SOP for collection / procurement provided	□ Yes □ No Assessors Comments:
Validation process of the collection/procurement procedure provided	□ Yes □ No Assessors Comments:
Validation of the sterilisation procedure where material/equipment used for collection/procurement are not single-use, provided	□ Yes □ No Assessors Comments:
3. **Testing**	
SOP for donor/ donation testing provided	□ Yes □ No Assessors Comments:
SOP for transporting the samples to the lab provided	□ Yes □ No Assessors Comments:
Validation of test kit provided	□ Yes □ No Assessors Comments:
4. **Processing**	
Process flow diagram provided	□ Yes □ No Assessors Comments:
Does the diagram point out the critical steps?	□ Yes □ No Assessors Comments:
Validation, process validation, stability and evaluation reports provided	□ Yes □ No Assessors Comments:

SOP for processing procedure provided	□ Yes □ No Assessors Comments:
SOP which details activities to minimise cross contamination provided	□ Yes □ No Assessors Comments:
SOP for assessing microbiological safety of the BTC provided	□ Yes □ No Assessors Comments:
Sterilisation or pathogen reduction validation information provided	□ Yes □ No Assessors Comments:
Validation of the processing provided	□ Yes □ No Assessors Comments:
Evaluation/ audit report of the third parties provided	□ Yes □ No Assessors Comments:
5. **Storage**	
SOP for storage process/ conditions/ shelf life provided	□ Yes □ No Assessors Comments:
Evaluation / stability report provided	□ Yes □ No Assessors Comments:
6. **Transport and delivery**	
SOP for transport and delivery provided	□ Yes □ No Assessors Comments:
SOP for BTC labelling provided	□ Yes □ No Assessors Comments:
Validation of the transport procedure provided	□ Yes □ No Assessors Comments:

Stability report provided	□ Yes □ No Assessors Comments:
7. **Distribution/Issue**	
SOP for release/issue criteria provided	□ Yes □ No Assessors Comments:
Validation of the new release/issue criteria provided	□ Yes □ No Assessors Comments:
8. **Exportation/Importation**	
SOP for exportation provided	□ Yes □ No Assessors Comments:
SOP for importation provided	□ Yes □ No Assessors Comments:
9. **New application/infusion method**	
SOP for new application/infusion method provided	□ Yes □ No Assessors Comments:
Validation report provided if new equipment required for new application/infusion method	□ Yes □ No Assessors Comments:
10. **New clinical indication**	
SOP for new clinical indication provided	□ Yes □ No Assessors Comments:
11. **New anatomical site**	
SOP for new anatomical site provided	□ Yes □ No Assessors Comments:

Module 5: Pre-Clinical Studies	
In- vitro Studies performed	□ Yes □ No Assessors Comments:
Full study / studies report provided	□ Yes □ No Assessors Comments:
Relevant Literature review / Bibliography for *In- vitro* studies	Literature search protocolacceptable: □ Yes □ No Assessors Comments: Literature search report acceptable: □ Yes □ No Relevant bibliography provided: □ Yes □ No Assessors Comments:
In- vivo studies performed	□ Yes □ No Assessors Comments:
Full study / studies report provided	□ Yes □ No Assessors Comments:
Relevant Literature review / Bibliography for *In- vivo* studies	Literature search protocol acceptable: □ Yes □ No Assessors Comments: Literature search report acceptable: □ Yes □ No Relevant bibliography provided: □ Yes □ No Assessors Comments:

Module 6: Clinical Information

Minimum Clinical Information	
	Assessors Comments:
BTC Characterisation	Assessors Comments:
Key clinical benefits of the innovation, if applicable	There is clinical justification for the innovation: □ Yes □ No Assessors Comments:
Alternative therapies or BTC, if any	Assessors Comments:
Clinical indications	Assessors Comments:
Novelty in clinical indication/target group	Assessors Comments:
The scientific rationale behind the proposition of a new clinical indication; and information on the earlier clinical indication	Scientific rationale is acceptable: □ Yes □ No Assessors Comments:
Supplementary information – Clinical indications	Assessors Comments:
Potential contra-indications	Assessors Comments:
Level of risk	Risk assessment has been performed correctly, takes into account all relevant aspects and is acceptable: □ Yes □ No Assessors Comments:
Risk assessment date	When was the risk assessment performed – Date (format: DD/MM/YYYY)

Relevant Bibliography	Literature search protocol acceptable: □ Yes □ No Assessors Comments: Literature search report acceptable: □ Yes □ No Relevant bibliography provided: □ Yes □ No Assessors Comments:
Other additional data	Additional data is acceptable: □ Yes □ No Assessors Comments:
Notify Library references	Assessors Comments:
Application/implant methods	Assessors Comments:
Specific application/implant methods	Assessors Comments:
Special skills or training required for application/administration of BTC	Assessors Comments:
Details of skills and training required	Training plan and/or other actions in place: □ Yes □ No Assessors Comments:
Application instructions, concentration(s) and dosage(s) of the BTC (as relevant)	Assessors Comments:
Immediate pre-application/ implantation preparation procedures	Assessors Comments:

Clinical Follow-Up Plan (CFUpP)	
Clinical Follow up plan attached	Assessors Comments:
Number of BTC applications/recipients planned to be included in the clinical follow-up; statistical methods and rationale used to determine the number of applications/recipients needed	Number of applications/recipients for follow-up justified and acceptable: □ Yes □ No Assessors Comments:
Duration of clinical follow- up and justification for it	Duration of clinical follow- up is justified and acceptable: □ Yes □ No Assessors Comments:
Planned follow-up procedures	The recipient monitoring/visits is sufficient: □ Yes □ No Relevant and sufficient targets are monitored: □ Yes □ No Procedure of collection, storage and future use of biological samples (if applicable) is defined and acceptable: □ Yes □ No Assessors Comments:
Planned data consistency assessment and/or data analysis including biometrics, statistics	Plan for data consistency assessment and/or data analysis is sufficient and acceptable: □ Yes □ No Assessors Comments:
Specific safety parameters defined for follow-up and data collection	Assessors Comments:
Detailed safety parameters	Relevant and adequate safety aspects will be followed up and data collected: □ Yes □ No Assessors Comments:
Specific efficacy parameters defined for follow-up and data collection	Assessors Comments:
Detailed efficacy parameters	Relevant and adequate efficacy aspects will be followed up and data collected: □ Yes □ No Assessors Comments:
Clinical follow-up results and conclusions	Clinical follow-up results and conclusions are justified and acceptable: □ Yes □ No Assessors Comments:

Clinical Investigation Plan (CIP)	
Copy of the CIP attached	Assessors Comments:
Objectives and purpose of the clinical investigation	Objectives and purpose of the clinical investigation are justified and acceptable: □ Yes □ No Assessors Comments:
Number of BTC applications/recipients planned to be included in the clinical investigation; statistical methods and rationale used to determine the number of applications/ recipients needed	Number of applications/ recipients for follow-up justified and acceptable: □ Yes □ No Assessors Comments:
Multicenter investigation	Assessors Comments:
List of centers and countries involved in the clinical investigation	Assessors Comments:
Inclusion criteria	The inclusion criteria are defined and acceptable: □ Yes □ No
Exclusion criteria	The exclusion criteria are defined and acceptable: □ Yes □ No
Control treatment (Recommended particularly when risk level is high)	Assessors Comments:
Details of control treatment (incl. randomisation, if applicable); Rationale of not using control treatment, if applicable	The use of control treatment or not using control treatment is justified and acceptable: □ Yes □ No Randomisation procedure acceptable: □ Yes □ No
Recruitment procedures and informed consent protocol for the recipients	Recruitment procedure acceptable: □ Yes □ No Information about the clinical investigation provided to recipients:□ Yes □ No Informed consent procedure acceptable:□ Yes □ No
Planned follow-up visits and procedures	The frequency of recipient monitoring/visits is sufficient: □ Yes □ No Relevant targets are monitored: □ Yes □ No Procedure of collection, storage and future use of biological samples (if applicable) is defined and acceptable: □ Yes □ No

Duration of the recipient participation	Duration of recipient participation is justified and acceptable: □ Yes □ No Assessors Comments:
Specific safety parameters defined for clinical investigation	Assessors Comments:
Detailed safety parameters	Relevant safety aspects will be followed up and data collected: □ Yes □ No
Specific efficacy parameters defined for clinical investigation	Assessors Comments:
Detailed efficacy parameters	Relevant efficacy aspects will be followed up and data collected: □ Yes □ No
Endpoints of the clinical investigation	Endpoints are justified and acceptable: □ Yes □ No Assessors Comments:
Methods for data collecting	Data collecting adequately described and acceptable: □ Yes □ No Assessors Comments:
Statistical protocols, data handling, record keeping and methodology for data analysis	Data analysis plan acceptable: □ Yes □ No Data storage adequately described and acceptable: □ Yes □ No Assessors Comments:
Discontinuation/ termination criteria specified	Assessors Comments:
Specific discontinuation/ termination criteria	Discontinuation/ termination criteria acceptable: □ Yes □ No
Good practices of clinical setting for BTC [adapted from GCP principles] will be followed in conducting the clinical investigation	Assessors Comments:
Independent Ethics Committee (IEC) decisions/opinions	Favourable decision/opinion exists: □ Yes □ No Assessors Comments:
Patient insurance has been acquired or already exists for this clinical investigation	Adequate insurance exists:□ Yes □ No Assessors Comments:

Appendices e.g. **agreement between BE/TE and clinicians/institutions** • **CVs of Principal Investigators**	Appendices adequate and acceptable: □ Yes □ No Assessors Comments:
Expected date for final report of the clinical investigation	Assessors Comments:
Clinical investigation results and conclusions	Clinical investigation results and conclusions are justified and acceptable: □ Yes □ No Assessors Comments:

Review and Evaluation Outcome:		
Inspection performed:	If yes: □ On-site □ Remote/virtual □ Desk-based Date of inspection:	
Inspection outcome:		
Authorisation Decision:		
Summary of application review based on risk level assigned		
Outcome of the risk analysis as performed by the applicant	Review Outcome	Authorisation to be granted
□ Negligible Risk	□ Complete set of data provided □ Benefit risk quantified and acceptable □ Insufficient data – benefit risk not assessable or does not justify risk	□ Full authorisation □ Refused
Assessors Comments:		

Summary of application review:		
Outcome of the risk analysis as performed by the applicant	Review outcome	Authorisation to be granted
□ Low Risk	□ Benefit risk estimated and expected benefit justifies expected risk □ Insufficient data – benefit risk not assessable or does not justify risk	□ Conditional authorisation □ Refused
□ Moderate Risk □ High Risk	□ Benefit risk estimated and expected benefit justifies expected risk □ Insufficient data – benefit risk not assessable or does not justify risk	□ Conditional authorisation □ Refused
Assessors Comments: If conditional authorisation granted, record details of number of patients, cases, centers where the BTC can be used, or other limitations.		
If conditional authorisation is granted, further information is required to be submitted in order to assess whether a full authorisation can be granted. The results and conclusions in relation to the CFUpP must be provided in the case of low risk applications, and the results and conclusions in relation to the CFUpP and CIP must be provided in the case of moderate and high risk applications.		
Estimated time for results and conclusions of CFUpP:		
Assessors Comments:		
Estimated time for results and conclusion CIP:		
Assessors Comments:		

Risk	Review outcome	Authorisation to be granted
□ Low Risk	□ Benefit risk estimated and expected benefit justifies expected risk □ Safety and efficacy demonstrated following submission of CFUpP □ Insufficient data – benefit risk ratio not assessable or does not justify risk	□ Conditional authorisation □ Full authorisation □ Refused □ Withdrawal
□ Moderate Risk □ High Risk	□ Benefit risk estimated and expected benefit justifies expected risk □ Safety and efficacy demonstrated following submission of CFUpP and CIP □ Insufficient data – benefit risk ratio not assessable or does not justify risk	□ Conditional authorisation □ Full authorisation □ Refused □ Withdrawal

Inspectors / Assessors who performed review:	
Name:	**Role:**

Appendix 4 Equivalences of the Overall Guideline and the Database

The following chart provides a comparison between the sections described in the Overall Guideline to authorisation on preparation process in BTC and the 'Framework for an electronically supported authorisation process' (Deliverable 9.2). The different information included in each of the modules is detailed.

WP5: Overall Guideline	WP9: Database
Module 1: Administrative Information – *BE/TE* data – Data of the responsible person for the PPD	Module 1: Administrative Information – Applicant information – BTC
Modules 2 and 3: Novelty and risk assessment – Description of BTC – Novelty Questions – Activity information – Risk Assessment	Module 2: Overview and summaries – Risk analysis – Quality overall summary – Non-clinical study reports overall summary – Clinical study reports overall summary
Module 4: Quality – Updated SOPs – Validation	Module 3: Quality – Activity information – SOPs – Validation
Module 5: Preclinical studies – *In-vitro/In-vivo* studies – Performed studies – Bibliography	Module 4: Non-clinical study reports – Non-clinical studies and related information – Bibliography – Reports
Module 6: Clinical Information – General clinical information – Clinical indication – CIP – CFUpP	Module 5: Clinical study reports – Clinical studies and related information – Bibliography – Efficacy reports – Safety reports – Other reports

Appendix 5 Acronyms

BE	Blood Establishment
BTC	Blood Tissue and Cell
CA	Competent Authority
CFUpP	Clinical Follow-Up Plan
CIP	Clinical Investigation Plan
CPP	Critical Processing Parameters
CQA	Critical Quality Attributes
DBD	Donation after Brain Death
DCD	Donation after Circulatory Death
ECAS	European Commission Authentication Service
EDQM	European Directorate of Quality of Medicines
EU	European Union
EUBD	European Blood Directive
EUBTCD	European Blood Tissues and Cells Directive
EuroGTP	European Good Tissue Practices
EUTCD	European Tissues and Cell Directive
GAPP	Facilitating the Authorisation of Preparation Process for Blood and Tissues and Cells
H	High
ICD	International Classification of Diseases
IEC	Independent Ethics Committee
KPI	Key Performance Indicator
L	Low
M	Moderate
MAR	Medically Assisted Reproduction
MS	Member State
N	Negligible
PPA	Preparation Process Authorisation
PPD	Preparation Process Dossier

SOP	Standard Operating Procedure
TC	Tissues and Cells
TE	Tissue and Cell Establishment
VISTART	Vigilance and Inspection for the Safety of Transfusion Assisted Reproduction and Transplantation

Appendix 6 Glossary

Acceptance criteria: Requirements needed to meet the relevant quality and safety standards in order to ensure an acceptable final product for human application. (EDQM T&C).

Accreditation: An attestation by a national accreditation body that a conformity assessment body meets the requirements set by harmonised standards and, where applicable, any additional requirements including those set out in relevant sectoral schemes, to carry out a specific conformity assessment activity (Regulation (EC) No 765/2008)

Audit: Periodic, independent and documented examination and verification of activities, records, processes and other elements of a quality system to determine their conformity with specific internal or external requirements. They may be conducted by professional peers, internal quality system auditors or auditors from certification or accreditation bodies. (EDQM T&C).

Applicants: European Blood/Tissue Establishments (BE/TE) that request Competent Authorities for authorisation for the clinical application of blood, tissues or cells (BTC).

Assisted reproductive technology: Means all treatments or procedures that include the in vitro handling of human oocytes, spermatozoa or embryos for establishing a pregnancy. This includes, but is not limited to, intra-uterine insemination, in vitro fertilisation, intracytoplasmic sperm injection, embryo transfer, gamete, germinal tissue and embryo cryopreservation, oocyte and embryo donation and gestational surrogacy (EDQM T&C).

Banking: Processing, preservation, storage and distribution of tissues and cells for human application or other purposes, including research and training. (EDQM T&C).

Benefit risk-analysis: For the purposes of this document this term refers to the consideration of whether the risks associated with the application of a BTC product, processed or applied in a novel way, are justified by the benefits for the patient upon application of the BTC product. Mosby's Medical Dictionary, 9th edition, © 2009, Elsevier

Blood: Whole blood collected from a donor and processed either for transfusion or for further manufacturing.

Blood component: Therapeutic components of blood (red cells, white cells, platelets, plasma) that can be prepared by centrifugation, filtration and freezing using conventional methodologies in blood establishment (EDQM Blood)

Blood establishment: Any structure or body that is responsible for any aspect of the collection and testing of human blood or blood components, whatever their intended purpose, and their processing, storage and distribution if intended for transfusion. This does not include hospital blood banks. (EDQM Blood)

Blood product: Any therapeutic product derived from human blood or plasma. (EDQM Blood)

Cells: The smallest transplantable and functional unit of living organisms.

Clinical benefit: The positive impact of (a) BTC therapy(ies) on the health and quality of life of an individual, expressed in terms of a meaningful, measurable, recipient-relevant clinical outcome(s), including outcome(s) related to diagnosis. (GAPP Technical Annex 3)

Clinical data: Information concerning safety or efficacy that is generated from the use of a BTC and is sourced from the following: clinical investigation(s) of the BTC concerned; clinical investigation(s) or other studies reported in scientific literature of the BTC in question; reports published in peer reviewed scientific literature on other clinical experience of the BTC in question; clinically relevant information coming from post authorisation surveillance. (GAPP Technical Annex 3)

Clinical evaluation: Clinical follow-up studies for monitoring predefined clinical outcome indicators to evaluate quality, safety and effectiveness/efficacy of BTC for a defined number of patients. (adapted from EDQM T&C)

Clinical Investigation Plan (CIP): A document that describes the rationale, objectives, design, methodology, monitoring, statistical considerations, organisation and conduct of a clinical investigation, prepared by the applicant(s) in the context of the authorisation request for clinical use of novel BTC therapies/BTC resulting from novel preparation process. (GAPP Technical Annex 3).

Clinical Follow-up Plan (CFUpP): The plan for monitoring the novel BTC recipient for a given time after clinical application/administration; may comprise of medical visits, tests, diagnostic procedures, samples etc. (GAPP Technical Annex 3)

CE-marked kit: Test kit marked by a manufacturer to indicate that the test kit is in conformity with the applicable requirements set out in Regulation (EU) 2017/746 on in vitro medical devices and other applicable Union harmonisation legislation providing for its affixing (modified from Regulation (EU) 2017/746)

Clinical indication: Medical reason that justifies the human use of a BTC.

Competent Authority: Organisation(s) designated by an EU Member State as responsible for implementing the requirements of the EUBTCDs. (Adapted from EuroGTPII).

Cryopreservation (for tissues and cells): Preservation and storage of viable tissues and cells (including gametes and embryos) to preserve viability, either by freezing or vitrification, or alternatively (to extend their viable life) by low-temperature storage. (EuroGTP II Guide).

Cryopreservation (for blood): Prolongation of the storage life of blood components by freezing.

Critical process parameter (CPP): A process parameter whose variability has an impact on a critical quality attribute and which therefore should be monitored and controlled to ensure the process produces the desired quality (Directive (EU) 2016/1214 Art. 1, GPG Blood)

Deceased donor: A person declared to be dead according to established medical criteria and from whom cells, tissues and organs have been recovered for the purpose of human application (EuroGTP II Guide)

Distribution (for T&C): The transportation and delivery of cells or tissues intended for human application (EUTCDs).

Distribution (for blood): The act of delivery to other blood establishments, hospital blood banks (EUBDs).

Donation (the process of): Donating human blood, tissues or cells intended for transfusion / human application (adapted from Directive 2004/23/EC)

Donation (types of biological material): The blood, tissues, and cells collected from the donors

Donor: A person in normal health with a good medical history who voluntarily gives blood or blood components for therapeutic use / every human source, whether living or deceased, of human cells or tissues (EDQM Blood and ETCD).

Donor Evaluation: The procedure for determining the suitability of an individual, living or deceased, as a donor of blood, cells or tissues (adapted from EDQM T&C).

Efficacy: Presence of desired (clinical) effects/patient outcomes depending on the mode of action of the BTC (GAPP Technical Annex 3)

Ethics Committee: An independent body established in a Member State in accordance with the law of that Member State and empowered to give opinions for the purposes of this Regulation, taking into account the views of laypersons, in particular patients or patients' organisations (EuroGTP II Guide)

Export: Act of transporting a BTC intended for human application to a third country outside the Union where it is to be processed further or used directly (adapted from EDQM T&C).

Follow-up: Subsequent evaluation of the health of a recipient for the purpose of monitoring the results of the BTC application, maintaining care and initiating post-application interventions. (GAPP Technical Annex 3)

Import: In this context, the act of bringing BTC into one country from another third one outside the Union for the purpose of human application or further processing (Adapted from EDQM T&C).

Informed consent: A person's voluntary agreement, based upon adequate knowledge and understanding of relevant information, to donate, to participate in research or to undergo a diagnostic, therapeutic or preventive procedure(EDQM T&C).

Issue: The provision of blood or blood components by a blood establishment or a hospital blood bank for transfusion to a recipient (EDQM Blood)

Kit: A set of components that are packaged together and intended to be used to perform a specific in vitro diagnostic, or a part thereof (Regulation (EU) 2017/746)

Medical assisted reproductive (MAR): Reproduction brought about through various interventions, procedures, surgeries and technologies to treat different forms of fertility impairment and infertility. These include ovulation induction, ovarian stimulation, ovulation triggering, all ART procedures, uterine transplantation and intra-uterine, intracervical and intravaginal insemination with semen of husband/partner or donor.

Microbiological quality: Fulfilment of a specific set of microbiological standards characteristics and criteria. Microbiological quality may also be seen as an indicator of the microbiological safety of the BTC. (GAPP Technical Annex 2. Adapted from EDQM T&C)

Microbiological safety: Approach to minimise the risk of contamination by viable microorganisms or micro-organism derived toxic substances. Microbiological safety of BTC results from the management of donor selection, procurement of BTC, testing and the preparation processes. (GAPP Technical Annex 2Adapted from EDQM T&C)

National accreditation body: The sole body in a Member State that performs accreditation with authority derived from the State (Regulation (EC) No 765/2008)

New anatomical site: The use of the BTC in a location on or within the recipient that is different to the standardised one.

Non-compliance: Failure to comply with accepted standards, requirements, rules or laws. (EDQM T&C).

Novelty: Any change that might affect the quality and/or the safety of the blood, tissues and cells and/or the safety of recipients'. This change includes a new BTC, a new procedure designed by the BE/TE, a new procedure adopted from another centre that has shown scientific evidence or the application of the BTC to treat a new clinical indication

Packaging: Including primary and secondary packaging, aims to protect tissues and cells and to present them to the operator (starting or in-process packaging) or to the clinical user (final packaging) in a suitable manner (EDQM T&C).

Partner donation: The donation of reproductive cells between a man and a woman who declare that they have an intimate physical relationship (Directive 2006/17/EC)

Pathogen reduction technologies: Procedures that irreversibly impede proliferation of pathogens in BTC, either by removal or inactivation with physical and/or chemical methods (EDQM Blood)

Procedure: A procedure controls a distinct process or activity, including the associated inputs and outputs. A series of tasks usually performed by one person according to instructions. (EDQM Blood)

Process: A set of related tasks and activities that accomplish a work goal. (EDQM Blood)

Processing (for blood): Any step in the preparation of a blood component that is carried out between the collection of blood and the issuing of a blood component. (EDQM Blood)

Processing (for tissues and cells): All operations involved in the preparation, manipulation, preservation and packaging of cells or tissues intended for human applications

Procurement: A process by which blood or blood components are made available (Directive 2004/33/EC)

Procurement (for tissues and cells): The procedure of removing cells, tissues or organs from a donor for the purpose of transplantation

Quality: As part of validation, means the action of verifying that any personnel, premises, equipment or material works correctly and delivers the expected results (Directive 2005/62/EC)

Quality System: The organisational structure, defined responsibilities, procedures, processes, and resources for implementing quality management and includes all activities which contribute to quality, directly or indirectly (Directives 2005/62/EC, 2006/17/EC)

Recipient: Person to whom human BTC are applied. (GAPP Technical Annex 3)

Reproductive cells: All tissues and cells intended to be used for the purpose of medically assisted reproduction (adapted from Directive 2006/17/EC)

Risk assessment: Identification of potential hazards with an estimation of the likelihood that they will cause harm and of the severity of the harm should it occur (EuroGTP II).

Safety: relative risk: proportional difference from a suggested baseline value (EuroGTP II)

Standard: The requirements that serve as the basis for comparison (Directive 2005/62/EC)

Significant change: Change that could significantly affect the quality and/or the safety of the BTC, or the safety of recipients and that is assessed as moderate or high risk. A significant change will have been identified through initial identification as a novelty and the subsequent risk assessment process described in EuroGTPII.

Standard: The requirements that serve as the basis for comparison. (EDQM Blood)

Standard operating procedures (SOPs): Detailed written procedures that give direction for performing certain operations. (EDQM Blood)

Storage (for blood): Maintaining the product under appropriate controlled conditions until distribution or issue(EDQM Blood)

Surveillance: Systematic and continuous collection, analysis, and interpretation of data, closely integrated with the timely and coherent dissemination of the results and assessment to those who have the right to know so that action can be taken. (EDQM Blood)

Traceability (for blood): The ability to trace each individual unit of blood or blood component derived thereof from the donor to its final destination, whether this is a recipient, a manufacturer of medicinal products or disposal, and vice versa. (EDQM Blood)

Testing: investigations performed on either donor or donation sample to determine any infectious disease risk associated with the donation (GAPP Technical Annex 2).

Third countries: Countries that are not members of the EU

Tissue: Anatomical parts of the human body composed of different types of cells connected to each other by a connective frame. Tissue are non-vascularized. Thus, they can be stored and they do not need any revascularization step to be grafted, transplanted, or applied.

Tissue Establishment: A tissue bank or a cell therapy unit or other unit of a hospital or another body where activities of processing, preservation, storage or distribution of human tissues and cells are undertaken. It may also be responsible for procurement or testing of tissues and cells

Sterilisation: Any process that eliminates or inactivates transmissible infectious agents (pathogens) containing nucleic acids, e.g. vegetative and spore forms of bacteria and fungi, parasites or viruses, present on a surface, in a fluid, in medication or in a compound such as biological culture media. Sterilisation can be achieved by applying the proper combinations or conditions of heat, chemicals, irradiation, high pressure and filtration. (EDQM T&C)

Validation: Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes; a process is validated to evaluate the performance of a system with regard to its effectiveness based on intended use. This evidence may include laboratory assessment of test kit performance. In the context of this document, the term ‘evaluation’ of test or method performance, can be considered to be part/all of any ‘validation’ (GAPP Technical Annex 2. Modified from Directive 2006/17/EC)

Validation plan: A document describing the activities to be performed in a validation, including the acceptance criteria for the approval of a process or method for routine use (GAPP Technical Annex 2. Adapted from WHO guidelines on transfer of technology in pharmaceutical manufacturing)

Validation report: A document in which the records, results and evaluation of a completed validation program are assembled and summarised (GAPP Technical Annex 2. Adapted from WHO guidelines on transfer of technology in pharmaceutical manufacturing)

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Technical Annex I to overall guidance: Evaluation and validation of the security and quality of changes to and innovation of Preparation Processes.

FACILITATING THE AUTHORISATION OF PREPARATION PROCESS FOR BLOOD, TISSUES AND CELLS

TECHNICAL ANNEX I TO OVERALL GUIDANCE: AUTHORISATION OF CHANGES IN DONATION, PROCUREMENT AND COLLECTION, PROCESSING, PRESERVATION, STORAGE AND DISTRIBUTION (INCLUDING LABELLING AND PACKAGE INSERTS)

1 Introduction

This document, Technical Annex I, extends the General Guidance to Preparation Process Authorisation (PPA) by providing recommendations to Competent Authorities for the evaluation of the safety and quality of preparation processes (PP) to be authorised. It provides guidance to Competent Authorities on how to assess the preparation process mainly if the process is innovative or if it is significantly changed.

Technical Annex I addresses the methods and criteria to be used in the authorisation of ***novel*** preparation processes, or ***changes*** to existing PP, in donation, procurement and collection, processing, preservation, storage and distribution (including labelling and packaging) and issuing in the four fields of Blood (B), Tissues and Cells (T&C), Haematopoietic Stem Cell Therapy (HSC) and Medically Assisted Reproduction (MAR).

Where questions of microbiological safety and testing are raised, Annex I refers to Annex II, which provides detailed recommendations. Where clinical evaluation is recommended, Annex I refers to Annex III, which provides detailed recommendations for clinical follow-up and clinical investigation.

The quality and safety of Blood, Tissues & Cells (BTC) intended for human application has a critical impact on patients. PPA are, with the exception of MAR where the intention is to facilitate the creation of a human life, conditioned by the quality and safety of the final products they prepare.

The evaluation of a preparation process will be based on the appraisal of its critical processing parameters (CPPs) and, where applicable, on the identified critical quality attributes (CQAs) of the products it prepares, again with the exception of MAR where it is nearly impossible to define the quality of reproductive tissues and cells and where Key Process Indicators (KPIs) are proposed instead[123]. These recommendations provide guidance on how to ensure these CQAs (KPIs) and CPPs are met through in vitro studies, process validation and clinical investigation and clinical follow up.

For a novel PP, it will be necessary to define the specific CQAs, or KPIs, and CPPs to be examined to determine the quality and safety of the PP and the products they prepare. These should be described by the applicant and assessed by the CA.

For the four fields covered by GAPP Appendix A to this Annex identifies:

- The existing types of BTC
- Known preparation processes
- Critical quality attributes
- Critical processing parameters
- +/- The expected validation or justification of the change or novelty following the result of the risk assessment

The following sections provide a general procedure for assessing a preparation process dossier focusing on how the innovation or the changes of the process may affect quality and safety, followed by detailed recommendations for each specific field.

2 Blood[a] - Specific aspects of preparation process authorisation

Blood and blood components are resulting from processes that are subject to change.

Changes areimplemented to improve the quality, safety or process efficiency in order to provide better protection to the donor and/or the recipient in the most efficient way. Changes may concern the process of collection, processing, transportation, additional transformation and storage as well as the medical devices and additives solutions like anticoagulants or storage solution used during all those steps.

The purpose of the authorisation of blood components is to assess the impact on the quality, safety, and if required the efficacy, of the implement change. This process of authorization is not intended to authorize a new medical device as this falls under the MDR2017/745 CE regulation.

The level of evaluation depends on the criticality of the impact and the benefit / risk ratio for patients, and potentially for blood donors, as well as on the change in respect to the existing preparation process of blood components listed in blood section of Appendix A.

Data-driven assessment of blood and blood components authorisation requests is typically based on complete data sets describing in detail preparation process procedures (e.g. flow diagram of donation, procurement, processing, storage and distribution of blood components) and on complete data sets describing the quality of the blood component until the expiry date.

The Preparation Process Authorization (PPA) procedure may consider, depending on member state legislation, data derived from clinical studies performed in preparation of the approval request for blood and blood components and/or clinical data derived from scientific literature. Availability of efficacy results about recipients treated with blood and blood component, resulting from novel Preparation Process, can represent additional information about the desired /proven effectiveness in terms of efficacy of the novel preparation process.

Risk-based decision-making by the competent authority involves an objective comparison of risks and benefits of the blood and blood components. An approval will be granted once the benefit-risk ratio as assessed on the evaluation of the submitted datasets indicates that the benefit justifies the risk.

Guidance on the assessment of methods to demonstrate achievement/maintenance of the critical characteristics/properties for each type of blood and blood components, in particular where changes are proposed/implemented in one of the preparation steps, follows. The guidance will take into account the degree of risk to the patient from the blood and blood components based on parameters such as historical data, degree of change in processing or testing.

[a] The mention of "blood" in this document refers to blood and its components intended for transfusion

2.1 Steps a Competent Authority may follow in processing a preparation process dossier

©	
1	**Assess changes regarding donation, collection and procurement and confirm conformity to GPGs and GCPs**
	• Control ethical requirement (informed consent, unpaid donation) • Verify type of donation (autologous or allogenic): allogenic transfusionentails risks of disease transmission that are absent in case of autologous transfusion • Evaluate the donor selection process: ▪ Is the extent of the information investigated sufficient to be complete (medical record, next of kin or donor risk assessment interview; general practitioner interview, specific file and previous results according to medical history? ▪ Are the eligibility criteria consistent with the methods and controls set during the process?
2	**Assess the specification for the product (critical quality attributes), the process (critical control parameters)and the relevant quality controls**
	• The Applicant should provide a written specification including: ▪ References to the research papers from which the specification is derived ▪ Expected characteristics (refer to Appendix A) ▪ Testing characteristics ([blood] grouping, microbiology etc.) Refert to Appendix A ▪ Assessment that the product meets specification before release ▪ Additives and all product packaging in particular primary packaging used from collection to distribution ▪ Equipment specification • Evaluate if the preparation process includes the following: ▪ Main steps of the preparation process ▪ Critical process parameters identified and ranges included; these should be justified by validation or operational qualification ▪ Monitoring of process parameters: are any steps included where quality control samples are taken and aligned with the list of quality control tests? ▪ Attached SOP ▪ Description of environmental conditions: are they duly monitored and consistent with the procedure (open vs close system)? ▪ Specifications regarding reagents: - Are they in contact with the tissue and packaging (in particular primary packaging) used from procurement to distribution duly listed? - Do they comply with a standard that minimises risk to the quality or safety of the processed product? - Are they CE marked vs appropriately validated? ▪ Qualification of the equipment: are specifications respected? ▪ Validation report attached to the PPD ▪ Optimization of the CPPs and, where necessary, tolerance levels. The rationale for the specified CPPs should be explained.
3	**Assess product/process evaluation protocol**
	• The protocol should clearly describe the following: ▪ Donor safety (if applicable) reporting any adverse incidents during collection ▪ Collection ▪ Processing ▪ How quality controls will be established and monitored

	▪ Clinical application: - Patient population to be transfused(e.g. age, indication for treatment, previous/concomitant therapies) - Method for monitoring the efficacy and patients' safety: standard medical practice, haemovigilance program (donor and patients), data collection in a scientific registry, clinical study (in this case the Medical/Ethical Committee approval might be needed) - Assessment of patient outcome. • Verify that GCP must be clearly adhered to • Verify IEB approval • Authorise the Clinical Investigation or verify clinical investigation authorisation (if another authority).
4	**Assess the implementation of the evaluation protocol**
	In case where CQA or KPI are to be maintained, assess the following : • Whether the product meets specification before release • Whether the validation report specifies the CQAs or KPIs that need to be satisfied • Whether the validation report defines the CQAs or KPIs and provides information on the tests performed to determine if the CQAs or KPIshave been achieved • Whether the validation report demonstrates that the process is reproducing the CQAs or KPIs consistentlyand whether validated assays to measure CQAs or KPIs are provided In case the change involves a modification or improvement of the CQAs or KPIs, assess the following: • Written specifications: ▪ References to the research papers from which the specification is derived ▪ Expected characteristics (refer to Appendix A) ▪ Testing characteristics (viability, residual cells measurement, microbiology etc.) Refer to Appendix A • Impact of the change on CQA or KPIs on clinical properties • Clinical expected evidences: ▪ Document evidence of clinical protocol being implemented ▪ Patient record, case report form, registry reports, ▪ Clinical application (patient inclusion/exclusion criteria) • Patient safety and efficacy data: ▪ Outcome assessment ▪ Adverse event and reaction reporting
5	**Analyse and report on results**
	• Receive report of results of the novel product/process validation or evaluation • Review results • Where an establishment is reliant on published data to support the planned work, they must be able to demonstrate that the methods they intend to follow directly mirror those in published reports and they must be able to demonstrate that they can reproduce the process (and results) in their own facility. In such situations look very closely at the equipment, reagents and protocols being employed, and the training that has been given to staff • Decide if: ▪ The product is efficacious and safe. ▪ The data supports the ability to produce the product on a regular basis The competent authority produces a report summarising findings which support or contest the case for a new preparation process
6	**Final approval process**

	Upon results of authorisation process, a full or conditional authorisation may be granted or refused, based on the process outcome. The listing of the Blood products may be modified to reflect the need of addition of a novel Blood component according to the national regulatory framework
7	**Develop codes and labelling if new product(s)**
	Request new code from the issuing bodies e.g. ISBT 128/Eurocode/SEC/ABC Codabar / Blood Coding systems. Label contents should describe the key attributes of the product(s) and conform to national standards and regulations
8	**Validation and authorisasion of the routine use of the PP by an establishment**
	"Process validation" to establish routine operation of the technique, normally attesting that agreed parameters are met. Tests may be supplemented by a limited set of assays selected from the investigational stage to allow setting of routine quality parameters. This may involve in vivo studies and normally would involve sampling at agreed times for routine testing
9	**Apply any post-authorisation studies[b] needed according to the level of risk**
	The CA should ensure that the studies proposed according to the level of risk determined in the assessment are applied. These studies will range from minimal process validation through routine/safety follow up program to a full clinical study based on GCP. See the EuroGTPII Guide *2.4 Definition of Studies Extent (Step 3)*
10	**Withdraw or suspend preparation process if surveillance reveals increased risk or if further developments render it relatively less beneficial**
11	**Decide on social security support and payment. Determine economic aspects.**

2.2 Evaluation criteria according to the types of blood components

2.2.1 Three step model of evaluation of blood components as an example

The duration of the evaluation and monitoring by the Competent authority is determined by the level of risk associated with the authorisation.

Step1: Initial intensive investigation (in vitro evaluation) which is destructive for the evaluated blood components. This stage applies to High (H) and Moderate (M) risk levels; evaluation procedures as described in section III. It should be carried out on a small number of units (number according to requirements of the blood competent authority, if applicable) of the blood component and over the entire shelf life of these products to validate their maximum shelf life.

Components produced during this stage **should not** be used for transfusion.

For a Low (L) level of risk, this stage is to be carried out on even smaller number than level of risk H and M of units (number according to requirements of the blood competent authority, if applicable) of the blood component and only to check the criteria that may be affected by the minor changes.

[b] To determine the extent of any studies and/or follow up required to insure the safety and efficacy of the tissues or cells.

Step2: Operational validation should be carried out on a larger number of units of blood components (e.g. 2 x 100 units in 2 different blood establishment's sites if possible for reproducibility). Depending on the MS, proceeding to this step may require approval of step 1 by the CA. For further details refer to Technical Annex II Chapter 1.

Components produced during this stage **can be used for transfusion** if they comply with the routine quality parameters.

This step applies to blood components with level of risk H or M.

If necessary clinical investigation or clinical follow-up will be carried out during this phase prior to approval, see Technical Annex III.

Step3: Routine surveillance or clinical follow-up, according to the level of risk defined by the applicant and approved by the competent authority, for a period and/or a number of patients proposed by the establishment and approved by the CA. See technical Annex III for details.

2.2.2 Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs) for evaluation of blood components

The following tables of evaluation requirements are derived from those used in the UK by the Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC)[4], the Medicines and Healthcare products Regulatory Agency (MHRA) and in France by the French National Agency for Medicines and Health Products Safety (Agence nationale de sécurité du médicament et des produits de santé, ANSM) and should serve as an example.

For High (H) Risk level, the selection of product's Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs) that need to be monitored is established by the supplier, on the basis of available scientific data, information provided by the manufacturer of the medical device (if applicable) and on the expected characteristics of the component. Some attributes listed below for levels of risk M and L for known blood components may be selected. The CA must approve the panel of CQAs and CPPs results submitted in the PPD.

For Moderate (M) and Low (L) Risk level, recommended tests are listed in the following tables for each type of blood components. The CQAs and CPPs required in step1 of the evaluation model above should be monitored by at least four (4) controls between the day of preparation of the final product and the expiry date.

For Negligeable (N) Risk level, SARE monitoring is sufficient.

Some components may need to be tested for a combination of parameters, e.g. apheresis red cells in a novel/experimental additive solution (AS) that are also leuco-depleted. In this case the sampling requirement includes that of a leuco-depleted red cell component and that of an experimental AS component.

Where novel plasticisers and additive solution are combined, the requirements for novel plasticiser are sufficient to cover both elements.

2.2.3 Evaluation of red cells components for transfusion

The following tables identify the required Critical Quality Attributes (CQAs)for High, Moderate and Low Risk Red cell authorisation dossiers depending on the type of novelty or change in the preparation process

Novel or modified characteristic / CQAto Verify	Novel pack	Novel Leuco-depletion filter	Novel centrifugation/Component separator	Novel anti-coagulant	Novel/Modified apheresis system	Novel additive solution	Novel plastic/ plasticiser	Novel Irradiation	Pathogen reduction
Unit volume (mL)	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L
Haematocrit (L/L) or %	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L
Haemoglobin (Hb) (g/unit)	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L
MCV (Mean corpuscular volume)	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L
Residual WBC (106/Unit)		H / M			H / M		H / M		
Supernatant K+ (mmol/L)	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L
Haemolysis (%)	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L
ATP or 2,3-DPG or % of spherocytes	H / M / L	H / M / L		H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L
pH				H / M	H / M	H / M	H / M	H / M	H / M
Lactate (mmol/L)	H / M			H / M		H / M	H / M	H / M	H / M
Glucose (mmol/L)	H / M			H / M		H / M	H / M	H / M	H / M
pCO2 (kPa)				H / M	H / M	#	#	#	#
pO2 (kPa)				H / M	H / M	#	#	#	#
Red cells microvesicles		#		#	#	H / M	H / M	#	#
24-hour recovery (%)				#		#	#	#	H/M
Leachables from plastic film in supernatant and cells*							H / M†*		

Novel or modified characteristic / CQAto Verify	Novel pack	Leuco-depletion filter	centrifugation/Component separator	Novel anti-coagulant	Novel/Modified apheresis system	Novel additive solution	Novel plastic/ plasticiser	Novel Irradiation	Pathogen reduction
Residual concentration of "added substances"									H / M / L
Osmotic fragility						#			

H = for High risk; M = for Moderate risk; L= for Low risk; # = optional; other tests are not excluded; *= normally undertaken by the manufacturer; †= also consider the effects of irradiation.

The following tables identify the required recorded Critical Process Parameters (CPPs) and performance criteria for High, Moderate and Low Risk Red cells authorisation dossiers for RBC depending on the type of novelty or change in the preparation process

For each parameter mean, SD, min, max and median value should be reported

Novel or modified characteristic / CPPto Verify	Novel pack	Leuco-depletion filter	centrifugation/ Component separator	Novel anti-coagulant	Novel apheresis system	Novel additive solution	Novel plastic/ plasticiser	Novel Irradiation	Novel Pathogen reduction
Collection time	H / M / L	H / M / L		H / M / L	H / M / L		H / M / L		
Storage temp. between collection and processing	H / M / L	H / M / L		H / M / L	H / M / L	H / M / L			H / M / L
Time delay between collection and processing of the step submitted to change	H / M / L	H / M / L	H / M / L			H / M / L	H / M / L	H / M / L	H / M / L
Temperature at the processing step submitted to change	H / M / L	H / M / L	H / M / L			H / M / L	H / M / L	H / M / L	H / M / L
Centrifugal force (RCF)	H / M / L		H / M / L	H / M / L			H / M / L		
Centrifugation time	H / M / L		H / M / L	H / M / L			H / M / L		
Time for separation	H / M / L		H / M / L	H / M / L			H / M / L		
Temperature at filtration		H / M / L							
Height of filtration		H / M / L							
Filtration time		H / M / L							
Leucocyte subsets (%) (d1)		H / M							
Hb loss (g) (post-filter) (d1)		H / M	H / M						
Volume loss (mL) (post-filter) (d1)		H / M	H / M						

Novel or modified characteristic / CPPto Verify	Novel pack	Leuco-depletion filter	centrifugation/ Component separator	Novel anti-coagulant	Novel apheresis system	Novel additive solution	Novel plastic/ plasticiser	Novel Irradiation	Novel Pathogen reduction
Storage temperature	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L
Storage time	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L

Planned studies may fall into more than one category in which case all indicated assays should be performed. d1 = Day 1.

2.2.4 Evaluation of platelet components for transfusion

The following tables identify the required Critical Quality Attributes (CQAs) for High, Moderate and Low Risk platelets authorisation dossiers depending on the type of novelty or change of preparation process.

Novel or modified characteristic / CQA to Verify	Novel/Modified apheresis system	Leuco-depletion	Pathogen reduction	Extended storage	Change in storage conditions (temp. Agitation…)	Novel Irradiation	New collection device, additive or anticoagulant	Novel plasticiser / plastic
Volume (d1)	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L
Platelet Concentration (G/L)	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L
Platelet content (x 1011 /unit)	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L
pH	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L
MPV (Mean platelets volume) (fL or µm3)	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L
Residual WBC (106/unit) (d1)	H / M / L	H / M / L	#				#	
Morphology, e.g. Swirl score	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L		H / M / L	H / M / L
Activation, e.g. beta thromboglobulin, CD62P (expression or soluble)	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L		H / M / L	H / M / L
Lysis, e.g. LDH	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L		H / M / L	H / M / L
Residual Red Cell Count (d1)		#	#	#			#	#
Plasma /PAS ratio (d1)	H / M	#	H / M	H / M	#	#	H/M	#
Metabolic activity:ATP, pH, Lactate, Glucose, pCO2, pO2	H / M	H / M	H / M	H / M	H / M	H / M	H / M	H / M
Function e.g. Aggregation Thromboelastography/ Thromboelastometry	H / M	#	H / M / L	H / M	H / M	H / M	#	#
Cytokines/chemokines	H / M	#	#	H / M	H / M	H / M	#	#
Platelet microvesicles	#	#		#	H / M	H / M	H / M	#
Residual content of			H / M					

Novel or modified characteristic CQA to Verify	Novel/Modified apheresis system	Leuco-depletion	Pathogen reduction	Extended storage	Change in storage conditions (temp. Agitation…)	Novel Irradiation	New collection device, additive or anticoagulant	Novel plasticiser / plastic
"added substances"								
Leachables from plastic film in supernatant and cells								H / M†

H = for High risk; M = for Moderate risk; L= for Low risk; # = optional; other tests are not excluded; *= normally undertaken by the manufacturer; †= also consider the effects of irradiation.

The following tables identify the required recorded Critical process parameters (CPPs) and performance criteria for High, Moderate and Low Risk platelets authorisation dossiers depending on the type of novelty or change of preparation process

For each parameter mean, SD, min, max and median value should be reported

Novel or modified characteristic / CPP to Verify	Novel/Modified apheresis system	Leuco-depletion	Pathogen reduction	Extended storage	Change in storage conditions (temp. Agitation…)	Novel Irradiation	New bag, additive or anticoagulant	Novel plasticiser / plastic
Collection time	H / M / L							
Storage temp. between collection and processing	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	#	#
Time delay between collection and processing of the step submitted to change		H / M / L*	H / M / L			H / M / L		
Temperature at the processing step submitted to change		M / L	H / M / L			H / M / L		
Time delay between collection and pooling†		H / M / L	H / M / L	H / M / L	H / M / L		H / M / L	H / M / L
Temperature at filtration		H / M / L						
Height of filtration		H / M / L						
Filtration time		H / M / L						
Leucocyte subsets (%) (d1)		H / M						
Platelet loss (%) (post-filter) (d1)		H / M	H / M					
Volume loss (mL) (post-filter) (d1)		H / M	H / M					
Total platelet/Storage bag volume ratio				H / M	H / M		H / M	H / M
Storage temperature	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L
Storage time	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L

†*for Pooled buffy coat platelet concentrates or pooled WB standard platelets; * filtration*

2.2.5 Evaluation of plasma for transfusion

The following tables identify the required Critical Quality Attributes (CQAs) for High, Moderate and Low Risk plasma authorisation dossiers depending on the type of novelty or change of preparation process.

The quality attributes of plasma are verified throughout the storage period (4 control steps between the day of preparation of the final product) and the expiry date (date of the application of a new process (T1) and 3 checks after storage-thawing on D1-14, at 6 months and at 12 months, respectively T2, T3 and T4). Other control points can be added for the validation of the extension of storage.

Novel or modified characteristic / CQAto Verify	Novel filter	New centrifuge/ component extractor	Novel anticoagulant	Novel plasticiser/ plastic	Novel/Modified apheresis system and /or new anticoagulant	Extended storage	Pathogen reduction	Novel Thawing process
Volume (mL)	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L
Residual WBC (d1)	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L			
Protein after thawing (g/L)	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L
Immunoglobulin (G, M, A) (g/L)	H / M	H / M	H / M	H / M	H / M	H / M	H / M	H / M
FVIII:C (IU/mL)	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L
Residual Platelets (d1)	H / M	H / M	H / M	H / M	H / M		H / M	
Residual Red cells (d1)	#	#			#		#	
PT ratio (Prothrombin time)	H / M		H / M	H / M	H / M	H / M	H / M	
Thromboelastography/ Thromboelastometry	H / M		H / M	H / M	H / M	H / M	H / M	
APTT ratio	H / M		H / M	H / M	H / M	H / M	H / M	H / M
Fibrinogen (g/L)	H / M		H / M	H / M	H / M	H / M	H / M	
FII, V, VII, IX, X, XI, (UI/mL)	H / M		H / M	H / M	H / M	H / M	H / M	
vWf:Ag	H / M		H / M	H / M	H / M	H / M	H / M	
vWf:RiCof	H / M		H / M	H / M	H / M	H / M	H / M	
AT III (Antithrombin), Protein C, Protein S	H / M		H / M	H / M	H / M	H / M	H / M	
TAT/Frag1.2/FPA + FXIIa	H / M / L		H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	

Novel or modified characteristic CQAto Verify	Novel filter	New centrifuge/ component extractor	Novel anticoagulant	Novel plasticiser/ plastic	Novel/Modified apheresis system and /or new anticoagulant	Extended storage	Pathogen reduction	Novel Thawing process
C3a (mg/L) and C5a (µg/L)	H / M / L		H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	
C1 inhibitor	H / M		H / M	H / M	H / M	H / M	H / M	
Alpha-2 anti-plasmin	H / M		H / M	H / M	H / M	H / M	H / M	
Plasminogen	H / M		H / M	H / M	H / M	H / M	H / M	
ADAMTS13							H / M	
Residual concentration of "added substances"							H / M / L	
Leachables from plastic film				H / M				

H = for High risk; M = for Moderate risk; L= for Low risk; # = optional; other tests are not excluded; *= normally undertaken by the manufacturer; †= also consider the effects of irradiation.

The following tables identify the required recorded Critical Process Parameters (CPPs) and performance criteria for High, Moderate and Low Risk plasma authorisation dossiers depending on the type of novelty or change of preparation process.

For each parameter mean, SD, min, max and median value should be reported

Novel or modified characteristic for FFP / CPPto Verify	Novel filter	New centrifuge/ component extractor	Novel anticoagulant	Novel plasticiser/ plastic	Novel/Modified apheresis system	Novel/Modified apheresis + anticoagulant	Pathogen reduction	Novel Thawing process
Collection time					H / M / L	H / M / L		
Storage temp. between collection and processing	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	
Time delay between collection and processing of the step submitted to change	H / M / L	H / M / L					H / M / L	
Delay between collection and filtration	H / M / L				H / M / L	H / M / L		
Height of filtration	H / M / L							
Filtration time	H / M / L							
Leucocyte subsets (%) (d1)	H / M / L							
Volume loss (mL) (post-filter) (d1)	H / M / L							
Time between collection and freezing	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L
Storage temperature	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	
Storage time	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	
Time of thawing								H / M / L

H = for High risk; M = for Moderate risk; L= for Low risk

2.2.6 Evaluation of Cryoprecipitate for transfusion

The following table identifies the required Critical Quality Attributes (CQAs) for High, Moderate and Low Risk cryoprecipitate authorisation dossiers depending on the type of novelty or change of preparation process.

Novel or modified characteristic / CQAto Verify	Novel filter	New centrifuge/ component extractor	Novel anticoagulant	Novel plasticiser/ plastic	Novel apheresis system	Novel/Modified apheresis + anticoagulant	Pathogen reduction	Novel Thawing process
Volume (mL)	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L
Residual WBC (d1)	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L		
FVIII:C (IU/mL)	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L
Fibrinogen (g/L)	H / M / L		H / M / L	H / M / L		H / M / L	H / M / L	
Residual concentration of "added substances"							H / M / L	
Leachables from plastic film				H / M				

H = for High risk; M = for Moderate risk; L= for Low risk

The following table identifies the required recorded Critical Process Parameters (CPPs) and performance criteria for High, Moderate and Low Risk Cryoprecipitate authorisation dossiers depending on the type of novelty or change of preparation process.

Novel or modified characteristic / for FFP CPP to Verify	Novel filter	New centrifuge/ component extractor	Novel anticoagulant	Novel plasticiser/ plastic	Novel apheresis system	Novel/Modified apheresis + anticoagulant	Pathogen reduction	Novel Thawing process
Collection time					H / M / L	H / M / L		
Storage temp. between collection and processing	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	
Time delay between collection and processing of the step submitted to change	H / M / L	H / M / L					H / M / L	
Time between collection and freezing	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L
Storage temperature	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L
Storage time	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L
Time of thawing								H / M / L

Novel or modified characteristic for FFP CPP to Verify	Novel filter	New centrifuge/ component extractor	Novel anticoagulant	Novel plasticiser/ plastic	Novel apheresis system	Novel/Modified apheresis + anticoagulant	Pathogen reduction	Novel Thawing process
Time of storage at +1°C	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L

H = for High risk; M = for Moderate risk; L= for Low risk.

2.2.7 Evaluation of changes on whole blood for transfusion

The recommended tests for the evaluation of whole blood are similar to those for the evaluation of red cells. If the intended use is for e.g. transfusion in trauma, where efficacy of the plasma and / or platelet content is also important, additional tests for these elements may also be required (Example: thromboelastography).

If however the data in the literature show that there is no impact of the preparation processes changes on the storage period of blood components, it is sufficient to provide data obtained before and after the changes without repeated control steps.

2.2.8 Evaluation of changes or new apheresis systems

Relevant information relating to the tolerance of donation by apheresis is also provided by documenting, for each of the procedures, before and after plasmapheresis:

- the donor's pulse and blood pressure,
- donors cyto-haematological constants (blood cellscount),
- any adverse reactions reported in the donor and in particular citrate reactions
- having had to have an intravenous administration of calcium
- method used to collect these tolerance data.

2.2.9 Evaluation of other Special cases of blood components for transfusion

Special case means the application of a blood or blood components for specific patients, without an investigational plan for indications or using conditions different for the approved ones, under the responsibility of the professional that prescribes it.

For the evaluation of special cases of blood or blood components, other than red cells, platelets, plasma and whole blood described above, it is recommended to seek the scientific advice of the competent authority for the evaluation procedure and the Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs) that need to be tested.

Evaluation can prove complicated for reasons such as small number of therapeutic uses, or new therapeutic indications which make it difficult to apply step 1 in vitro with destruction of the blood components and step 2 in vivo for the validation of the process on 2x100 blood components.

For example, pre-deposited autologous blood components are not described above. However, they comply with the routine criteria for collection, processing and testing, storage, distribution and issue that are approved by competent authorities for blood transfusion. Also, evaluation of similar allogeneic blood components can be applied to pre-deposited autologous blood components.

Apheresis granulocytes are blood components that are rare and used to treat specific patients who are generally in treatment failure.

The evaluation of the quality of rare blood components, such as granulocytes and similar blood components requires establishing routine follow-up, follow-up registers, or cohorts in cooperation with the competent authority who will have full access to the observations and results. Refer to

Technical Annex III for details about Clinical Investigation Plan (CIP) and Clinical Follow-Up Plan (CFUpP).

Another example is the new therapeutic indication for plasma: COVID-19 convalescent plasma (CCP).

COVID-19 convalescent plasma complies with the routine criteria for donation, collection, processing and testing, storage, distribution and issue that are approved by competent authorities for plasma transfusion. It's innovative character is due to the fact that it contains anti-SARS-CoV-2antibodies and the new therapeutic indication is not provided for in the usual international recommendations for the transfusion of plasma. If the preparation process of CCP is identical to that of already existing plasma and its quality and safety characteristics are well established, it is not necessary to perform step 1 and 2 evaluation as it is only a question of therapeutic indication. Its evaluation will therefore be based on monitoring its use in clinical setting (refer to Technical Annex III for details). A virus neutralisation test or a binding antibody IgG test can be used to directly or indirectly determine, in vitro, the titre of neutralising antibodies in donated CCP.

3 Haematopoietic Progenitor/Stem Cells (HPC/HSC) - Specific aspects of preparation process authorisation

Haematopoietic progenitor cells (HPC) transplantation represents one of the most widely used forms of cell therapy. HPC transplantation has its origins in pioneering work performed in the 1950's and 1960's and is today an established procedure for many acquired or inherited disorders of the hematopoietic system, benign or neoplastic, including those of the immune system, and as enzyme replacement in metabolic disorders[6].

HPC are obtained from living donors only, either from the same patient (in the case of autologous transplantation) or from a fully or partly HLA-matched allogeneic related or unrelated donor. Cells for transplantation are sourced from bone marrow, peripheral blood and cord blood. Mononuclear cells are not used for transplantation but are a source for donor-lymphocyte infusion (DLI) which has an established role in the management of disease relapse after allo-HCT. For autologous purposes, HPC are obtained almost exclusively from peripheral blood stem cells HPC(A) and used to accelerate haematopoietic recovery after high doses of chemotherapy. In the allogeneic setting, the HPC graft source depends on the age and size of the donor and recipient – i.e., paediatric or adult donor, since some countries do not permit G-CSF administration and apheresis in paediatric sibling donors – and the type of disease (malignant or non-malignant), as well as the transplant protocol (myeloablative, reduced intensity, T-cell replete or deplete haplo-identical transplantation). HPC(M) are still the preferred source in allogeneic paediatric transplantation from compatible related or unrelated donors.

The majority of HPC are provided using two technologies: procurement of bone marrow and apheresis. Unstimulated mononuclear cells are also procured by apheresis from the circulating blood.

Processing of minimally manipulated HPC is intended to provide appropriate conditions for preservation and storage or to improve the risk-benefit ratio of autologous or allogeneic HPC transplantation. It does not affect the main biological property of the procured cells, which is to support the marrow re-populating ability (MRA) and the establishment of haematopoietic chimerism in a myeloablated or immunosuppressed recipient in allogeneic transplant. Processing of MNC(A) mainly involves adjustment of volume and cell number according to the clinical protocol used.[c]

Preparation processes for HSCT include filtration, volume reduction, red blood cell depletion, plasma removal, cell selection, storage (short- and long-term), cryopreservation, thawing, washing and transportation.

[c] Preamble taken from Chapter 22, EDQM Guide to the Quality and Safety of Tissues and Cells for Human Application, 4th edition, 2019[7]

HPC are associated with multiple complications as consequences of immunological incompatibility, iatrogenic toxicities, microbiological contamination and manufacturing/administrative errors and can lead to severe adverse events or reactions which may be acute or delayed. The HPC medical community established registries early in the development of HPC transplantation to gather data on patients and their outcomes. Among the best known is the European Society for Blood and Marrow Transplantation (EBMT)[8] with over 700,000 transplants registered and representing a unique resource for further investigation and development in the field. The Registry encompasses all HSCT procedures for all indications. The clinical content of the EBMT Registry is decided by EBMT researchers through the Working Parties. The EBMT registry isdescribed as a source of Real World Data (RWD) under WP 8.3 Technical Annex III to overall guidance: assessing clinical data as part of Preparation Process Authorisation (PPA).

The regulatory provisions and European recommendations relating to tissues and cells, in particular for quality, safety and efficacy, referred to in this chapter are those mentioned in the sources and methods section and in particular the main categories of tissues identified in the EuroGTP II Guide and part B of the EDQM T&C guide 4th Edition.

For other aspects such as the methods of preparation of tissues and cells, it will be relevant to refer directly to the EDQM T&C Guide. Concerning the cells and donor testing requirements, microbiological testing and the clinical data requirements, the reader should consult Technical Annexes II and III respectively.

The tables in Appendix A set out the critical quality attributes (CQAs) and critical processing parameters (CPPs) for a range of tissues and cells that are commonly used for human application. The tables are based on current expert guidance and are intended to be used by Competent Authorities as a reference resource when reviewing and authorising preparation processes.

The use of different CQAs, CPPs or thresholds may be permissible, but any deviation from the recommendations should be justified by the tissue establishment (TE) and supported by appropriate evidence and validation.

For the authorisation of HPC preparation processes the CA will need to verify a combination of criteria, some relevant to the claimed process step regardless of the type of cells, others specific to the cells and the finished product.

These criteria, either Critical Process Parameters (CPP) (whose variability has an impact on a critical quality attribute and which therefore should be monitored or controlled to ensure the process produces the desired quality) or critical quality attributes (CQA) (physical, chemical, biological or microbiological property or characteristics that should be within an approved limit, range or distribution to ensure the desired component quality) will be defined for acceptance in the following tables. The basis by which process parameters and quality attributes were identified as being critical or non-critical should be clearly documented, considering the results of any risk assessment activities.

Acceptance criteria reported here should be understood as a recognised range or limits that do not need any further study or validation or a specific authorisation. These limits may still be extended after proper validation.

“Recognised” means on a scientific basis, published in the literature, set out in the EDQM T&C guide or legally fixed in the European directives. When criteria are defined in EDQM monographs, repetition is avoided by simply referring to them. Where values are indicated, they refer to the 4th (and later current) edition of the guide to make the reference more concrete. The extension of limits in the Guide may be considered if there is sufficient validation to guarantee quality and microbiological safety, under the authorisation of the relevant Competent Authority.

Where criteria are qualified as “non defined” they must be set and justified by the TE. Validation data must be submitted to demonstrate that the specified limits are met to be authorised by the relevant Competent Authority.

3.1 Steps a Competent Authority may follow in processing a preparation process dossier

1	**Assess changes regarding to donation, collection and procurement and confirm conformity to GCP**
	Consider the following: • Ethical requirement (informed consent, unpaid donation) • Type of donor (autologous, allogenic):allogenic transplantation entails risks of disease transmission that are absent in case of autologous transplantation Assess the donor selection process : • Ensure that the submitted information is sufficient and complete (medical record, donor risk assessment interview, general practitioner interview, specific file and previous results according to medical history) • Verify the consistency of the eligibility criteria with the methods and controls set during the process
2	**Assess the specification for the product, the process and the controls**
	• The Applicant should provide a written specification including: ▪ References to the research papers from which the specification is derived. ▪ Expected characteristics (refer to Appendix A) ▪ Testing characteristics ([blood] grouping, microbiology etc.) Refert to Appendix A ▪ Assessment that the product meets specification before release ▪ Additives and all product packaging in particular primary packaging used from collection to distribution ▪ Equipment specification • Evaluate if the preparation process includes the following: ▪ Main steps of the preparation process ▪ Critical process parameters identified and ranges included; these should be justified by validation or operational qualification ▪ Monitoring of process parameters: are any steps included where quality control samples are taken and aligned with the list of quality control tests? ▪ Attached SOP ▪ Description of environmental conditions: are they duly monitored and consistent with the procedure (open vs close system)? ▪ Specifications regarding reagents: - Are they in contact with the tissue and packaging (in particular primary packaging) used from procurement to distribution duly listed? - Do they comply with a standard that minimises risk to the quality or safety of the processed product? - Are they CE marked vs appropriately validated? ▪ Qualification of the equipment: are specifications respected? ▪ Validation report attached to the PPD Optimization of the CPPs and, where necessary, tolerance levels. The rationale for the specified CPPs should be explained.
3	**Assess product/process protocol**
	• The protocol should clearly describe the following: ▪ Process ▪ How quality controls will be established and monitored ▪ Clinical application : - Patient population to be treated (e.g., age, indication for treatment, previous/concomitant therapies) - Clinical application method

	- Method for monitoring the patients' safety and efficacy: standard medical practice, vigilance program, data collection in a scientific registry, clinical trial (in this case the Medical/Ethical Committee approval might be needed) - Donor safety (if applicable) ▪ Outcome assessment ▪ Reports of any adverse incidents during collection, production and/or clinical application • Verify that GCP areclearly adhered to • Verify IEB approval • Authorise the Clinical Investigation or verify the clinical investigation authorisation (if another authority)
4	**Assess the implementation of the protocol**
	In case where CQA are to be maintained, assess the following : • Whether the product meets specification before release • Whether the validation report specifies the CQAs that need to be satisfied • Whether the validation report defines the CQAs and provides information on the tests performed to determine if the CQAs have been achieved • Whether the validation report demonstrates that the process is reproducing the CQAs consistently and whether validated assays to measure CQAs are provided In case the change involves a modification or improvement of the CQAs, assess the following: • Written specifications: ▪ References to the research papers from which the specification is derived ▪ Expected characteristics (refer to Appendix A) ▪ Testing characteristics (viability, microbiology etc.) Refer to Appendix A Evaluate the impact of the change on CQA on clinical properties.
5	**Analyse and report on results**
	• Receive report of results of the novel product/process validation or evaluation • Review results • Where an establishment is reliant on published data to support the planned work, they must be able to demonstrate that the methods they intend to follow directly mirror those in published reports and they must be able to demonstrate that they can reproduce the process (and results) in their own facility. In such situations look very closely at the equipment, reagents and protocols being employed, and the training that has been given to staff • Decide if: ▪ The product is efficacious and safe. ▪ The data supports the ability to produce the product on a regular basis The competent authority produces a report summarising findings which support or contest the case for a new preparation process
6	**Obtain final approval process**
	Issue authorisation which may be subject to requiring more information or other conditions e.g. patient follow-up and monitoring in routine use. Three types of decisions can be made by the national competent authority after a request of authorisation of a new process: • Full authorisation, • Conditional authorisation, • Refusal The listing of the BTC may be modified to reflect the use of a novel preparation process.
7	**Develop codes and labelling if new product(s)**
	Request new code from the issuing bodies e.g. ISBT 128/Eurocode/SEC/ABC Codabar. Label contents should describe the key attributes of the product(s) and conform to national standards and regulations.
8	**Validation and authorise the use of the PP by an establishment**
	"Process validation" to establish routine operation of the technique, normally attesting that agreed parameters are met.

	Tests may be supplemented by a limited set of assays selected from the investigational stage to allow setting of routine quality parameters. This may involve in vivo studies and normally would involve sampling at agreed times for routine testing.
9	**Apply any post-authorisation studies[d] needed according to the level of risk**
	The CA should ensure that the studies proposed according to the level of risk determined in the assessment are applied. These studies will range from minimal process validation through routine/safety follow up program to a full clinical study based on GCP. See the EuroGTPII Guide *2.4 Definition of Studies Extent (Step 3)*
10	**Withdraw or suspend preparation process or BTC if surveillance reveals increased risk or if further developments render it relatively less beneficial**
11	**Decide on social security support and payment. Determine economic aspects.**

3.2 Key Criteria to take into consideration in evaluating a novel preparation process

This guide aims to inform competent authorities on what key criteria should be assessed for changes in a selection of the most important preparation processes for HPC. The Competent Authority should use the tables below for regulatory decision-making based on the widely accepted EuroGTPII mechanism for risk assessment.

3.2.1 Critical Quality Attributes (CQAs) for evaluation of HPC preparation processes

The following tables of evaluation requirements serve as an example.

For High (H) Risk level, the selection of product Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs) that need to be monitored is established by the tissue establishment, on the basis of available scientific data, information provided by the manufacturer of the medical device (if applicable) and on the expected characteristics of the component. Some attributes listed below for levels of risk M and L for known HPC components may be selected. The CA must approve the panel of Critical Quality Attributes (CQAs) and Critical process parameters (CPPs).

For Moderate (M) and Low (L) Risk level, recommended tests for monitoring CQAs and CPPs are listed in the following tables for each type of HPC.

For Negligeable (N) Risk level, SARE monitoring is sufficient.

[d]https://tool.goodtissuepractices.site/To determine the extent of any studies and/or follow up required to assure the safety and efficacy of the tissues or cells.

3.2.2 Haematopoietic progenitor cells (HPC) collection

The following table identifes the required Critical Quality Attributes (CQAs) for High, Moderate and Low Risk authorisation dossiers depending on the type of novelty or change in the HPC collection

Novel or modified process / CQAto verify	Bone marrow harvest	Peripheral blood apheresis	Cord blood collection	MNC apheresis
Packaging	H / M / L	H / M / L	H / M / L	H / M / L
Duration of collection	H / M	H / M	-	H / M
Volume collected	H / M / L	H / M	H / M / L	H / M
Haematocrit in the collected material	H / M / L	H / M / L	H / M / L	H / M / L
Yield	H / M / L	H / M / L	H / M / L	H / M / L
CBC numbers and differential	-	-	H / M / L	-
Microbiology	H / M / L (to validate collection technique)	H / M / L (to validate collection technique)	H / M / L (to validate collection technique)	H / M / L (to validate collection technique)

3.2.3 Haematopoietic progenitor cells (HPC) processing

The following table identifies the required Critical Quality Attributes (CQAs) for High, Moderate and Low Risk authorisation dossiers depending on the type of novelty or change in the preparation process

Novel or modified process / CQA to verify	Filtration (Bone marrow only)	Anticoagulant	Washing	Cell-sorting techniques	Plasma-rich plateletsremoval	RBC depletion	Volume reduction	Cryopreservation	Storage	Thawing	Transporation
Packaging								H / M / L	H / M / L		H / M / L
Short-term storage and transport conditions			H / M / L					H / M / L	H / M / L		
Time between collection and cryopreservation			H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L		H / M / L
TNC count in the starting material (except for CB)	H / M / L		H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	
TNC viability in the starting material (except for CB)	H / M / L		H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	
CD34+ or CD3+ count in the starting material (except for CB)		H / M / L	H / M / L	H / M / L	H / M / L	H / M / L		H / M / L	H / M / L	H / M / L	
Platelet count in the starting material	H / M / L	H / M / L	H / M / L	H / M / L							

Novel or modified process / CQA to verify	Filtration (Bone marrow only)	Anticoagulant	Washing	Cell-sorting techniques	Plasma-rich plateletsremoval	RBC depletion	Volume reduction	Cryopreservation	Storage	Thawing	Transporation
Haematocrit in the starting material	H / M / L		H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	
Granulocytes count in the starting material	H / M / L		H / M / L	H / M / L	H / M / L	H / M / L		H / M / L	H / M / L	H / M / L	
Nucleated RBCs (before cryopreservation (erythroblasts for cord blood)	H / M / L		H / M / L	H / M / L	H / M / L	H / M / L	H / M / L				
If CD34+ selection is performed, then count CD3+			H / M / L	H / M / L				H / M / L	H / M / L	H / M / L	
CFU growth after thawing			H / M(only to validate the technique)	H / M(only to validate the technique)	H / M(only to validate the technique)	H / M(only to validate the technique)		H / M (only to validate the technique)	H / M (only to validate the technique)	H / M	
Microbiology			H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	H / M / L	
Temperature (validate the transportation process including for short periods)				H / M / L	H / M / L	H / M / L		H / M / L	H / M / L	H / M / L	H / M / L
Functional cryoprotectant			H / M / L (to validate technique)					H / M / L	H / M / L		
TNC count (before and after cryopreservation, as applicable)								H / M / L	H / M / L	H / M / L	

Novel or modified process / CQA to verify	Filtration (Bone marrow only)	Anticoagulant	Washing	Cell-sorting techniques	Plasma-rich plateletsremoval	RBC depletion	Volume reduction	Cryopreservation	Storage	Thawing	Transporation
TNC viability (before and after cryopreservation, as applicable)		H / M / L						H / M / L	H / M / L	H / M / L	
CD45 cell viability			H / M / L	H / M / L	H / M / L	H / M / L		H / M / L	H / M / L	H / M / L	
Viable CD34+ counts (before and after cryopreservation, as applicable)		H / M / L						H / M / L	H / M / L	H / M / L	
Viable MNC counts (before and after cryopreservation, as applicable)								H / M / L	H / M / L	H / M / L	
MNC viability (before and after cryopreservation, as applicable)		H / M / L						H / M / L	H / M / L	H / M / L	
CD34+ or CD3+ viability (before and after cryopreservation, as applicable)		H / M / L						H / M / L	H / M / L	H / M / L	

4 Tissues and Cells - Specific aspects of preparation process authorisation

This section provides guidance for Competent Authorities assessing preparation process dossiers relating to tissues or cells. It focuses on how innovation or changes to a process may affect the quality and safety of such samples.

For all tissues or cells, some or all of the following steps take place prior to end use of the material:

- donor identification;
- donor assessment based on medical history and lifestyle considerations;
- donor testing –markers for infectious disease ;
- procurement;
- transport of procured tissues or cells to a processing facility;
- reception at the tissue establishment;
- processing, including QC testing;
- preservation;
- distribution for end use.

A change to any of these steps could have an impact on the quality, safety and efficacy of a product.

This section focuses on how changes to processing, preservation, transport including their environment, or quality control methods, or changes to CQAs, reagents or packaging, could have an impact on the quality and safety of a product. The impact of novelty is also considered.

Changes that may affect the microbiological safety of a product, or its efficacy, are addressed in Technical Annex II and Technical Annex III respectively.

4.1 General Principles

Each change or novelty has its own risk.

Each preparation process should be evaluated with regard to its novelty or the extent of the change that is being proposed, as these factors are linked to the level of risk associated with the process.

The EuroGTP II tool should be used by establishments and Competent Authorities to evaluate the degree of novelty of, or the scale of change to, a preparation process, and the concomitant risk.

The following summarises the principal levels of risk identified using this tool, and provides examples of the types of change or innovation that may result in a given classification:

Risk level	Examples of novelty or change
High	• First man usage of a novel tissue/cell product • The use of an established tissue/cell for a novel indication • Modification of a CQA that may impact the quality, safety or efficacy of the product
Moderate	• A significant change to a preparation process which affects the quality, safety or efficacy of the product, such as addition or deletion of a product preparation step or changes to the products and materials coming into contact with the tissues/cells • Changes to the conditions under which the tissues/cells are transported (for example, the duration or temperature of transportation) • Changes to nature of the tissue retrieved, the type of donors retrieved (for example, living, deceased, multi-organ retrieval), or the retrieval procedure • Changes to the primary packaging of the finished product • Addition of any product of biological origin entering in the composition of the finished product or used during its preparation, or a change to a product of biological origin entering in the composition of the finished product or used during its preparation
Low	• The introduction of an established preparation process in a new tissue establishment
Negligible	• A minor change such as the substitution of one reagent for another of a similar quality

A more detailed list of examples related to the different levels of risk is provided in the Appendix A7.3.3

4.2 Principles of process validation

Process validation should comply with the recommendations of Chapter 8.10, Process Validation, of the EDQM T&C Guide.

As a minimum, validation studies should be carried out by applying 'worst case' scenarios. The equipment used for validation studies should be fully qualified and measuring devices should be calibrated to traceable standards. Validation experiments should be repeated at least in triplicate, although the number of required replicates will depend on the degree of variability in the data and take in cosideration whether the staff is suitably trained.

Where validation is based on data from published studies, the relevant publications should be filed as part of the validation record. In such cases, the TE should demonstrate that they can effectively reproduce the published process with the same results in their facility (operational validation). Copies of the relevant SOP and the results of the operational validation should be provided to demonstrate that the process is equivalent to that applied in the scientific literature. Where specific steps have been significantly modified or adapted, separate validation should confirm that these changes have not invalidated the method.

If validation is based on retrospective evaluation of the clinical results for tissues or cells supplied by the establishment (i.e. for well-established processing procedures), collected and analysed data should include the number of tissues or cells implanted following processing by the method under consideration, and the time period (start and end dates/times) during which these implantations occurred. It should be demonstrated that, where a vigilance system was already in place at the time, clinical users were informed of the procedure for reporting adverse reactions.

Where validation is based on studies carried out by the establishment itself, reports should include the following elements:

a. A validation plan that specifies the critical parameters to be assessed and the acceptable result thresholds for these parameters;
b. A documented methodology; and
c. All results obtained, clear description with relevant interpretation.

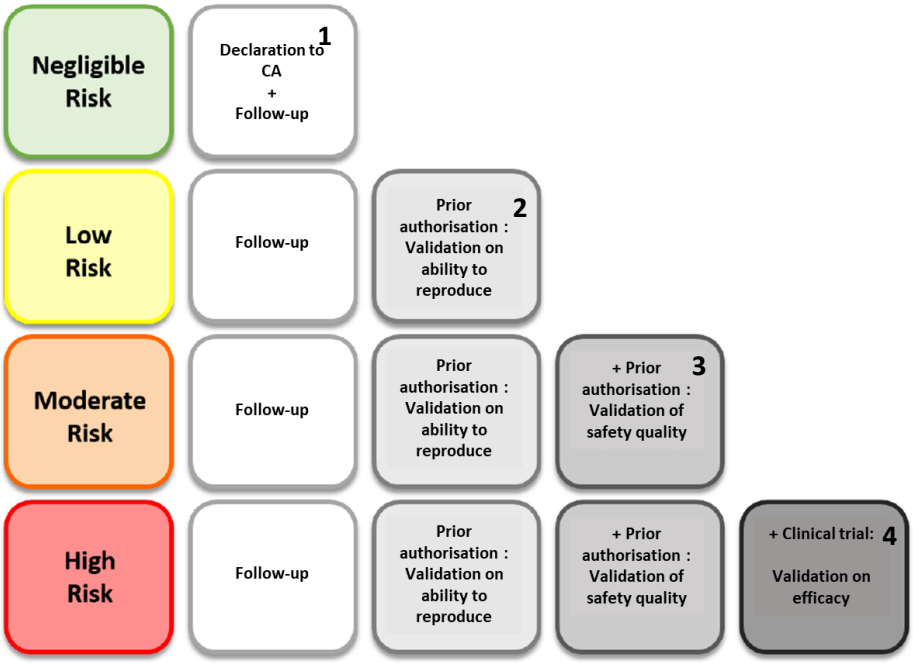
In all cases, there should be a signed declaration of validation acceptance or rejection by the QM or RP.

4.3 Data tables and risk levels

In Appendix A, tables define the main preparation process steps for a range of commonly used tissues and cells as well as the critical criteria (CQAs/CPPs). The tables have been designed following the criteria set out in the EDQM T&C guide, 4th edition.

In the tables cited above, any steps or criteria for which a change or novelty is associated with negligible risk, are highlighted in green. The information included in these green boxes should be shared with the Competent Authority when the authorisation preparation process is required. Changes that are associated with low or moderate risk are highlighted in yellow and orange respectively. Steps or criteria for which a change or novelty are classified as high risk are highlighted in red. The validation of such changes should include clinical evaluation.

For low, moderate and high risk changes or novelty, the information set out in the table should be provided to the Competent Authority, in addition to the information set out for lower risk tiers, as set out below:



4.4 Steps a Competent Authority may follow in processing a preparation process dossier

1 PRELIMINARY REVIEW	
1.1	**Assess whether the dossier is complete and provides enough information for a thorough evaluation**
	Does the submitted dossier: • Include a brief description and/or flowchart with main steps of the preparation process • Identify the critical process parameters, including ranges • Specify when quality control samples will be taken and is this information aligned with the list of quality control tests set out in the dossier • Include relevant standard operating procedures • List all reagents that come into contact with the tissue and packaging (in particular, primary packaging) used from procurement to distribution • Include a validation report?
1.2	**Considerations for assessing the degree of novelty**

	When assessing the degree of novelty ascribed by the TE using the latest version of the EURO GTPII tool, it is recommended to perform some relevant considerations, including whether: • The type of tissue or cell has been previously prepared and issued for clinical use by the establishment • The starting material used to prepare the BTC has been obtained from the same donor population previously used by the establishment for this type of BTC • The starting material for the BTC has been procured/collected using a procedure used previously by the establishment for this type of BTC • The BTC has been prepared by a procedure (processing/preparation, decontamination or preservation) used previously in the establishment for this type of BTC • The BTC ha been packaged and stored using a protocol and materials used previously in the establishment for this type of BTC • The BTC will be applied/infused clinically using an application/infusion method used previously; or whether • The establishment has provided this type of BTC for a same clinical indication and/or it has been applied/infused into a same anatomical site.

2 REVIEW STAGE : EVALUATION OF SUBMITTED INFORMATION	
2.1	**Assess changes relating to donation, collection and procurement**
	Consider the following : • Whether the consent process has changed, including whether the donation is voluntary and unpaid • Type of donor : ▪ Deceased : evaluate the risk of degradation of the tissue over time after death ▪ Living : whether the medical history is reported accurately by the donor, when applicable ▪ Autologous or allogenic : allogenic transplantation entails risks of disease transmission that are absent in case of autologous transplantation Assess donor selection process : • Ensure that the submitted information is sufficient and complete (e.g. medical record, next of kin or donor risk assessment interview, general practitioner interview, specific file and previous results according to medical history) • Verify the consistency of the eligibility criteria with the methods and controls set during the process Assess collection process : • Air quality and microbiological controls of the environment (none vs operating room) • Number of persons involved during the procurement and the time • Whether the microbiological risk are controlled at this step and how they can be further mitigated during the process Assess storage and transport conditions : • Whether the timing is clearly defined • Whether the temperature is clearly defined and monitored (continuously or not, recorded or not) • Whether labeling is clear enough to avoid mix up and misuse
2.2	**Assess product and process and controls**
	Verify the description of the preparation process (flowchart) and ensure it clearly describes the following : • Critical process parameters with clearly identified ranges justified by validation or operational qualification • Whether the environmental conditions are : ▪ Duly monitored

	▪ Controlled ▪ Consistent with the procedure (open vs closed system) • Whether their standard minimises risk to the quality or safety of the processed product (CE marked ancillary products and materials vs validated) • Whetherthe equipment is duly qualified and maintained and whether their specifications are fulfilled Assess the validation report : Verify how the CPPs have been optimised and, where necessary, how their tolerance levels have been set. The rationale for the specified CPPs should be clearly explained.
2.3	**Assess changes regarding the CQA**
	In case where CQA are to be maintained, assess the following : • Whether the product meets specification before release • Whether the report validation specifies which Critical Quality Attributes (CQAs) need to be satisfied in order to ensure the tissues or cells are not rendered clinically ineffective or harmful by the preparation process • Whether the validation report clearly defines the CQAs and provides information on the tests performed to determine whether the CQAs have been achieved • Whether the validation report demonstrates that the process is reproducing the CQAs consistently and whether validated assays to measure CQAs are provided If the change involves a modification of the CQAs : • Written specifications should include : ▪ References to the research papers from which the specification is derived ▪ Expected characteristics (refer to Appendix A) ▪ Testing characteristics (viability, residual water, measurement, microbiology etc.) Refer to Appendix A • Assess the impact of the change to CQA on clinical properties : ▪ Document evidence of clinical protocol being implemented e.g. patient record, case report form, registry reports ▪ Evaluate clinical application : - Patient population to be treated (e.g. age, indication for treatment, previous/concomitant therapies) - Clinical application method - Method for monitoring the patients' safety and efficacy of the treatment: standard medical practice, vigilance program, data collection in a scientific registry, clinical trial (in this case the Medical/Ethical Committee approval might be needed) - Donor safety (if applicable) ▪ Assess the outcome ▪ Report of any adverse incidents during collection, production and/or clinical application
2.4	**Analyse and report on results**
	Where an establishment is reliant on published data to support the planned work, they must be able to demonstrate that the methods they intend to follow directly mirror those in published reports and they must be able to demonstrate that they can reproduce the process (and results) in their own facility. In such situations look very closely at the environment, equipment and materials, reagents and protocols being employed, and the qualification of the staff. Decide if the product if efficacious and safe. At least, the clinical, biological and statistical data need to support the ability to produce the product on a regular basis.

3 AUTHORISATION	
3.1	**Grant or refuse authorisation**

	If the process is authorised : • Request more information or other conditions e.g. patient follow-up and monitoring in routine use, if relevant • Request new code from the issuing bodies e.g. ISBT 128/Eurocode/SEC/ABC Codabar. Label contents should describe the key attributes of the product(s) and conform to national standards and regulations.

4 POST AUTHORISATION	
4.1	**Post-autorisation steps**
	• Monitor ongoing incident • Review of additional data submitted by the TE to support a full authorisation • If such data is not submitted, follow-up with the TE to understand the reason for any delays and any associated risks • Full authorisation, extension to the conditional authorisation, or revocation of the authorisation • If full authorisation, update of associated records/databases

5 Medically Assisted Reproduction -Specific aspects of preparation process authorisation

5.1 General considerations about the validation procedure

5.1.1 Preliminary remarks about applicability of EuroGTPII guide in the context of GAPP

EuroGTP II represents the tool for TE to evaluate novelty and risk of a new technical process for the recipient. Regarding the assessment of novelty, a process could be novel for a TE but not for a MS (or for the field of MAR). If the process is already registered as an authorised method in a MS but is new for the TE, the CA can decide to either include the new technical process in the existing authorisation or licensing of the TE or proceed with the full assessment.

Conversely, a completely new process in the field will require an evaluation and authorisation by the CA as described below, and according to its level of novelty and risk as defined in EuroGTPII.

For the risk evaluation defined by the EuroGTPII tool, it is important to note that MAR is not limited to the sole recipients but also includes the embryos and any future children.

5.1.2 Adapting Risk Reduction Strategies and Extent of Validation to MAR

This section concerns the four levels of risk identified in EuroGTPII. As validation is mentioned involving both non-clinical and preclinical studies, it should be emphasized that these steps may impact the authorisation procedure. Non-clinical as well as preclinical studies require a specific authorisation procedure, which is part of Experimental Clinical Research and are not part of GAPP. Once validated the results may lead to a new authorisation procedure for clinical application in the context of an enlarged population. Depending on the MS, these steps may be the responsibility of a different CA.

5.1.3 How a CA might define a change impacting a biological process in MAR

We can distinguish four levels of “change” which are assessed according to the increasing level of potential risk. This approach is based on the existence of a supplementary critical step (unlisted in Appendix A and with any potential impact on quality and safety) and relied on risk evaluation as part of Euro GTPII.

5.1.3.1 Minimal novel change

If the change is purely technical and does not introduce or modify a critical step or a supplementary manipulation of gametes or embryos that may affect their quality and/or safety of the donor and patient, we can consider it to be a minimal change. Risk assessment will show a negligible or low risk (Euro GTPII score 0 to 2 and >2-6 respectively).

Minimal changes to preparation processes relied to negligible risk as referred to EuroGTPII (score 0-2) should be documented and if confirmed as such by the CA, followed up preferably at a national level.

Minimal changes to preparation processes relied to low risk as referred to EuroGTPII (score >2-6) should be included in a validation process. The change should be notified to the CA and followed up. The technical performance of TE should be monitored and comparable with reference values or published studies.

Routine/safety follow-up procedures are required in both cases, as stated in good practice guidelines. Follow-up procedures should focus on assessing efficacy and quality while comparing the clinical follow-up with the results obtained before the implementation of the change in the process. Notification to the CA and tracing of the change will allow a long-term follow-up at a national/regional level.

5.1.3.2 Moderate novel change

If the change involves an additional critical step or a supplementary manipulation of gametes or embryos, it is considered a moderate change. Risk assessment will show a moderate risk (Euro GTPII score 7 to 22). **Such a significant change should be submitted for authorisation by the CA.**

Validation is necessary and should include a range of additional quality controls performed to monitor Critical Process Parameters (CPPs) and Critical Quality Attributes (CQAs). The impact of the implemented changes on gametes, embryos and gonadic tissue should be carefully monitored in pre-clinical[e] and clinical studies.

A safety follow-up program is necessary. For more details refer to technical Annex III.

5.1.3.3 Major novel change

If the process is completely new, with a risk assessment showings a high risk (Euro GTPII score over 22), an experimental phase and preclinical and/or non clinical studies are required before clinical application. Regarding major changes, it should be emphasized that there will be at least **2 levels of authorisation by the CA**. **The first level, following pre-clinical and / or non clinical studies, will**

[e] Pre-clinical studies are considered those with material that is not applied to the patient, meaning that it not transferred, nor applied for any other clinical use.

authorise clinical application on a limited number of patients. The second level, depending on the results of the first level, will extend the authorisation to all potentially concerned patients.

A validation and a range of additional quality controls performed to monitor Critical Process Parameters (CPPs), Critical Quality Attributes (CQAs), and the impact of the implemented changes is required. This validation should include non-clinical studies (preferably studies showing the experimental procedure is safe in animals) and nonclinical studies. When experimental treatments encompass a laboratory IVF phase, non clinical studies will examine, monitor and record in detail at least the structural integrity of the gametes, embryos or gonadal tissue. Between non clinical and clinical studies, an authorisation process has to be completed.

For clinical application and follow up programs refer to Technical Annex III.

5.2 Steps a Competent Authority may follow in processing a preparation process dossier

1	**Record the rationale for the change in the process**

	• What is the origin of the change / concerned process
	  ◦ Derived from R&D work and/or clinical practice
	  ◦ To fulfil an unmet clinical need or improve existing processes
	• In case the preparation process is derived from R&D, evaluate whether the expected benefits outbalance the expected risks
	  ◦ Critically appraise data from the literature or data from the assessment of potential risks
	  ◦ Consider the clinical outcome
	• Data will be further used to demonstrate that preparation process validation has been completed specifying all key points (critical steps and key performance indicators) which will allow the full process to be well controlled If the process is new for the TE, but is already registered as an authorised method by the CA, follow up according to existing accreditation or licensing procedures

2	**Assess the degree of novelty**
	• Does the process include the introduction or modification of a critical step, or an additional manipulation? • New method of incubation • New method of cryopreservation • New primary packaging • New reagent • What is the level of risk according to the EURO GTP II score?
3	**Assess the process and controls**
	=> Based on this information, is the change to be considered minimal (low or negligible), moderate or major? (see section 2.3.3) • Which CQAs have been selected for assessing the process adaptation, and the rationale for their selection? Which limits have been predefined for these CPPs and the rationale? Which CQA values are expected to improve or to be maintained in relation to the values before the change introduction.
3a	**Minimal or moderate risk**
	Have validation procedures been prepared, including a follow-up program as described in 5.1.3.1 and 5.1.3.2?
3b	**Major risk**
	• Has an informed consent been prepared? • Has the study to be submitted to Ethical Committee approval?

	• Has a clinical study been developed as described in 5.1.3.3? How many patients will be included in the study (study group and controls) and when results will be analyzed?
4	**Assess the impact of the adaptation on the CPPs**
	At completion of the validation/study period, In relation to the selected CPPs • Are the CPP values within the predefined limits? • Does the process adaptation result in an improvement/maintenance of the preselected CPPs as predicted (in step 3) • Where CPPs deviate from the predefined limits, is the rationale provided? • Are the clinical outcomes assessed? • Are any serious adverse events reported related to the different steps of the process?
5	**Does the implementation of the new process require any requalification of the staff?**
	Might be required with a fully novel process : • Application for authorization (major risk)…….
6	**Obtain final approval process**
	The CA issues the authorization, which may be subject to requiring more information or other conditions e.g. patient follow-up and monitoring in routine use
7	**Validate the change in the process by the TE**
	• "Process validation" to establish that the changed process meets the agreed parameters. • Clinical Follow-up Plan (CFUpP) or Clinical Investigation Plan (CIP) to be prepared according to the level of change (II.3.3), (see also WP8).

For notification / authorisation of each of the processes depending on the identified level of risk, MAR TEs should document the details for all critical steps and process parameters and calculate and assess performance indicators. More specifically, the addition of a critical step or a supplementary manipulation of gamete(s) or embryo(s), changes in the equipment and ancillary products used should be clearly risk assessed, and justified. Performance indicators should, whenever possible, be compared to published values and/or performance indicators related to standard already authorized processes. As a general rule, when introducing changes in the donation, procurement, collection, processing, preservation, storage and distribution, performance indicators must not to be lower than standard performance indicators (see Table below). Changes should aim to optimise the overall safety and efficacy of the process or at least simplify it without reducing its efficacy or decreasing its safety.

Change-control procedures should ensure enough supporting data to demonstrate that the changed process results in a product of the desired quality, consistent with the approved specifications, the estimated cost, extra-resources needed for a novel process and new risks emerging from the novel process. The likely impact of the change of facilities, systems and equipment on the final product should be evaluated (including a risk analysis). The need for, and the extent of, any re-validation should be determined. The need of requalification of the staff should be re-assessed (EDQM 4th edition of the Guide, section 2.10)

The procurement, testing, processing, storage and distribution of gametes and embryos should be subjected to comprehensive risk assessment to allow identification of those steps where most of the quality system controls are required and where validation of procedures is necessary. A 'process flow' diagram listing all relevant steps, processes, reagents, quality control, tests, environment and equipment can form the basis for the assessment exercise. Risk assessment should include an estimation of the severity of any identified hazard and an estimation of the probability that the hazard will result in harm. Probability should be assessed based on evidence and experience whenever possible. (EDQM 4th edition of the Guide, section 2.17)

Any data concerning the safety of introducing a change in a process should be provided when available. Once authorised, such a change should be traced and followed through the activity reports collected at the national level with a special emphasis on public health aspects (maternal and children's health status). Changes need to stay in accordance with general principles of respect for privacy, integrity, no ownership or patenting of human species, informed consent, and prohibition of cloning.

Competency values for the performance indicators included (ESHRE Special Interest Group of Embryology and Alpha Scientists in Reproductive Medicine, 2017) (The competency values reflect the minimum performance a laboratory should achieve).

PI/KPI	**Calculation**	**Competency value (%)**
Sperm motility post-preparation (for IVF and IUI)	progressively motile sperm x 100 all sperm counted	90%
IVF polyspermy rate	no. fertilized oocytes with > 2PN x 100 no. COCs inseminated	<6%
1 PN rate (IVF)	no. 1PN oocytes x 100 no. COCs inseminated	<5%
1 PN rate (ICSI)	no. 1PN oocytes x 100 no. MII oocytes injected	<3%
Good blastocyst development rate	no. good quality blastocysts on Day 5 x 100 no. 2PN/2PB oocytes on Day 1	≥30%
ICSI damage rate	no. damaged or degenerated x 100 all oocytes injected	≤10%
ICSI normal fertilization rate	no. oocytes with 2PN and 2PB x 100 no. MII oocytes injected	≥65%
IVF normal fertilization rate	no. oocytes with 2PN and 2PB x 100 no. COCs inseminated	≥60%
Failed fertilization rate (IVF)	no. cycles with no evidence of fert'n x 100 no. of stimulated IVF cycles	<5%
Cleavage rate	no. cleaved embryos Day 2 x 100 no. 2PN/2PB oocytes on Day 1	≥95%
Day 2 Embryo development rate	no. 4-cell embryos on Day 2 x 100 no. normally fertilized oocytes [a]	≥50%
Day 3 Embryo development rate	no. 8 cell embryos on Day 3 x 100 no. normally fertilized oocytes[a]	≥45%
Blastocyst development rate	no. blastocysts Day 5 x 100 no. normally fertilized oocytes[a]	≥40%
Successful biopsy rate	no. biopsies with DNA detected x 100 no. biopsies performed	≥90%
Blastocyst cryosurvival rate	no. blastocysts appearing intact x 100 no. blastocysts warmed	≥90%
Implantation rate (cleavage stage)[b]	no. sacs seen on ultrasound[c] x 100 no. embryos transferred	≥25%
Implantation rate (blastocyst stage)[b]	no. sacs seen on ultrasound[c] x 100 no. blastocysts transferred	≥35%

The Indicator values presented here were derived relative to cycles that met the criteria for a "reference population". With the exception of Indicators with specific qualifiers identified, these criteria were: female patients <40 years old; own fresh oocytes; ejaculated spermatozoa (fresh or frozen); no PGD/PGS (PGT); and all insemination methods (i.e. routine IVF and ICSI).

6 Final considerations

Initially divided into three sub-groups in Blood, Tissues and Cells and MAR, the experts agreed to further split the second sub-group into Tissues and Cells and Haematopoietic Stem Cells due to their specificities. The sub-groups then started by clarifying an overall vision of the authorisation procedures in their fields in order to identify the products, critical processing parameters, critical quality attributes and, for MAR, key process indicators that applied. Having identified these aspects in the first part of the joint action they then clarified the ways in which they were used to evaluate the impacts of quality safety and efficacy on the BTC products of changes to or innovations in preparation processes.

The vast majority of the information (products, CQA, etc.) presented in this annex derive from the EDQM Blood and Tissue guides. This illustrates that the guidelines have two parts, on the hand there is fixed procedural advice and on the other variable, specific changing information which needs to be kept up to date, and is kept up to date, by the constant efforts of the EDQM editorial team and the experts. This also implies that GAPP will require regular updating in order to take into account future evolutions in the field of BTC.

Ideally the guidance will be built into a knowledge driven guidance system that will build on the evolving European Recommendations such as maintained by EDQM, incorporating national and regional regulations and linked into EUROGTP II so providing precise guidance to a national or regional competent authority presented with the request to authorise a change to an existing, or the introduction of a novel, preparation process.

This could hopefully build on the conceptual framework developed by WP9. It would of course integrate the overall guidance, the safety guidance and clinical investigation and follow-up guidance.

7 Appendix A Critical Quality Attributes (CQA) and Critical Processing Parameters (CPP) Tables

The CQAs, CPPs and PPs identified in Appendix A are an instantaneous snapshot of a constantly evolving set of information which are included to illustrate the procedures a CA will follow, and to provide an initially useful and useable guideline. The major part of this is drawn from external sources information will need appropriate updating. Questions of keeping the recommendations and the referential up to date is addressed in the conclusion.

7.1 Blood

7.1.1 List of existing blood and blood components

This section collates all the blood components listed in the EDQM Blood Guide and Directive 2004/33/EC. This list presents the basis for identifying “novel” blood components (i.e. those which have not yet been registered).

7.1.1.1 Whole blood and red cells

7.1.1.1.1 Whole blood

Whole blood means blood collected from a single donor and processed either for transfusion or further manufacturing:

- Whole blood,
- Whole blood, Leucocyte depleted.

7.1.1.1.2 Red cells

- Red cells (RC),
- Red cells in additive solution (RC AS),
- Red cells, buffy coat removed (RC BCR),
- Red cells, buffy coat removed in additive solution (RC BCR-AS),
- Red cells, leucocyte-depleted (RC LD),

- Red cells, leucocyte-depleted, in additive solution (RC LD-AS),
- Red cells, leucocyte-depleted, in additive solution (RC LD-AS) for Neonates and Infants,
- Red cells, irradiated,
- Red cells for Neonatal and Infant Small Volume Transfusion,
- Red cells, Leucocyte-Depleted, suspended in Fresh Frozen Plasma, for Exchange Transfusion,
- Red cells, Leucocyte-Depleted (RCC LD) for Intrauterine Transfusion,
- Redcells, Washed (W),
- Red cells, Cryopreserved (Cryo).

7.1.1.2 Platelets

7.1.1.2.1 Platelets, recovered, single unit

- Platelets, recovered, single unit in plasma
- Platelets, recovered, single unit, leucocyte-depleted in plasma
- Platelets, recovered, single unit, leucocyte-depleted, for neonatal Use.

7.1.1.2.2 Platelets, recovered, pooled (Rec, Pool)

- Platelets, recovered, pooled, in plasma
- Platelets, recovered, pooled, in Additive Solution (Rec, Pool, AS) and plasma
- Platelets, recovered, pooled, leucocyte-depleted, in plasma
- Platelets, recovered, pooled, leucocyte-depleted, in Additive Solution, and plasma
- Platelets, recovered, pooled, pathogen reduced (Pool, PR)
- Platelets washed.

7.1.1.2.3 Apheresis Platelets

- Apheresis Platelets (AP),
- Apheresis Platelets, in Additive Solution (AP, AS),
- Apheresis Platelets, leucocyte-depleted (AP LD),

- Apheresis Platelets, leucocyte-depleted, in Additive Solution (AP LD- AS),
- Apheresis Platelets, Cryopreserved,
- Apheresis Platelets, Pathogen Reduced (AP, PR)

7.1.1.3 Plasma and cryoprecipitate

7.1.1.3.1 *Plasma*

- Plasma, fresh-frozen (FFP),
- Quarantined (FFP),
- Plasma, fresh-frozen, Pathogen Reduced (FFP PR),
- Plasma, fresh-frozen, cryoprecipitate-depleted.

7.1.1.3.2 *Cryoprecipitate*

- Cryoprecipitate**,**
- Cryoprecipitate, Pathogen Reduced.

7.1.1.3.3 Granulocytes

- Granulocytes, apheresis,
- Granulocytes, Pooled.

7.1.2 Specifications/Quality criteria of Blood Components

In the blood field the quality of a process will usually be evaluated by the quality of the blood component obtained.

All the criteria for the quality, storage, transport and labelling of blood and blood components identified in the EDQM Blood Guide were selected. These criteria are the basic key elements for the evaluation of “novelty in changes” of blood components and can be included in this document (without direct reference to the EDQM guide) since they are relatively stable having been unchanged for many years. For full blood component monographs refer to the corresponding chapters of the EDQM Blood guide which contains the minimum standards for blood establishments and hospital blood banks that have to be met to comply with European Directives listed at the beginning of this section.

The EDQM Blood guide should also be referred to for other aspects such as the methods of preparation of blood and blood components, probably via the platform being developed by the GAPP project WP9.

Finally, for blood testing requirements and clinical data requirements, refer respectively to the deliverables of GAPP WP5 (WP7) and WP8.

7.1.2.1 Whole blood and red cells

	Volume (mL) of unit	Haemoglobin (g) content per unit	Haematocrit	Haemolysis (%) of unit	Leucocytes (× 10^6)per unit	Other residual components per unit
Frequency of control	As determined by Statistical Process Control (SPC)[f]					
Whole Blood (WB)	400 - 500 (1)	≥ 45	Not specified	≤ 0.8% (2)(3)	NA	NA
Whole Blood Leucocyte Depleted (WB LD)	400 - 500 (1)	≥ 43	Not specified	≤ 0.8% (2)(3)	≤ 1 (3)	NA
Red cells (RC)	280 mL ± 50 mL (4)	≥ 45	0.65–0.75(3)	≤ 0.8% (2)(3)	NA	NA

[f]The SPC is determined by the blood establishment according to the volume of its production in blood components. As for all other aspects of quality, implementation of SPC demands understanding and commitment on the part of the management of the blood facility. It must be included in the quality system of the facility, and a training programme should be introduced for senior management as well as operational staff. Plans must be made for data collection, including of control charts, and all matters dealing with changes detected in processes, especially sudden situations. Regular reviews of processes against SPC data should take place, with the specific objective of continuous improvement.

	Volume (mL) of unit	Haemoglobin (g) content per unit	Haematocrit	Haemolysis (%) of unit	Leucocytes ($\times 10^6$)per unit	Other residual components per unit
Frequency of control	As determined by Statistical Process Control (SPC)[f]					
Red cells in additive solution (RC AS)	Depends on process(4)	≥ 45	0.50–0.70(3)	≤ 0.8% (2)(3)	NA	NA
Red cells , Buffy Coat Removed (RC BCR)	250 ± 50(4)	≥ 45	0.65–0.75(3)	≤ 0.8% (2)(3)	≤ 1.2×10^9 (4)	NA
Red cells, Buffy Coat Removed in additive solution (RC BCR AS)	Depends on process(4)	≥ 43	0.50–0.70(3)	≤ 0.8% (2)(3)	≤ 1.2×10^9 (3)	NA
Red cells Leucocyte Depleted (RC LD)	Depends on process(4)	≥ 40	0.65–0.75(3)	≤ 0.8% (2)(3)	≤ 1 (3)	NA
Red cells Leucocyte Depleted in additive solution (RC LD AS)	Depends on process(4)	≥ 40	0.50–0.70(3)	≤ 0.8% (2)(3)	≤ 1 (3)	NA
Red cells Apheresis (RC Aph)	Depends on process(4)	≥ 40	0.65–0.75(3)	≤ 0.8% (2)(3)	≤ 1 (3)	NA
Red cells Apheresis in	Depends on	≥ 40	0.50–0.70(3)	≤ 0.8% (2)(3)	≤ 1 (3)	NA

	Volume (mL) of unit	Haemoglobin (g) content per unit	Haematocrit	Haemolysis (%) of unit	Leucocytes (× 10^6)per unit	Other residual components per unit
Frequency of control	As determined by Statistical Process Control (SPC)[f]					
additive solution (RC Aph AS) (7)	process(4)					
Red cells Washed (RC W) (8)	Depends on process(4)	≥ 40	0.40–0.70(3)	≤ 0.8% (2)(3)	≤ 1 (3)	Protein supernatant ≤ 0.5 g (3)(5)
Red cells , Cryopreserved (RC Cryo) (8)	≥ 185 mL (4)	≥ 36	0.35–0.70(3)	As clinically prescribed	≤ 1 (3)	Hb supernatant ≤ 0.2 g (3)(6) Maximum 20 mOsm (3)(6)
Red cells, Leucocyte-Depleted (RC LD) for Intrauterine Transfusion	As clinically prescribed	As clinically prescribed	0.70-0.85 (3)	As clinically prescribed	≤ 1 (3)	To be defined

1. Excluding the volume of anticoagulant (not taking into account the anticoagulant and preservative solution)

2. % of red cells mass: As determined by SPC, a minimum of 90 % of units tested should meet the required value at the end of the shelf life.

3. As determined by SPC, a minimum of 90 % of units tested should meet the required value at the end of the shelf life.

4. Including the volume of residual anticoagulant.

5. Total residual quantity of supernatant protein not taking into account the albumin possibly added by the resuspension solution.

6. As determined by SPC, Hb supernatant ≤ 0.2 g per unit in the final suspending solution; Maximum 20 mOsm/L above osmolarity of resuspending fluid.

7. Can be leucocyte depleted and/or suspended in additive solution

8. Shelf-life reduced to 24 hours if processed in an open system

Statistical Process Control (SPC) is determined by the blood establishment according to the volume of its production of blood components. As for all other aspects of quality, implementation of SPC demands understanding and commitment on the part of the management of the blood facility. It must be included in the quality system of the facility, and a training programme should be introduced for senior management as well as operational staff. Plans must be made for data collection, including of control charts, and all matters dealing with changes detected in processes, especially sudden situations. Regular reviews of processes against SPC data should take place, with the specific objective of continuous improvement.

7.1.2.2 Platelets

	Volume (mL) of unit	pH of unit	Platelet content ($\times 10^{11}$) per unit	Leucocytes ($\times 10^{6}$) per unit
Frequency of control	As determined by SPC			
Platelets, Recovered, Single Unit (PR SU), prepared by the platelet-rich plasma	≥ 40 (1)(2)	≥ 6.4 (3)	≥ 0.6 (2)	≤ 0.2×10^{3} (2)
Platelets, Recovered, Single Unit (PR SU), prepared by the buffy coat method	≥ 40 (1)(2)	≥ 6.4 (3)	≥ 0.6 (2)	≤ 0.05×10^{3} (2)
Platelets, Recovered, Pooled (PRP)	To be defined (1)(2)	≥ 6.4 (3)	≥ 2.0 (2)	≤ 1.0×10^{3} (2)

	Volume (mL) of unit	pH of unit	Platelet content (× 10^{11}) per unit	Leucocytes (× 10^{6}) per unit
Frequency of control	As determined by SPC			
Platelets, Recovered, Pooled Leucocyte-Depleted (PRP LD)	To be defined (1)(2)	≥ 6.4 (3)	≥ 2.0 (2)	≤ 1.0 (2)
Platelets, Recovered, Pooled, in Additive Solution (PRP AS)	To be defined(1)(2)	≥ 6.4 (3)	≥ 2.0 (2)	≤ 0.3 × 10^{3} (2)
Platelets, Recovered, Pooled, Leucocyte-Depleted, in Additive Solution (PRP LD AS)	To be defined(1)(2)	≥ 6.4 (3)	≥ 2.0 (2)	≤ 1.0 (2)
Platelets, Recovered, Pooled, Pathogen-reduced (PRP PR)	To be defined(1)(2)	≥ 6.4 (3)	≥ 2.0 (2)	≤ 1.0 (2)
Apheresis Platelets, (AP) Standard Unit	To be defined(1)(2)	≥ 6.4 (3)	≥ 2.0 (2), ≥ 0.5 for neonates and infants	≤ 1.0 × 10^{3} (2)
Apheresis Platelets, Leucocyte-Depleted (AP LD)Standard Unit	To be defined(1)(2)	≥ 6.4 (3)	≥ 2.0 (2), ≥ 0.5 for neonates and infants	≤ 1.0 (2)
Apheresis Platelets, in Additive Solution (AP AS) Standard Unit	To be defined(1)(2)	≥ 6.4 (3)	≥ 2.0 (2), ≥ 0.5 for neonates and infants	≤ 1.0 × 10^{3} (2)
Apheresis Platelets, Leucocyte-Depleted (AP LD) Standard Unit	To be defined(1)(2)	≥ 6.4 (3)	≥ 2.0 (2), ≥ 0.5 for neonates and infants	≤ 1.0 (2)
Apheresis Platelets, Pathogen Reduced (AP	To be defined(1)(2)	≥ 6.4 (3)	≥ 2.0 (2)	≤ 1.0 (2)

	Volume (mL) of unit	pH of unit	Platelet content (× 10^{11}) per unit	Leucocytes (× 10^{6}) per unit
Frequency of control	As determined by SPC			
PR)				
Platelets, Cryopreserved	50-200 mL (4)	NA	> 50 % of the pre-freeze platelet content (4)	Depends on original component
Platelets, Washed	NA (4)	NA	≥ 2.0 (2)	≤ 1.0 (2)

1. Including the volume of residual anticoagulant solution. 40 mL per 0.6 × 10^{11} of platelets.

2. As determined by SPC, a minimum of 90 % of units tested should meet the required value.

3. As determined by SPC, all tested units must comply. pH measured (+ 22 °C) at the end of the recommended shelf-life Measurement of the pH in a closed system is preferable to prevent CO_2 escape. Measurement may be made at another temperature and then corrected.

4. Frequency of control: All units.

7.1.2.3 Plasma and cryoprecipitate

	Volume (mL) of unit	Factor VIII (IU/100 mL) of unit	Fibrinogen (g/L) per unit	Residual Leucocytes ($\times 10^6$) per unit	Residual Platelets ($\times 10^9$) per unit	Residual RC ($\times 10^9$) per unit
Frequency of control	As determined by SPC					
Fresh Frozen Plasma (FFP) Quarantine	Stated volume ± 10 % (1)	≥ 70 (2)(3)	NA	≤ 100.0 (3)	≤ 50.0 (3)	≤ 6.0 (3)
Fresh Frozen Plasma, Pathogen Reduced (FFP PR)	Stated volume ± 10 % (1)	≥ 50 (2)(3)	NA	≤ 100.0 (3)	≤ 50.0 (3)	≤ 6.0 (3)
Fresh Frozen Plasma, Pathogen Reduced Leucocyte-depleted (FFP PR LD)	Stated volume ± 10 % (1)	≥ 50 (2)(3)	≥ 60%	≤ 1.0 (4)	≤ 50.0 (3)	≤ 6.0 (3)
Cryoprecipitate	30-40 mL (5)	≥ 70 Von Willebrand Factor 100 IU per unit (6)	≥ 140 mg per unit	NA	NA	NA
Cryoprecipitate, Pathogen Reduced	Depends on system used	≥ 50 per single unit Von Willebrand Factor 100 IU per	≥ 140 mg per unit	NA	NA	NA

	Volume (mL) of unit	Factor VIII (IU/100 mL) of unit	Fibrinogen (g/L) per unit	Residual Leucocytes ($\times 10^6$) per unit	Residual Platelets ($\times 10^9$) per unit	Residual RC ($\times 10^9$) per unit
Frequency of control	As determined by SPC					
		single unit (6)				
Fresh Frozen Plasma, Cryoprecipitate depleted (7)	Stated volume ± 10 %	Not stated	Not stated	NA	NA	NA

1. Including the volume of residual anticoagulant solution.

2. Factor VIII content: Average (after freezing and thawing).

3. As determined by SPC, a minimum of 90 % of units tested should meet the required value per **liter** of plasma.

4. As determined by SPC, a minimum of 90 % of units tested should meet the required value per **unit** of plasma.

5. This table is designed for quality control of cryoprecipitate obtained from FFP derived from one unit of whole blood. In the event that apheresis FFP is used as a starting material, the volume may be different.

6. Only required if component used for treatment of haemophilia and/or vWD patients respectively.

7. Levels of labile factors V and VIII and fibrinogen reduced

8. Average (after freezing and thawing): ≥ 60 % of the potency of the freshly collected plasma unit

7.1.2.4 Granulocytes

	Volume (mL)	Granulocytes (× 10^{10})	Other
Apheresis Granulocytes (AG)	≤ 500 (1)(2)	At least 1.5–3.0 ×10^{8} granulocytes/kg body weight of recipient. Achieve clinical dose: e.g. adult patient of 60 kg = 0.9-1.8 × 10^{10} granulocytes per unit (2)	Significant content of red cells and platelets. Must be irradiated
Granulocytes, Pooled	As defined locally (1)(2)	≥ 5 × 10^{9}/unit (2)	Significant content of red cells and platelets. Must be irradiated

1. Including the volume of residual anticoagulant solution

2. Frequency of control: all units.

7.1.3 Storage and Transport requirements for Blood Components

	Storage temperature	Storage time	Transport temperature	Transport time
Whole blood for preparation of blood components	+ 20 °C to + 24 °C	≤ 24h	+ 20 °C to + 24 °C	≤ 24h
Whole blood. for transfusion	+ 2°C to + 6 °C	35 days in CPDA-1 (1)	≤ + 10 °C	≤ 24h
Red cells	+ 2°C to + 6 °C	35 days in CPDA-1 (1)	≤ + 10 °C	≤ 24h
Red cells Cryopreserved	– 60 °C to – 80 °C in an electric freezer and when a high glycerol method is used – 140 °C to – 150 °C if stored in vapour-phase liquid nitrogen and when a low glycerol method is used	≥ 30 years	(2)	(2)
Red cells thawed	+ 2°C to + 6 °C	≤ 24h	(3)	(3)
Platelets recovered	+ 20°C to + 24 °C (4)	≤ 5 days (5)	(6)	(6)

Apheresis platelets	+ 20°C to + 24 °C (4)	≤ 5 days (5)	(6)	(6)
Platelets Cryopreserved	≤ – 80 °C in an electric freezer £ – 150 °C if stored in vapour-phase liquid nitrogen	³ 1 year (7)	(2)	(2)
Platelets thawed	+ 2°C to + 6 °C	≤ 24h	+ 20 to + 24 °C (8)	(8)
FFP	≤ – 25 °C	≤ 36 months	(9)	(9)
	– 18 °C to – 25 °C	≤ 3 months		
FFP Thawed	+ 20°C to + 24 °C	≤ 4h (10)	(10)	(10)
	+ 2°C to + 6 °C	≤ 24h (10)		
FFP Cryoprecipitate-Depleted	≤ – 25 °C	≤ 36 months	(9)	(9)
	– 18 °C to – 25 °C	≤ 3 months		
FFP Cryoprecipitate-Depleted Thawed	(12)	(12)	(12)	(12)
Cryoprecipitate	+ 2°C to + 6 °C	≤ 24h	(11)	(11)
	≤ – 25 °C	≤ 36 months		
Cryoprecipitate Thawed	(12)	(12)	(12)	(12)
Apheresis Granulocyte	+ 20°C to + 24 °C	(13)	(14)	(14)
Granulocyte Recovered	+ 20°C to + 24 °C	(13)	(14)	(14)

1. The storage time depends on the processing system and the anticoagulant/preservative solution used.
2. If transport in the frozen state is unavoidable, storage conditions must be maintained transportation.
3. Transport of thawed, reconstituted red cells is limited by the short storage time. Storage conditions must be maintained during transport
4. Under conditions which guarantee that their viability and haemostatic activities are optimally preserved especially under constant agitation
5. Storage may be extended to 7 days, in conjunction with appropriate detection or reduction of bacterial contamination
6. During transportation, the temperature of *Platelets, Rec, Pool* must be kept as close as possible to the recommended storage temperature and, upon receipt, unless intended for immediate therapeutic use, the component must be transferred to storage under the recommended conditions.
7. If storage will be extended for more than one year, storage at – 150 °C is preferred.
8. Thawed platelets must be used as soon as possible after thawing. If short-to-intermediate storage is required, the component must be kept between + 20 °C to + 24 °C.
9. The storage temperature must be maintained during transport. Unless for immediate use, the packs must be transferred at once to storage at the recommended temperature.
10. Once thawed, the component must not be refrozen and should be transfused as soon as possible. If delay is unavoidable, the component may be stored and should be used within 4 hours if maintained at 22 ± 2 °C or 24 hours if stored at 4 ± 2 °C. For management of major bleeding, thawed FFP that has been stored at 4 ± 2 °C can be used for up to 5 days, but it should be borne in mind that extended post-thaw storage will result in a decline in the content of labile coagulation factors.
11. The storage temperature must be maintained during transport. The receiving hospital blood bank must ensure that the *Cryoprecipitate, PR* has remained frozen during transit. Unless for immediate use, the *Cryoprecipitate, PR* must be transferred immediately to storage at the temperature stated above.
12. Before use, *Cryoprecipitate* must be thawed in a properly controlled environment at + 37 °C immediately after removal from storage. Dissolution of the precipitate must be encouraged by careful manipulation during the thawing procedure. In order to preserve labile factors, *Cryoprecipitate, PR* must be used as soon as possible following thawing. It must not be re-frozen.
13. *Granulocytes, Apheresis* are not suitable for storage and must be transfused as soon as possible after collection. If unavoidable, storage must be limited to the shortest possible period.
14. The unit must be transported to the user in a suitable container between + 20 and + 24 °C, but without agitation.

7.1.4 Labelling recommendations for Blood Components

The labelling must comply with the relevant national legislation and international agreements. The following information must be shown on the label or contained in the component information leaflet, as appropriate:

	WB	RCC	Platelets recovered	Apheresis platelets	FFP	Cryoprecipitate	Apheresis Granulocyte	Granulocytes recovered
Producer's identification	✓	✓	✓	✓	✓	✓	✓	✓
Unique identity number	✓	✓	✓	✓	✓	✓	✓	✓

	WB	RCC	Platelets recovered	Apheresis platelets	FFP	Cryoprecipitate	Apheresis Granulocytes	Granulocytes recovered
Name of the blood component	✓	✓	✓	✓	✓	✓	✓	✓
Name of the PRT used			✓ for platelets PR	✓ for platelets PR	✓ for FFP PR	✓ for FFP PR	NA	NA
ABO and RhD groups	✓	✓	✓	✓	✓	✓	✓	✓
Blood group phenotypes other than ABO and RhD (optional)	✓	✓	NA	NA	NA	NA	NA	NA
Date of donation	✓	✓	✓	✓	✓	✓	✓	✓
Date of expiry (and time of expiry, when required)	✓	✓	✓	✓	✓(1)	✓(1)	✓	✓
Name of the anticoagulant solution	✓	✓	✓	✓	✓	✓	✓	✓
Name and volume of the additive solution	NA	✓ for RCC AS	✓ for platelets AS	✓ for platelets AS	NA	NA	NA	NA
Name and volume of the washing solution	NA	✓ for RCC	NA	NA	NA	NA	NA	NA

	WB	RCC	Platelets recovered	Apheresis platelets	FFP	Cryoprecipitate	Apheresis Granulocyte	Granulocytes recovered
		Wash						
Name and volume of the cryoprotective solution	NA	✓ for RCC Cryo	NA (Not applicable)	✓ for platelets Cryo	NA	NA	NA	NA
Additional component information (for example: irradiated, leucocyte-depleted, number of donations combined to make the pool, quarantined etc.) if appropriate	P	✓	✓	✓	✓	✓	✓	✓
Volume or weight of the blood component	✓	✓	✓	✓	✓	✓	NA	NA
Number of platelets (average or actual, as appropriate)	NA	NA	✓	✓	NA	NA	NA	NA
Number of granulocytes	NA	NA	NA	NA	NA	NA	✓	✓
Relevant HLA and/or HPA type, if required	NA	NA	NA	✓	NA	NA	✓	✓
Storage temperature	✓	✓	✓	✓	✓	✓	✓	✓

	WB	RCC	Platelets recovered	Apheresis platelets	FFP	Cryoprecipitate	Apheresis Granulocyte	Granulocytes recovered
Provide information: "The component must not be used for transfusion if there is abnormal haemolysis or other deterioration"	✓	✓	NA	NA	NA	NA	NA	NA
Provide information: "The component must be administered through an approved blood administration set"	✓	✓	✓	✓	✓	✓	✓	✓

1. If the operations are carried out by the blood establishment, after thawing, the date of expiry could be changed to the appropriate date (and time) of expiry. The storage temperature must also be changed accordingly. This is not a possible requirement, if thawing is performed outside the blood establishment.

7.2 Haematopoietic Stem/Progenitor Cells

The terms Haematopoietic Stem Cells and Haematopoietic Progenitor Cells are both used. Haematopoietic Stem Cells are characterised by their capacity to replicate and produce all types of blood cell. In consequence this Annex addresses the authorisation of Haematopoietic Stem Cell preparation processes.

7.2.1 List of existing Haematopoietic Stem Cells in the EDQM T&C guide

1. Haematopoietic stem cells from bone marrow – HSC(M)
2. Haematopoietic stem cells from umbilical cord blood – HSC(CB)
3. Haematopoietic stem cells from peripheral blood apheresis – HSC(A)
4. Mononuclear cells from unstimulated peripheral blood apheresis – MNC(A)

7.2.2 Specification/ Critical Quality Attributes of HSC, Bone Marrow, Apheresis, Cord Blood, Mononuclear Cells

The Appendix A represents an expert consensus on key processes and critical parameters for the preparation of haematopoietic stem cells (cord blood, peripheral blood, bone marrow and mononuclear cells) based on established references including the EDQM Guide for Tissues and Cells, FACT-JACIE Standards, NETCORD-FACT Standards, the EBMT Handbook and the scientific literature.

It should be noted that some of the parameters are not defined by absolute values as there may not be robust evidence to substantiate specific values and can be the subject of medical decision-making. In those cases, the tissue establishment is expected to support their approach with validated evidence.

Procurement and processing of HSC falls under EU Directive 2004/23/EC and its implementing directives.

7.2.3 EU Legislation in Tissues and cells

The legal framework defining the safety and quality standards for tissues and cells is set out in Directive 2004/23/EC24, also referred to as the European Tissues and Cells Directive, adopted in 2004 by the European Parliament and Council. It covers all steps in the transplant process from donation, procurement, testing, processing, preservation and storage to distribution.

To help implement this basic act, the Commission proposed and adopted, in close collaboration with EU MS, the following implementing Directives:

Commission Directive 2006/17/EC25 regarding certain technical requirements for the donation, procurement and testing of human tissues and cells

Commission Directive 2006/86/EC26 concerning traceability requirements, notification of serious adverse reactions and events, additional technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells

- **Commission Directive 2015/56527 amending Directive 2006/86/EC as regards certain technical requirements for the coding of human tissues and cells**
- **Commission Directive 2015/56628 implementing Directive 2004/23/EC concerns the procedures for verifying the equivalent standards of quality and safety of imported tissues and cells.**
- **Commission Decisions 2010/453/EC29 and Commission Directive 2012/39/EU30, as well as Commission Decision C(2015) 446031address some further specific aspects.**
- **It is important to note that EU countries can always choose to apply more stringent rules to the quality and safety of tissues and cells then the ones outlined above32.**
- **The Commission is currently carrying out the first formal evaluation of the EU blood and tissues and cells legislation22.**

Table 2.

More information can be found at:

https://ec.europa.eu/health/blood_tissues_organs/tissues_en.

Where HSC are procured as starting materials for an advanced therapy medicinal product (ATMP), procurement and storage prior to manufacturing fall under the aforementioned Directives while any further manipulation falls under Regulation (EC) No 1394/2007. Further information can be found at https://ec.europa.eu/health/human-use/advanced-therapies_en.

(Microbiological aspects of cells donations are covered by GAPP Technical Annex II)

Table 2

Activity	*CPP/CQA*	*HSC from Cord blood*	*HSC from BM*	*HSC from peripheral blood*	*MNC from peripheral blood*
Procurement	Source	Cord blood collection	Bone marrow harvest	Apheresis	Apheresis
	Techniques for blood collection from the cord vein	In utero and ex utero collection give similar results[79]	N/A	N/A	N/A
	Cord blood collection volume	50-200 ml tare (unrelated and related UCB)	N/A	N/A	N/A
	Identity	HLA[79]	HLA	HLA	HLA
	Blood group and Rh type	ABO Rh blood group for allogenic product	ABO Rh blood group for allogenic product[7]	ABO Rh blood group for allogenic product [7]	ABO Rh blood group for allogenic product [7]
Transportation to TE	Temporary storage and transport conditions	Should be validated[7]	Should be validated but it is commonly accepted:	Should be validated but it is commonly accepted:	Should be validated but it is commonly accepted:
	Time between collection and cryopreservation	<48hrs for unrelated CBU; <72hrs for related CBU[7,9,10]	RT if < 6h, +2-8°C if > 24h, max storage in non-frozen state ≤ 72[7,11]		
Processing	TNC count in the starting material	Should be validated[7,9,11]	Should be validated / no specification but required for the process		Should be validated

Activity	*CPP/CQA*	*HSC from Cord blood*	*HSC from BM*	*HSC from peripheral blood*	*MNC from peripheral blood*
	TNC viability in the starting material	N/A	Should be validated		
	CD34+ or CD3+ count in the starting material	N/A	Should be validated	Should be validated	Should be validated
	Platelet count in the starting material	N/A	N/A	Should be validated	N/A
	Haematocrit in the starting material	N/A	Should be validated / specification required to manage ABO incompatibility for allogeneic product		Should be validated
	Granulocytes count in the starting material	N/A	N/A	< 40%	N/A
	Filtration	N/A	Should be validated / specification required to manage ABO incompatibility for allogeneic product	N/A	N/A
	Volume reduction	21 ml/validated data (unrelated and related CBU)[79]	Should be validated - cell loss must be evaluated and expected recoveries defined[7,11]		

Activity	*CPP/CQA*	*HSC from Cord blood*	*HSC from BM*	*HSC from peripheral blood*	*MNC from peripheral blood*
	TNC count before cryopreservation	≥5 x 108 for unrelated CBU [7, 9]	Autologous transplantation -2 × 108 TNC/kg Allogeneic transplantations - 3 × 108TNC/kg [11]		≥2x108/kg
	TNC viability before cryopreservation	≥85% for unrelated CBU ≥70% for related CBU [7,9]	≥85%		
	Viable CD3+ counts before cryopreservation	N/A	N/A	N/A	$1x10^6$ /kg - $1x10^8$/kg
	Viable CD34+ counts before cryopreservation	≥$1.25x10^6$ for unrelated CBU[79]	≥ $1x10^6$ /kg	≥ 2x1 0^6/kg	N/A
	CD34+ cell viability before cryopreservation	≥85% (unrelated and related CBU[7]	≥85%	≥ 95%	N/A
	Viability of CD45 cells before cryopreservation	N/A	N/A	N/A	N/A
	Nucleated RBCs before cryopreservation	Should be counted(unrelated and related CBU)[79]	N/A	N/A	N/A
	MNC cell	N/A	N/A	N/A	≥95%

Activity	*CPP/CQA*	*HSC from Cord blood*	*HSC from BM*	*HSC from peripheral blood*	*MNC from peripheral blood*
	viability before cryopreservation				
	Viable MNC counts before cryopreservation	N/A	N/A	N/A	3.10^8/kg
	CD34+ selection before cryopreservation	N/A	Should be validated	Should be validated	N/A
	RBC depletion if major ABO incompatibility	N/A	RBC < 0,20 ml/kg[11]	RBC < 0,20 ml/kg[11]	RBC < 0,20 ml/kg [11]
	Plasma removal if minor ABO incompatibility	N/A	N/A	Should be validated[11]	Should be validated [11]
	Thrombocyte removal if necessary (i.e. $350000x10^6$/ml)	N/A	N/A	> $6x10^{11}$ / bag	N/A
	CD3+ if CD34+ selection	N/A	CD3+ < $2x10^4$/kg	CD3+ < $2x10^4$/kg	N/A
	CFU growth before cryopreservation	Should be performed (unrelated and related CBU) [79]	Should be performed (clonogenicity: 15-20%)	Should be performed (clonogenicity: 15-20%)	N/A
	Microbiology	Negative for aerobes, anaerobes, fungus for unrelated CBU; in related	Use is not precluded but requires treatment strategy	Use is not precluded but requires treatment strategy	Use is not precluded but requires treatment strategy

Activity	*CPP/CQA*	*HSC from Cord blood*	*HSC from BM*	*HSC from peripheral blood*	*MNC from peripheral blood*
		CBU any positive tests must include identity and antibiogram(s))[79]	Patient informed consent should be obtained	Patient informed consent should be obtained	Patient informed consent should be obtained
	UCB and maternal sample testing for infectious diseases	HIV1, HIV2, HCV, HBV, Syphilis, CMV; other according to the applicable law and regulations)[79]	N/A	N/A	N/A
	Donor/Patient testing for infectious diseases	N/A	HIV1, HIV2, HCV, HBV, Syphilis, CMV; other according to the applicable law and regulations[7]	HIV1, HIV2, HCV, HBV, Syphilis, CMV; other according to the applicable law and regulations[7]	HIV1, HIV2, HCV, HBV, Syphilis, CMV; other according to the applicable law and regulations[7]
	Identity	ABO/Rh blood group ; HLA (-A,-B,-C, -DRB1) low resolution testing *** (unrelated and related CBU) [79]	N/A	N/A	N/A
	Other	Hemoglobinopathies (unrelated and related CBU)	N/A	N/A	N/A
	Medical review and quality	Checked before banking[79]	N/A	N/A	N/A
Storage	Temperature	In either liquid or vapour-phase liquid nitrogen below −140 °C or −150	In either liquid or vapour-phase liquid nitrogen with procedure for quarantine	In either liquid or vapour-phase liquid nitrogen with procedure for quarantine	In either liquid or vapour-phase liquid nitrogen with procedure for quarantine

Activity	CPP/CQA	HSC from Cord blood	HSC from BM	HSC from peripheral blood	MNC from peripheral blood
		°C [79]	/isolation of infected/suspected/untested products	/isolation of infected/suspected/untested products	/isolation of infected/suspected/untested products
	Cryoprotectant	10% DMSO and 1 % Dextran-40 [79]	5-10% DMSO [11]	5-10% DMSO[11]	5-10% DMSO[11]
	Freezing Bags	Designed/approved for cryopreservation of human cells and placed into metal cassettes for protection during freezing, storage, transportation and shipping.[79]	Designed/approved for cryopreservation of human cells and placed into validated containers for protection during freezing, storage, transportation and shipping.	Designed/approved for cryopreservation of human cells and placed into validated containers for protection during freezing, storage, transportation and shipping.	Designed/approved for cryopreservation of human cells and placed into validated containers for protection during freezing, storage, transportation and shipping.
	Packaging and labelling	ISBT128, Eurocode, Single European Code (SEC)[7]	ISBT128, Eurocode, Single European Code (SEC)[7]	ISBT128, Eurocode, Single European Code (SEC)[7]	ISBT128, Eurocode, Single European Code (SEC)[7]
		The EDQM Guide, 4th edition, p 281 states: "the primary packaging must be made of a biologically compatible material. Cryopreservation requires the use of low-temperature-resistant packaging, which can also withstand contact with liquid nitrogen"			
Distribution	TNC count	Should be performed[79]	Should be performed[7]	Should be performed[7]	Should be performed[7]
	TNC viability	≥ 70%[1]	≥ 70%	≥ 70%	≥ 70%

Activity	*CPP/CQA*	*HSC from Cord blood*	*HSC from BM*	*HSC from peripheral blood*	*MNC from peripheral blood*
	CD45 cell viability	N/A	N/A	N/A	N/A
	Viable CD34+ counts	Should be performed (unrelated and related CBU)[9]	Auto - ≥2x10^6/kg Allo - ≥4.0 × 10^6/kg	Auto - ≥2x10^6/kg Allo - ≥4.0 × 10^6/kg	N/A
	Viable MNC counts	N/A	N/A	N/A	0,1-1x10^6/kg
	MNC viability	N/A	N/A	N/A	≥ 70%
	CD34+ or CD3+ viability	≥ 70% (unrelated and related CBU)[9]	≥ 80%	≥ 80%	≥ 70%
	CFU growth	Growth (unrelated and related CBU)[7]	Growth	Growth	N/A
	Identity	HLA(-A, -B, -DRB1) high resolution (unrelated and related CBU); HLA-C high resolution for unrelated CBU[7,9]	N/A	N/A	N/A
	Donor follow-up, medical review and quality	Checked before release[9]	N/A	N/A	N/A
	DMSO, in case of cryopreserved HSC	N/A	<1 ml/kg recipient body weight [7,11]	<1 ml/kg recipient body weight[7,11]	<1 ml/kg recipient body weight[7,11]

Activity	*CPP/CQA*	*HSC from Cord blood*	*HSC from BM*	*HSC from peripheral blood*	*MNC from peripheral blood*
	Cluster of cells	N/A	Absence	Absence	Absence
	Microbiology	Use is not precluded but requires treatment strategy	Use is not precluded but requires treatment strategy	Use is not precluded but requires treatment strategy	Use is not precluded but requires treatment strategy

Abbreviations: CBU, Cord Blood Unit; CFU, Colony Forming Units; DMSO, Dimethyl Sulphoxide; HLA, Human Leukocyte Antigen; N/A, Not Applicable; RBC, Red Blood Cells; RT, Room Temperature; TE, Tissue Establishment; TNC, Total Nucleated Cells; UC, Unrelated Cord Blood.

* The Tissue Establishment's quality system is subject to the requirements of Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004.

** Methods: manual using HES for RBC sedimentation or other proprietary reagents; semi-automated bottom-and-top; fully automated and programmable closed systems.

*** Verification also of maternal HLA haplotype should add additional safety to the validation of HLA typing.

7.3 Tissues and Cells (other than HSC and Reproductive T&C)

The following tables are presented following the EuroGTPII Guidance -chapter 4- to ensure consistency throughout European projects:

The common specifications at key stages for all types of tissue are presented in seven tables:

- Donation: Donor characteristics
- Procurement: Procurement process and environment
- Processing/Storing/Transport: Processing and environment
- Reagents
- Microbiological testing
- Storage conditions
- Transport conditions

The specifications for Ocular, Placental, Skin, Cardiovascular, Musculoskeletal, Adipose and islets of Langerhans are then presented in specific tables.

7.3.1 Common specifications and transversal issues

7.3.1.1 Donor characteristics

A change or a novelty related to the donor characteristics should be evaluated in the light of relavant elements such as :

- Compliance with ethical requirement (informed consent, unpaid donation)
- Evaluate if the type of donod (deceased, living, autologous, allogenic] has an impact of the quality or safety of the product
    - what is the risk of degradation of the tissue over time after death?
    - how is the medical history reported ?
    - Are the risks related to allogenic transplantation vs autologous fully
- Evaluate the changes or novelties for the donor selection process :
    - is the extent of the information investigated sufficient to be complete (medical record, next of kin or donor risk assessment interview; general practitioner interview, specific file and previous results according to medical history ?…

- are the eligibility criteria consistent with the methods and controls set during the process?
- is any extension of donor selection criteria and relative contra indication justified by a risk analysis ?

What should be specified in a PPD					*What needs to be justified in case of change*		
Criteria	Situation	Accepted Critical Quality Attribute	Accepted Critical Process Parameter	References	*Case of change at low risk*	*Novelty or changes to the situation is at moderate risk*	*Case of change at high risk*
Donor screening	Autologous	Tested for Minimum mandatory Testing*		EUTCD 2006/17/CE Annex II GAPP WP7 table 7.1	*Add new testing appropriate to local or emerging disease*		
	Allogenic	Negative results for Minimum mandatory Testing: Ag/Ab VIH-1,2 Hepatitis B (AgHBs) and C (Ab) Syphilis Additional testing when relevant: +/- HTLVI/II		EUTCD 2006/17/CE Annex II GAPP WP7 table 7.1 National regulations ECDC alert	*Add new testing appropriate to local or emerging disease* *New supplier of reagents*	*Changes in testing with same restrictions*	*Changes in testing with lower restrictions*

What should be specified in a PPD					*What needs to be justified in case of change*		
Criteria	Situation	Accepted Critical Quality Attribute	Accepted Critical Process Parameter	References	*Case of change at low risk*	*Novelty or changes to the situation is at moderate risk*	*Case of change at high risk*
		+/- NAT testing for VIH HBV HCV depending on local regulation +/-others related to specific risk					
Time for collecting blood samples for testing	Living		Must be precised At the time of donation or, if not possible, ≤7 days post donation	EUTCD 2006/17/CE Annex II		*Changes in duration with longer period*	
	Deceased DBD		Just prior to death or, if not possible, as soon as possible after death and in any case ≤ 24 hours after death.	EUTCD 2006/17/CE Annex I			
	Deceased DCD						*any longer period should be fully justified and validated regarding the reliability of the tests*
Donor selection	Contraindications	Absence of absolute contraindication		EUTCD 2006/17/CE Annex I			*No change authorized*

What should be specified in a PPD					*What needs to be justified in case of change*		
Criteria	Situation	Accepted Critical Quality Attribute	Accepted Critical Process Parameter	References	*Case of change at low risk*	*Novelty or changes to the situation is at moderate risk*	*Case of change at high risk*
		Absence of specific contraindication	Determine which chronic, systemic autoimmune disease could have a detrimental effect on the quality of the tissue to be retrieved which vaccination with a live attenuated virus may have a risk of transmission which substance whose Ingestion of, or exposure to may be transmitted to recipients in a dose that could endanger their health. which type or dosage and duration of treatment with immunosuppressive agents could invalidate test results of donor blood samples	EUTCD 2006/17/CE Annex I		*Changes with lower restrictions (reducing control on impact on the tissues or cells, enlargement of acceptance criteria)*	
	Donor age	To be justified and precised if to be considered as quality					

What should be specified in a PPD					*What needs to be justified in case of change*		
Criteria	Situation	Accepted Critical Quality Attribute	Accepted Critical Process Parameter	References	*Case of change at low risk*	*Novelty or changes to the situation is at moderate risk*	*Case of change at high risk*
		criteria or absolute limit					
	HLA testing	If compatibility is justified					

7.3.1.2 Procurement procedures& environment

What should be specified in a PPD	*What needs to be justified in case of change*

Criteria	Situation	Accepted Critical Quality Attribute	Accepted Critical Process Parameter	References	*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
Time from death to procurement	body not refrigerated*		As soon as possible and within 12 hours after death if	EDQM T&C guide chapter 6	*Changes with upper restrictions*	*Changes in duration with longer period and temperature with higher limit with no impact on CQA*	
	body refrigerated within 6 hours		As soon as possible and within 24 hours after death *				
Retrieval procedures	Conditions	Accepted Initial bioburden should be defined	Aseptic conditions**	EUTCD 2006/17/CE Annex II GAPP WP7 table 7.1		*Changes on environmental conditions with lower qualification*	
	If a validated sterilisation procedure is included in the manufacturing process	Initial bioburden accepted should be defined	Clean condition could be accepted			*Changes on upper limit of the initial accepted bioburden*	
	Processing step at the procurement stage	Initial bioburden accepted should be defined	In-process (active) environmental-monitoring Sample of procured tissues should be cultured with validated culture method Not defined***	EDQM T&C guide chapter 6 §6.4.1			
	Time from	Not defined***	To be registered			*Changes in*	

What should be specified in a PPD					*What needs to be justified in case of change*		
Criteria	Situation	Accepted Critical Quality Attribute	Accepted Critical Process Parameter	References	*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
	procurement to processing					*duration with longer period*	
			Describe Reconstruction procedure in case of deceased donor				
Material			Validated, sterile instruments, CE-marked devices (where available) sterile single-use materials (e.g. drapes, fluids, gloves…)		*Changes of supplier or new supplier*	*Changes of sterility parameters or non CE marked or not for human use instruments*	
Facilities	Classification (particles and microbiological contamination)	ISO standards according to the claimed classification		EDQM T&C guide chapter 7 ISO 14644-1 EU GMP		*Changes on environmental conditions with lower qualification*	
			Classification claimed in accordance with the length of the procedure, the number of people present during the procurement, the possible reduction of bioburden.	EDQM T&C guide chapter 6			
Packaging			Validated sterile packaging Outer container with a				

What should be specified in a PPD					*What needs to be justified in case of change*		
Criteria	Situation	Accepted Critical Quality Attribute	Accepted Critical Process Parameter	References	*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
			tamper-evident seal.				
Labelling			Unique donation number or code type of tissue date ID of procurement organisation.	EDQM TC guide Chapter 14.6			*No change authorized*

*** Where limits are not defined in the literature, they must be set and justified by the TE and validation data must submitted to demonstrate that the specified limits are met. Such parameters must be supported by written justification and be authorised by the relevant Health Authority

7.3.1.3 Processing and environment

What should be specified in a PPD					*What needs to be justified in case of change*		
Criteria	Situation	Accepted Critical Quality Attribute	Accepted Critical Process Parameter	References	*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
Mechanical action	Dissection	Absence of residual tissue or cells (if applicable)	Macroscopic control	EUTCD 2006/17/CE Annex II GAPP WP7 table 7.1		*Changes in method should demonstrate the efficacy of the step to achieve the same CQA*	
	Cleansing or washing	Absence of residual tissue Absence of immunogenic cells (if relevant) Absence of chemical residues (if needed)	Macroscopic control Validated method where CQA have been demonstrated	Euro GTPII guidance		*Changes in method should demonstrate the efficacy of the step to achieve the same CQA*	
	Cutting, grinding, shaping and sizing	Precise description of the tissues: Measurements (length, surface, volume, diameter) Shape Granularity Not defined**	Validated method where CQA have been demonstrated			*Changes in method should demonstrate the efficacy of the step to achieve the same CQA*	

What should be specified in a PPD					*What needs to be justified in case of change*		
Criteria	Situation	Accepted Critical Quality Attribute	Accepted Critical Process Parameter	References	*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
		Impact on structural integrity or expected quality of the tissue (strength, softness, resistence, torsion, elasticity, morphological integrity, absence of abnormalities anatomopathologist	Validated method where CQA have been demonstrated			*Changes in method should demonstrate the efficacy of the step to achieve the same CQA*	
Decontamination	Antibiotic disinfection	No microbiological growth tested on individual product	Composition not defined* Incubation time and temperature not defined*.	EDQM T&C guide Chapter 10		*Changes in method should demonstrate the efficacy of the step to achieve the same CQA with respect to the CQA of the tissues or cells* *Choice of the type of antibiotics selected, the expected spectrum of action, the incubation time*	*Changes in method with lower efficacy and less stringent CQA should be evaluated in respect to clinical requirements*
		Residual antibiotic level	Not define, to be validated	EDQM T&C guide Chapter 10			

What should be specified in a PPD					*What needs to be justified in case of change*		
Criteria	Situation	Accepted Critical Quality Attribute	Accepted Critical Process Parameter	References	*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
						and temperature should be justified.	
	Viro-inactivation	Absence of viral contamination	Successive preparation steps not define, to be validated (reagents, time, temperature) Choice of virus similar to the virus that may contaminate a tissue. Such types include enveloped, non-enveloped, DNA and RNA viruses			*Changes in method should demonstrate the efficacy of the step to achieve the same CQA with respect to the CQA of the tissues or cells.*	*Changes in method with lower efficacy and less stringent CQA should be evaluated in respect to clinical requirements*
	Final sterilisation (gamma irradiation, ebeam)	Sterility Assurance Level on Sterile product:	SAL<10^{-6}	European Pharmacopoeia		*Changes in method should demonstrate the efficacy of the step to achieve the same CQA with respect to the CQA of the tissues or cells.*	*Changes in method with lower efficacy and less stringent CQA should be evaluated in respect to clinical requirements*
		Absence of bacterial, viral or fungal contamination	Validated potency on a theoretical initial biocharge of Gram-positiveand	EN 1040 standard and/or Committee for Proprietary Medicinal Products (CPMP)			

What should be specified in a PPD					*What needs to be justified in case of change*		
Criteria	Situation	Accepted Critical Quality Attribute	Accepted Critical Process Parameter	References	*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
			Gram-negative bacteria, spores and fungi, and known relevant 'resistant' species, relevant species of enveloped and non-enveloped viruses with different particle sizes	guidelines			
Dehydratation		Residual water content / active water content <5 % / 0.2 - 0.5 Aw	Duration and temperature of the cycle not defined*, to be validated			*Changes in duration or temperature applied during the cycle to be validated*	
Cryopreservation		Nature of the cryoprotectant Residual trace after washing	Composition not defined Dosage and duration of incubation Washing step before graft to be validate (nb of bath,		*Change of supplier*	Changes in the choice of the cryoprotectant selected; changes in the CPP	

What should be specified in a PPD					*What needs to be justified in case of change*		
Criteria	Situation	Accepted Critical Quality Attribute	Accepted Critical Process Parameter	References	*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
			dilution, duration)				

7.3.1.4 Reagents

For products or materials coming into contact with tissues and cells at any step (medical devices, medicines, others):

- Name.
- Name and address of manufacturer.
- Qualification/status of the product (CE marking for medical devices, licensing for medicines, others).
- Quality control measures including, ,where appropriate, tests performed, methods applied and their validation and acceptance criteria, or quality guarantees (manufacturers analysis certificate).
- Justification of the choice of the products or materials non CE marked coming into contact with procured tissues and cells.
- Justification of the choice of packaging (compatibility of the packaging with the tissues or cells).

What should be specified in a PPD					*What needs to be justified in case of change*		
Criteria	Situation	Critical Quality Attribute	Critical Process Parameter	References	*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
Critical reagents	Medical device	critical quality attributes, with acceptance limits;	directions for sampling and testing, or reference to procedures	In accordance with Directive 93/42/EEC	*Changes of supplier*	*Changes for a non CE marked reagent or not for human use*	
	In vitro diagnostic medical devices.	critical quality attributes, with acceptance limits ;		In accordance with Directive 98/79/EC			
	Antibiotics *And medicinal products*	critical quality attributes, with acceptance limits ;		the reference (if any) to a pharmacopoeia	*Changes for same category with same*	*Changes for another category with*	if

What should be specified in a PPD					*What needs to be justified in case of change*		
Criteria	Situation	Critical Quality Attribute	Critical Process Parameter	References	*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
					spectrum of action	*different spectrum of action – changes in dosage*	
Maximum storage time		storage conditions and precautions		following manufacturer instructions		*Changes in duration for longer period*	
Composition		Certificate of analysis or of compliance from the manufacturer, available for each reagent used				*Any use in a manner that is not consistent with the instructions of the manufacturer*	

7.3.1.5 Reliability of microbiological testing

What should be specified in a PPD					*What needs to be justified in case of change*		
Criteria	**Situation**	**Critical Quality Attribute (L)**	**Critical Process Parameter (L)**	**References**	*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
Donor	Haemoculture (if relevant)		Positive results might not predict of the result of the tissues and exclude their use				
	Swab		Positive results might not predict of the result of the tissues and exclude their use				
Sampling	Pre-processing on samples for initial bioburden estimation	Negative or low virulent microorganisms given a decontamination procedure is followed	collection of representative sample			*Changes in nature or localisation or number or volume of samples collected should be justified*	
	Sample for In process control		After each open step	EDQM T&C guide chapter 10			
	Samples representing Final product including packaging	Negative	1-2% of all final packages	Eur pharmacopoeia			

What should be specified in a PPD		*What needs to be justified in case of change*
Next step about microbiological contamination	See Technical Annex II	

7.3.1.6 Storage conditions

What should be specified in a PPD					*What needs to be justified in case of change*		
Criteria	Situation	Critical Quality Attribute	Critical Process Parameter	References	*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
Control of temperature	Room temperature for dehydrated, fully glycerolised.	+15°C ≤ t° ≤ +25°C	Validation on Structural integrity and/or viability	EDQM T&C guide chapter 11	*Change of equipment*	*Changes in extending limits of the duration of storage period, or of the range of temperature should be validated to demonstrate the maintain of the CQA of the product*	
	Organo-culture	+28°C ≤ t° ≤ +37°C	Maximum storage time limit must be defined following manufacturer's recommendation for each media bottle and on the cumulative whole duration Validation on Structural integrity and/or viability				
	Cooled	+8°C ≤ t° ≤ +15°C	Validation on Structural integrity and/or viability				
	Refrigerated	+2°C ≤ t° ≤ +8°C	Validation on Structural integrity and/or viability				

What should be specified in a PPD					*What needs to be justified in case of change*		
Criteria	Situation	Critical Quality Attribute	Critical Process Parameter	References	*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
	Frozen	t° ≤ -15°C	Validation on Structural integrity and/or viability				
	Deep-frozen	-80°C ≤ t° ≤ -60°C	Validation on Structural integrity and/or viability				
	Cryopreserved	t° ≤ -140°C	Validation on Structural integrity and/or viability				
Duration			Maximum storage time limit must be defined and validated in extreme condition				
Primary packaging for finished product	Not defined*	Sterile CE marked or validated Not defined *	Not defined * radiation resistance validated	1	*Changes of supplier*		
Labelling	Unique	Unique identification number or code (single European code SEC) - type of tissue and cells - expiry date - temperature range		EDQM T&C guide, chapter 14			*No change authorised*

7.3.1.7 Transport conditions

What should be specified in a PPD					What needs to be justified in case of change		
Activity	Situation	Critical Quality Attribute	Critical Process Parameter	References	*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
Outer packaging	Room temperature	+15°C ≤ t° ≤ +25°C		EDQM T&C guide chapter 11		*Changes in extending limits of the duration of storage period, or of the range of temperature should be validated to demonstrate the maintain of the CQA of the product*	
	Organ cultured	At room temperature or +28°C ≤ t° ≤ +37°C					
	Refrigerated	on ice or device					
	Frozen	t° ≤ -15°C					
	Deep-frozen	Container with dry ice or qualified cooling systems.					
	Cryopreserved	Dry-shipping containers vapor-phase nitrogen < −140 °C).	Dry shipper validated for a length of time at least >48h before expiry date				
Duration			Upper time limit defined				
Packaging	Outer Packaging		Resistance to shocks and temperature variations	1 Chapter 14, 3	*Changes of supplier*		

What should be specified in a PPD					What needs to be justified in case of change		
Activity	Situation	Critical Quality Attribute	Critical Process Parameter	References	*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
Labelling	Labelling outer packaging	HUMAN TISSUE Identification of originated TE identification of OHRA destination HANDLE WITH CARE DO NOT IRRADIATE	Single European Code (SEC)	EDQM T&C guide, chapter 14			*No changes authorized*

7.3.2 Specific Criteria

7.3.2.1 General considerations

The T&C field evolves. Each new of the successive updates of the EDQM guide for Q&S of T&C makes it the main reference.

The Monographs dedicated to each specific tissue are the relevant source to define CQA or CPP, respectively in its paragraph « critical properties » and « quality control requirement »

The following tables, as a general guidance, describe the main steps a TE should control for a whole preparation process. Some of the common topics where specifically addressed in the first part and tables, in such cases the tables will refer to them. Some of the criteria should be read in addition to the monographs.

The level of proof or of validation can be adapted by CA to enforceable requirements such as those set in the monographs

Changes or novelties range from :

- Cases where CQA are to be maintained
    - Assessment that the product meets specification before release :
        - Does the report validation specify the Critical Quality Attributes (CQAs) necessary to be satisfied the tissues or cells are not rendered clinically ineffective or harmful by the preparation process?
        - Does the validation report precisely define the CQAs and provide information on the tests performed to determine whether the CQAs have been achieved?
        - Does the validation report demonstrate that the process is reproducing the CQAs consistently? Are validated assays provided to measure CQAs?

- Cases where the change involves a modification of the CQAs
    - **Written specifications to include**:
        - Provide references to the research papers from which the specification is derived.
        - Expected characteristics See part 1
        - Testing characteristics (viability, residual water, measurement, microbiology etc.) See part 1
    - **Evaluate the impact of the change on CQA on clinical properties**
        - Document evidence of clinical protocol being implemented e.g. patient record, case report form, registry reports

- Clinical application
    - Patient population to be treated (e.g. age, indication for treatment, previous/concomitant therapies)
    - Clinical application method
    - Method for monitoring the patients' safety and efficacy: standard medical practice, vigilance program, data collection in a scientific registry, clinical trial (in this case the Medical/Ethical Committee approval might be needed)
    - Donor safety (if applicable)
- Outcome assessment
- Report of any adverse incidents during collection, production and/or clinical application

7.3.2.2 Ocular Tissue

Contexte and general information

- Tissue retrieved from a deceased donor as a whole globe or as a corneoscleral disc;
- Source material for ocular surface reconstruction, or endothelial cells replacement by keratoplasty to restore vision or for architectonic purpose to maintain the integrity of the globe;
- Used after a cold storage period or after an organ-culture period;
- Among the categories of ocular tissue: cornea; sclera; limbal stem cells are used for clinical application
    - Cornea
        - outermost layer of the eye, central and transparent. It contains no blood vessels. The cornea receives oxygen and nutrients from the tears and the vitreous humour from the anterior chamber. The cornea is a concave disc (0,5mm thickness, 8 to 10 mm diameter) and acts as a lens. Its main characteristic and property is to be transparent to let light enter into the eye. A cornea graft is the replacement of damaged tissue by healthy tissue. Cornea grafts have no alternative treatment
        - Among the categories of cornea: full or partial thickness cornea either for anterior lamellar or endothelial keratoplasty
    - Sclera
        - The sclera is the white highly irrigated layer surrounding the eye. Sclera is used as pieces of patches to repair ocular surface disorders (dry eye syndrome) or as 'carrier' for prosthesis after enucleation
    - Limbal Stem cells

- Limbal Stem Cells are situated at the junction between the Sclera and the cornea. This ring of tissue constitutes a veritable barrier that prevents conjunctivital cells and blood vessels from invading the epithelial surface of the cornea. The guarantee the crystalline transparency of the cornea. They are grafted by the transplant of the corneal scleral ring.

List of existing monographs for ocular tissue in the EDQM T&C guide

1. Organ-cultured corneal donor tissue for (deep) anterior lamellar keratoplasty (ALK/DALK)
2. Cold-stored corneal tissue for (deep) anterior lamellar keratoplasty (ALK/DALK)
3. Organ-cultured corneal tissue for Descemet membrane endothelial keratoplasty (DMEK)
4. Cold-stored corneal tissue for Descemet membrane endothelial keratoplasty (DMEK)
5. Organ-cultured corneal tissue for Descemet stripping automated endothelial keratoplasty (DSAEK)
6. Cold-stored corneal tissue for Descemet stripping automated endothelial keratoplasty (DSAEK)
7. Organ-cultured corneal tissue for penetrating keratoplasty (PK)
8. Cold-stored corneal tissue for penetrating keratoplasty (PK)

What should be specified in a PPD							*What needs to be justified in case of change*		
	Acceptance criteria to release cornea for						*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
Critical processing parameter (CPP) / Critical Quality Attribute (CQA)	Architectonic PK Stromal patch	PK	DMEK	DALK	DSAEK	References *			
Time between death and procurement	See table 7.3.1.2 for "Procurement procedures& environment: common specifications" Up to 72h if specifically validated					1		*Extension of duration should demonstrate the absence of impact on*	

What should be specified in a PPD							*What needs to be justified in case of change*		
	Acceptance criteria to release cornea for						*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
Critical processing parameter (CPP) / Critical Quality Attribute (CQA)	Architectonic PK Stromal patch	PK	DMEK	DALK	DSAEK	References *			
								cornea CQA	
donor age limits	no upper age limit					3		*Extension of donor age should demonstrate the absence of impact on cornea CQA*	
Corneoscleral ring	Not defined	Not defined	≥9mm	≥2mm	≥2mm	1			
Clear inner diameter	≥7,5mm	≥7,5mm	NA	≥7,5mm	NA			*Acceptance of smaller inner diameter should be justified*	
Structural integrity	Absence of stromal scar or opacity	Absence of Stromal opacities	Tears should be noted	Absence of Stromal opacities	NA	1		*The structural characterisation of the cornea shall be*	

What should be specified in a PPD							*What needs to be justified in case of change*		
	Acceptance criteria to release cornea for						*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
Critical processing parameter (CPP) / Critical Quality Attribute (CQA)	Architectonic PK Stromal patch	PK	DMEK	DALK	DSAEK	References *			
								assessed to evaluate the impact of a change in the preparation process by anatomical exam	
Endothelial structure	NA	No Guttata, no severe polymegathism or pleomorphism	No Guttata, no severe polymegathism or pleomorphism	NA	No Guttata, no severe polymegathism or pleomorphism	1		*The characterisation of the endothelium shall be assess to evaluate the impact of a change by staining method such as alizarine red marquage.* *Counting shall*	
Final Endothelial cell count	1000 to 2000 cells/mm²	≥2000cells/mm²	≥2000cells/mm²	1000 to 2000 cells/mm²	≥2000cells/mm²	1	*Changes in the method of evaluation with no changes claimed in*		*Changes in decreasing the upper limit in the indication to be validated regarding*

What should be specified in a PPD							*What needs to be justified in case of change*		
	Acceptance criteria to release cornea for						*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
Critical processing parameter (CPP) / Critical Quality Attribute (CQA)	Architectonic PK Stromal patch	PK	DMEK	DALK	DSAEK	References *			
							CQA	*be validated with internal or external quality control (standard grid, comparison between member staff, or between TE).*	*clinical efficacy*
Viability	Not defined	Not defined	Not defined	Not defined	Not defined	1	*Changes in the method of evaluation with no changes claimed in CQA*	*Evaluation shall be assess by staining dead cells (trypan blue for example) revealing no large dead zone (common limit applied is <2%).* *Changes in*	

What should be specified in a PPD							*What needs to be justified in case of change*		
	Acceptance criteria to release cornea for						*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
Critical processing parameter (CPP) / Critical Quality Attribute (CQA)	Architectonic PK Stromal patch	PK	DMEK	DALK	DSAEK	References *			
								higher rate should be validated.	
Cell loss	NA	≤25%	≤25%	NA	≤25%	1		*The preparation process is validated to demonstrate the maintain of the endothelium density along the time storage and to guaranty No cell loss between the initial cell count and the prior to deswelling count >25%.* *Changes in upper limit*	

What should be specified in a PPD							*What needs to be justified in case of change*		
	Acceptance criteria to release cornea for						*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
Critical processing parameter (CPP) / Critical Quality Attribute (CQA)	Architectonic PK Stromal patch	PK	DMEK	DALK	DSAEK	References *			
								should be validated	
thickness	Full	Full	-	Reevaluate after cutting	Reevaluate after cutting	1	*Method of evaluation*		
Microbiological	Negative-to-date microbiological testing (on culture medium 10ml) where the cornea stayed at least 3 days					1	*Changes in the testing method with no changes claimed in CQA*		*Enlargement on acceptance criteria or diminution of the duration of analysis to be validated on a clinical model*
Packaging	Sterile transparent containers with medium					1	*Changes of suppliers*	*To be validated if not for human used or non CE marked*	
Culture	Clear sterile No evidence of microbial growth: No turbidity no change of color					1		*Changes in culture media*	*If new culture media, new*

What should be specified in a PPD							*What needs to be justified in case of change*		
	Acceptance criteria to release cornea for						*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
Critical processing parameter (CPP) / Critical Quality Attribute (CQA)	Architectonic PK Stromal patch	PK	DMEK	DALK	DSAEK	References *			
medium evaluation	Either organ cultured or cold stored during time length at temperature as recommended by the manufacturer.							*to be validated to demonstrate its ability to preserve cornea fonctionnality and viability.* *No negative interaction between components and tissues should be evaluated*	*supplier, first in man*
Culture time	Not defined for the different kinds of use the cornea is intended for Check before release								
Deswelling medium or final	Duration (min max) Expiry date							*Changes in extending duration shall be validated to*	

What should be specified in a PPD							*What needs to be justified in case of change*		
	Acceptance criteria to release cornea for						*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
Critical processing parameter (CPP) / Critical Quality Attribute (CQA)	Architectonic PK Stromal patch	PK	DMEK	DALK	DSAEK	References *			
preparation								*demonstrate its ability to preserve cornea fonctionality and viability* *No negative interaction between components and tissues should be evaluated*	
Preimplantation preparation	Trephination	Trephination	Manual endothelial peeling vs none if precut	Semi automated cutting and thickness evaluation vs None if precut in TE	Semi automated cutting and thickness evaluation vs None if precut in TE	1		*Validation of the efficacy and reproductibility of the method*	

What should be specified in a PPD							*What needs to be justified in case of change*		
	Acceptance criteria to release cornea for						*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
Critical processing parameter (CPP) / Critical Quality Attribute (CQA)	Architectonic PK Stromal patch	PK	DMEK	DALK	DSAEK	References *			
Sclera					ethanol (≥ 70 % v/v), glycerol (≥ 85 % v/v)	1			

1. EDQM Guide to the quality and safety of tissues and cells for human application, 4th Ed; chapter 17.

2. EEBA Technical guidance for ocular tissue v11 - 01/02/2020

3. Armitage WJ; Preservation of human cornea;Transfus Med Hemother 2011;38:143–147

7.3.2.3 Placental tissue

Contexte and general information

Placental membranes:

- are the tissues, that surround and protect the foetus. The amnion is the inner membrane, the chorion the outer one. Both attached to the placenta

- are collected during delivery under caesarean section (vaginal delivery could only be accepted if a further validated sterilisation process is intended)
- are separated during processing from the placenta and cut into patches of various sizes then deep frozen or further processed: freeze dried, lyophilized, that can lead to other forms such as a spray, for example
- Amniotic membrane is a translucent soft and strong covering membrane. Its anti-fibriotic, anti-angiogenic and anti-proteatic properties give the amnion the benefits of reducing inflammation and scarring while promoting a better epithelialization
- is used for biological dressing and healing purpose in ophthalmology and dermatology, and as a substrate for cell growth in different clinical applications
- There are two major categories of amniotic membrane: cryopreserved (deep frozen) amniotic membrane (patches) and dehydrated (lyophilized) patches or spray.

The EDQM T&C guide had a single monograph for Amniotic membranes

- Amniotic membrane (AM) for biological dressing

What should be specified in a PPD				*What needs to be justified in case of change*		
Amniotic membrane Activity	Critical processing parameter (CPP) / Critical Quality Attribute (CQA)	Acceptance Criteria	References *	*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
Procurement	Tissue retrieval at the time of birth	Donations of tissue during a scheduled C-section is preferred	1		If procurement of tissue during vaginal delivery, validated sterilisation procedures should be applied to the processed AM to eliminate microbiological bioburden	
Transportation to TE	Time and temperature in transit	Recommended as short as possible <24h at 2-8 °C	1		*See: Transport conditions: common specifications table*	
		If at room temperature <2h before processing				
Processing	Physical and biological properties of AM Structural integrity Cell viability (if applicable)	Not defined*	1		*Process to be validated by anatomopathologist exam on AM structure to assess its characterisation*	*Changes in AM structure or biological properties to be validated regarding clinical efficacy*
	Microbiology - pre and post	Negative[a]	1		*Process to be validated to*	

What should be specified in a PPD				*What needs to be justified in case of change*		
Amniotic membrane Activity	Critical processing parameter (CPP) / Critical Quality Attribute (CQA)	Acceptance Criteria	References *	*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
	processing				*guaranty no growth of microorganism*	
	Residual antibiotics (if used during processing)	Not defined*	1	*Changes of supplier*	*To be tested and measured at the validation step of the PPA*	
	Residual glycerol / cryopreservative concentration (if applicable)	Not defined*	1		*To be characterised*	
	Residual water content / active water content (if lyophilized)	a residual moisture of 1-6 % (w/w) or available water (aW) of < 0,5 is recommended	1		*To be characterised*	
Storage	Time and temperature of storage	Cryoprotected AM - -80°C or <-140°C, expiry linked to storage temp. Distribution should be in dry ice or liquid nitrogen dry-shipper	1		*See Storage conditions: common specifications*	
		Frozen AM - temp between -15°C and -80°C, expiry linked to storage temp. Distribution should be at similar temperature as was used during storage	1			
		Heat-dried AM - storage at room temperature, shelf life should be justified	1			
		Air-dried AM - storage at room temperature, shelf life should be justified	1			

What should be specified in a PPD				*What needs to be justified in case of change*		
Amniotic membrane Activity	Critical processing parameter (CPP) / Critical Quality Attribute (CQA)	Acceptance Criteria	References *	*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
		Lyophilised (freeze-dried) AM - storage at room temperature, shelf life should be justified	1			
		Glycerolised AM - storage 2-8°C for up to 2 years Distribution should be at 2-8°C	1			
Distribution and Transport Conditions	Frozen and Deep Frozen	Container with dry ice or qualified cooling systems.	1			
	Cryopreserved	Dry-shipping containers vapor-phase nitrogen < −140 °C).	1		*See transport condition*	
	Lyophilized	At room temperature				
	Labelling	ISBT128, Eurocode, Single European Code (SEC)	1			
Before graft	Thawing or rehydratation	As described the procedure				

References:

1. EDQM Guide to the quality and safety of tissues and cells for human application, 4th Ed; chapter 18.

2 - Directives 2004/23/EC and 2006/86/EC

A positive result prior to processing may not preclude processing of a tissue if validated decontamination or sterilisation methods are used. Acceptance limits for microbial load and exclusion criteria must be defined.

* Where limits are not defined in the literature, they must be set and justified by the TE and validation data must be submitted to demonstrate that the specified limits are met.

7.3.2.4 Cutaneous Tissue

Contexte and general information

- Tissue retrieved from deceased donors after brain death (DBD) or circulatory death (DCD) and more rarely on living donor during aesthetic reduction surgery;
- It is the largest tissue, covering the body surface (1,7m² on average), consisting of two main parts: an outer layer, the epidermis, and an inner layer, the corium (or dermis).
- It is a protective barrier against microorganisms, a shield to the inner body from mechanical and other injuries and performs a number of vital functions; acts as an insulator against heat and cold.
- It is procured under aseptic conditions with a dermatome.
- The characteristics of skin grafts is split-thickness and full-thickness grafts. They consist of the entire epidermis and adermal component of variable thickness.
- It is used for wound healing (burns, ulcers…) and regeneration. Human skin graft is the gold standard treatment for patients suffering from extended burns.
- Among the categories of skin: Cryopreserved and deep-frozen skin allografts; Lyophilised skin allografts; De-epidermised skin and acellular dermis

List of existing monographs for skin in the EDQM T&C guide

1. Acellular dermal matrix (ADM)
2. Deep-frozen skin allografts
3. Glycerol-preserved skin allograft

What should be specified in a PPD	*What needs to be justified in case of change*

(CPP) / (CQA)	fresh skin	deep-frozen skin	cryopreserved skin	glycerolized skin	lyophilized	De-epidermised skin acellular dermal matrix	References	*In case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
Time between death and procurement	NA	Preferably as described in table transversal specification 48hrs max if preservation of quality and microbiological safety of the tissue is validated					EDQM Guide T&C ; chapter 19			
Technique for procurement	scalpel	dermatome	dermatome	dermatome	dermatome					
Characterisation of the procured tissue	full thickness	Graft thickness must be recorded: full thickness vs split thickness: thin (0.008-0.012 in/0.2-0.3 mm), medium (0.012-0.018 in/0.3-0.45 mm) thick (0.018-0.030 in/0.45-0.75 mm).					EDQM Guide T&C ; chapter 19 and monograph 19.1		*Justify compliance with medical indication.*	
Microbiology - pre processing of skin samples for initial bioburden estimation	Negative or low virulent * microorganisms given a decontamination procedure is followed						GAPP WP 7		*Method of détection*	*Modification in the composition or load of the accepted initial bioburden*
Transport	Not defined* must be validated with or without antibiotics						EDQM Guide T&C	*Composition of the mediawith*	*Composition of the media with*	

What should be specified in a PPD								What needs to be justified in case of change		
(CPP) / (CQA)	fresh skin	deep-frozen skin	cryopreserved skin	glycerolized skin	lyophilized	De-epidermised skin acellular dermal matrix	References	*In case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
Media							; chapter 19	*similar CQA*	*significant modifications*	
Temporary storage and transportation to TE **Temperature in transit**	2 to 8°C if viability is to be preserved	2 to 8°C	2 to 8°C if viability is to be preserved	Not defined* ambiant temperature	Not defined* ambiant temperature			*See relevant table in section 7.3.1*		
Duration	not defined*		Not defined* with or without antibiotics	Not defined* with or without antibiotics	Not defined* with or without antibiotics			*See relevant table in section 7.3.1*		

What should be specified in a PPD								*What needs to be justified in case of change*		
(CPP) / (CQA)	fresh skin	deep-frozen skin	cryopreserved skin	glycerolized skin	lyophilized	De-epidermised skin acellular dermal matrix	References	*In case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
Time between procurement and processing	as soon as possible if viability is expected	up to 72hrs if adequate buffering capacity	as soon as possible if viability is expected	up to 72hrs if adequate buffering capacity	up to 72hrs if adequate buffering capacity		1	*See relevant table in section 7.3.1*		
Microbiology - in processing	Not defined*	Not defined*	Not defined*	Not defined*	Not defined*		1 - chapter19. 5.1.	*See relevant table in section 7.3.1*		
sizing	not defined: cm^2/ in^2	not defined: cm^2/ in^2	not defined: cm^2/ in^2	not defined: cm^2/ in^2	not defined: cm^2/ in^2			*describe*		
Cell viability (if applicable)	Not defined	NA	Not defined*	NA	NA				*Justify choice of percentage and impact*	
Structural integrity	Not defined* Normal epidermal/dermal structure	Not defined* Normal epidermal/dermal structure	Not defined* Normal epidermal/dermal structure	Not defined* Normal epidermal/dermal structure	Not defined*	Not defined*			*Validate with anatomopatho-logical exam*	

What should be specified in a PPD								What needs to be justified in case of change		
(CPP) / (CQA)	fresh skin	deep-frozen skin	cryopreserved skin	glycerolized skin	lyophilized	De-epidermised skin acellular dermal matrix	References	*In case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
Glycerol concentration	NA	Not defined*	Not defined*	(50% - 70% - 85%) Not defined*	NA	NA	European pharmacopoeia monograph 0497		*Justify composition of the solution* *Validate the efficacy of protection*	
Cryoprotectant	NA	Not defined* (DMSO, glycerol)		NA	NA	NA			*Analyse viability prior and after cryopreservation*	
Control-rate freezing procedure	NA	Not defined*	Not defined*	NA	NA	NA				
Decontamination	ATB cocktail composition validated Not defined*	ATB cocktail composition validated Not defined*	ATB cocktail composition validated Not defined*	NA	NA	NA	*EDQM Guide T&C ; chapter 8*		*Justify composition of the solution* *Validate the efficacy of protection*	

What should be specified in a PPD								*What needs to be justified in case of change*		
(CPP) / (CQA)	fresh skin	deep-frozen skin	cryopreserved skin	glycerolized skin	lyophilized	De-epidermised skin acellular dermal matrix	References	*In case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
Decellularisa-tion process	NA	NA	NA	NA	NA	Histological staining and DNA quantification assay	1, 4		*Validate the effectiveremoval of cells and cellular components;* *Validate the effective removal of microbial contamination and any potentially toxic microbialproducts (e.g. endotoxins);* *Validate the effective removal of undesirable and potentiallytoxic reagents;* *Test*	*Clinical efficacy*

What should be specified in a PPD								What needs to be justified in case of change		
(CPP) / (CQA)	fresh skin	deep-frozen skin	cryopreserved skin	glycerolized skin	lyophilized	De-epidermised skin acellular dermal matrix	References	*In case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
									maintenance of desired ECM structural characteristics.	
Residual antibiotics (if used during processing)	Not defined*	Not defined*	Not defined*	NA	Not defined*				*Identify of any residual processing chemicals*	
Residual glycerol / cryopreservative concentration (if applicable)	NA		Not defined*	Not defined*	Not defined*					
Residual water content / active water	NA		NA	NA	<5 % / 0.2 - 0.5 Aw	<5% if lyophilised				

What should be specified in a PPD								*What needs to be justified in case of change*		
(CPP) / (CQA)	fresh skin	deep-frozen skin	cryopreserved skin	glycerolized skin	lyophilized	De-epidermised skin acellular dermal matrix	References	*In case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
content (if applicable)										
Microbiological final testing	No evidence of microbiological growth	No evidence of microbiological growth	No evidence of microbiological growth	No evidence of microbiological growth	No evidence of microbiological growth	No evidence of microbiological growth	No evidence of microbiological growth			
Thawing	NA	Not Define	Not Define	NA	NA					
Washing	not defined	NA	NA	Not Define			not defined			
Rehydratation	NA	NA	NA	NA	Not Define					

1 - EDQM Guide to the quality and safety of tissues and cells for human application, 4th Ed

2 - SaBTO Microbiological Safety Guidelines

3 - Directives 2004/23/EC and 2006/86/EC

[a] Positive results prior to processing may not preclude processing of tissue if validated decontamination or sterilisation methods are used. Acceptance limits for microbial load and exclusion criteria must be defined.

* Where limits are not defined in the literature, they must be set and justified by the TE and validation data must be submitted to demonstrate that the specified limits are met.

7.3.2.5 Cardiovascular Tissue

Cardiovascular Tissue

- Is composed of all the elements that ensure the circulation of blood in the body from heart to the organs and the extremities of the limbs.
- Among cardiac tissues there are heart valves (pulmonary, aortic, rarely mitral), non-valved conduits or patches and pericardium.

Heart Valves

- are provided by the dissection of the valves from the heart of a deceased donor or a living donor receiving a heart transplant.
- are a source material for pulmonary, aortic, rarely mitral, hardly ever tricuspid valve homografts
- Human heart valves are used cryopreserved or decellularized for the replacement or reconstruction of failing heart valves
- Used in transplantation, heart valves have less potential risk for infections than artificial heart valves and represent a gold standard in congenital disorders.

Blood Vessels

Arteries or veins procured on deceased donor, or living in case of saphenectomy
Is an essential source material for the replacement of failing vessels
Used with best results in life threatening infection of the prosthetic and/or native vascular tissue in cases of high grade stenosis and thrombosis with no other possibility of treatment
Among the category of vascular tissue: femoral arteries, and also ascending aorta, aortic arch, descending aorta, iliac arteries, aorto-iliac bifurcation, saphenous vein, vena cava with iliac veins,

List of existing monographs for Cardiovascular tissue in the EDQM T&C guide

1. Cryopreserved femoral artery allograft, antibiotic decontaminated.
2. Cryopreserved heart valve allograft, antibiotic decontaminated

What should be specified in a PPD				*What need to be justified in case of change*		
Activity	Critical processing parameter (CPP) / Critical Quality Attribute (CQA)	Acceptance Criteria	References	*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
Procurement	Time between death and procurement (deceased donors)	12 hours or up to 24 if the body has been cooled within 6 hours hrs	2			
	Donor age range	Not defined The following limits are not absolute but provided as a quality criteria Arteries male 17-45 years of age female 17-60 years of age Aortic valves 32 weeks' gestation to 60 years of age Pulmonary valves 32 weeks' gestation to 70 years of age	1			
Transportation to TE	Temperature and Time in transit	2-8°C To allow same day processing of tissue	1			
	Media	crystalloid transport solution				
Processing	Time between procurement and processing	<24 hrs Time from procurement of the heart to dissection and disinfection.	1			
	Time between procurement and storage	<72hrs for the total ischaemia time (cardiac arrest to cryopreservation and storage)				
	Microbiology - pre and post processing	Negative[a]	1			
	Residual antibiotics (if used	Not defined*				

What should be specified in a PPD				*What need to be justified in case of change*		
Activity	Critical processing parameter (CPP) / Critical Quality Attribute (CQA)	Acceptance Criteria	References	*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
	during processing)					
	Residual cryopreservative concentration (if applicable)	Not defined*				
	Rim of myocardium or mitral leaflet (valves)	2 mm depth surrounding base of vessel	1			
	Calcification (valves/vessels); Atheroma (vessels)	None visible	1			
	Stenosis or dilation (vessels)	None visible	1			
	Cuts or significant haematomas (vessels)	None	1			
	Functionality tests (competency) (valves)	Native biomechanical / hydrodynamic properties unaltered	1			*If changes impact on functional test*
	Annular diameter (valves/vessels)	Must be measured Not defined*				
	Residual decellularisation reagents (if used during processing)	Not defined* *effectiveremoval of cells and cellular components;* *effective removal of microbial contamination and any potentially toxic microbial products (e.g. endotoxins);* *effective removal of undesirable and potentially toxic reagents;* *maintenance of desired ECM structural characteristics.*			*Change of method evaluate impact of ethylene oxide exposure, gamma irradiation and electron-beam irradiation, and the alteration of ECM structure and mechanical properties*	*Clinical evaluation of fonctionnality*
Storage	Time and temperature of storage	decellularised tissue -				

What should be specified in a PPD				*What need to be justified in case of change*		
Activity	Critical processing parameter (CPP) / Critical Quality Attribute (CQA)	Acceptance Criteria	References	*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
		cryopreserved tissue - <-80°C or in vapour phase liquid nitrogen <-140°C, expiry linked to storage temp.	1			
Distribution and Transport Conditions	Frozen and Deep Frozen	Container with dry ice or qualified cooling systems.	1			
	Cryopreserved	Dry-shipping containers vapor-phase nitrogen < −140 °C).	1			
	Labelling	ISBT128, Eurocode, Single European Code (SEC)	1			
Before graft	Thawing	As described in the procedure				

1 - EDQM T&C Guide, 4th Ed, chapter 20.

2 - SaBTO Microbiological Safety Guidelines

[a] positive results prior to processing don't necessarily preclude processing of tissue if validated decontamination or sterilisation methods are used. Acceptance limits for microbial load and exclusion criteria must be defined

* Where limits are not defined in the literature, they must be set and justified by the TE and validation data must submitted to demonstrate that the specified limits are met

7.3.2.6 Musculoskeletal Tissue

7.3.2.6.1 Musculoskeletal tissue

Composed of all the elements, massive bones and soft tissues that ensure the structure and rigidity of the body.

7.3.2.6.2 Bones

Cortico cancellous bone transplants are collected from living donors during surgery carried out for the benefit of the patient, mainly as femoral heads collected during hip surgery; or procured from deceased donors as whole bone.

Used as structural grafts or for filling purpose in skeletal defects in orthopaedic surgery including maxillofacial indications. Bone filling grafts are also used in dental surgery.

7.3.2.6.3 Cartilage

Cartilage is a very dense smooth connective tissue without blood vessels and nerves that covers joints. Cartilage is abrased with increasing age and has a low regeneration. Cartilage defects of can be repaired by a mosaic plastic where abnormal cartilage is filled with bone-cartilage-cylinders.

7.3.2.6.4 Ligaments and tendons

Ligament is a short band of tough, flexible fibrous connective tissue which connects two bones or cartilages or holds together a joint.Tendon is a flexible but inelastic cord of strong fibrous collagen tissue attaching a muscle to a bone In many cases ligaments and tendons need to be grafted during bone and cartilage transplantation.

7.3.2.6.5 Bone Matrix

The intercellular substance of bone, consisting of collagenous fibres, ground substance, and inorganic salts.

- List of existing monographs for Musculoskeletal tissue in the EDQM T&C guide

1. Cancellous bone chips
2. Cortical bone struts
3. Patellar tendon allografts

What should be specified in a PPD							*What needs to be justified in case of change*		
	Acceptance criteria for musculoskeletal for						*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
Critical processing parameter (CPP) / Critical Quality Attribute (CQA)	**Cryopreserved structural bone**	**Cryopreserved cancellous bone**	**Dehydrated viroinactivated sterilised cancellous bone**	**Demineralized viroinactivated sterilised bone matrix**	**Cryopreserved soft tissues**	**References ***			
donor age limits	Preferred 15-55 years	no upper age limit	no upper age limit	no upper age limit	15-45 years cartilage meniscus 15-65 years tendons	1			

What should be specified in a PPD							*What needs to be justified in case of change*		
	Acceptance criteria for musculoskeletal for						*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
Critical processing parameter (CPP) / Critical Quality Attribute (CQA)	**Cryopreserved structural bone**	**Cryopreserved cancellous bone**	**Dehydrated viroinactivated sterilised cancellous bone**	**Demineralized viroinactivated sterilised bone matrix**	**Cryopreserved soft tissues**	**References ***			
Microbiology - pre processing on the tissue and microbiology of rinsing solutions	no microbiological growth	no microbiological growth	positive results prior to processing may not preclude processing of tissue if validated decontamination or sterilisation method used. Acceptance limits for microbial load and exclusion criteria must be defined		no microbiological growth	1			
Transport media	none or validated composition of solution buffered at physiological pH +/- nutritional osmotic elements +/- antibiotic cocktail					1			
Primary	validated sterile packaging					1			

What should be specified in a PPD							*What needs to be justified in case of change*		
	Acceptance criteria for musculoskeletal for						*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
Critical processing parameter (CPP) / Critical Quality Attribute (CQA)	**Cryopreserved structural bone**	**Cryopreserved cancellous bone**	**Dehydrated viroinactivated sterilised cancellous bone**	**Demineralized viroinactivated sterilised bone matrix**	**Cryopreserved soft tissues**	**References ***			
packaging									
Temporary storage temperature	≤-15°C on procurement site if viability is not claimed	≤-15°C on procurement site if viability is not claimed	+2°C to +8°C		Not defined	1			
Temporary storage duration and time	Not defined *	Not defined*	less than 12hrs if viability s claime d		Not defined				

What should be specified in a PPD							*What needs to be justified in case of change*		
	Acceptance criteria for musculoskeletal for						*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
Critical processing parameter (CPP) / Critical Quality Attribute (CQA)	**Cryopreserved structural bone**	**Cryopreserved cancellous bone**	**Dehydrated viroinactivated sterilised cancellous bone**	**Demineralized viroinactivated sterilised bone matrix**	**Cryopreserved soft tissues**	**References ***			
before processing or storage									

Specifications (Critical processing parameter (CPP) / Critical Quality Attribute (CQA))	Cryopreserved structural bone	Cryopreserved cancellous bone	Dehydrated cancellous bone	Demineralized bone matrix	Cryopreserved soft tissues
Microbiology - pre processing on	no micobiological growth	no micobiological growth	Initial bioburden	Initial bioburden	no micobiological growth

Specifications (Critical processing parameter (CPP) / Critical Quality Attribute (CQA))	Cryopreserved structural bone	Cryopreserved cancellous bone	Dehydrated cancellous bone	Demineralized bone matrix	Cryopreserved soft tissues
the tissue and microbiology of rinsing solutions					
Sizing	volume or weight or size and shape or X-ray	volume or weight or size and shape or X-ray	volume and shape		
Cleansing defatting	NA	NA	batch release on a validated chemical and physical treatment or validated supercritical CO2 method % residues evaluation		
Dehydratation	NA	NA			
Viroinactivation	NA	NA	batch release on a validated inactivation or elimination of micro-organisms method		

Specifications (Critical processing parameter (CPP) / Critical Quality Attribute (CQA))	Cryopreserved structural bone	Cryopreserved cancellous bone	Dehydrated cancellous bone	Demineralized bone matrix	Cryopreserved soft tissues
Duration				validated method on osteoinductive activity (in vivo or in vitro)	
Terminal sterilisation					
Cell viability					if claimed
Morphology and integrity	Not defined*	Not defined*	Not defined*	Not defined*	Not defined*
Cryoprotectant	Not defined				
Residual cryopreservative concentration (if applicable)	Not defined				
Residual antibiotics (if					

Specifications (Critical processing parameter (CPP) / Critical Quality Attribute (CQA))	Cryopreserved structural bone	Cryopreserved cancellous bone	Dehydrated cancellous bone	Demineralized bone matrix	Cryopreserved soft tissues
used during processing)					
Microbiology - post processing on the tissue and Microbiology of rinsing solutions	no evidence of microbial growth	no evidence of microbial growth	sterile	sterile	

Activity	Type of processing and tissue	Critical processing parameter (CPP) / Critical Quality Attribute (CQA)	Acceptance Criteria	References *
Procurement		Time between death and procurement (deceased donors)	12h and up to 24h if refrigerated within 4 to 6 hours	1
		donor age limits	60-65 years up 18 for living allogeneic donation	1

Activity	Type of processing and tissue	Critical processing parameter (CPP) / Critical Quality Attribute (CQA)	Acceptance Criteria	References *
		Pre processing culture	Swab techniques and Biopsy	2
Transportation to TE		Hypothermic transfer	≤ −15 °C	1,2,3
		transportation immediate after procurement	within 12 hours	1,2,3
Processing	Deep freezing bone allografts	The bone allograft stays one month in deep freezer - 80 2. Distribution,	gamma-irradiation at 25-30 kGy (must be validated)	1
	Deep freezing soft tissues	The tissue stays one month in deep freezer - 80 2. Distribution	no gamma-irradiation 2. gamma-irradiation at 15-17kGy (must be validated)	1
	Cryopreservation Osteoarticular allografts	no gamma -irradiation	Cryopreservation at <-140 but first cryoprotectant (glycerol, dimethyl sulfoxide (DMSO)) are added to the medium to protect cells against freezing injury. 2. Distribution	1

Activity	Type of processing and tissue	Critical processing parameter (CPP) / Critical Quality Attribute (CQA)	Acceptance Criteria	References *
	Freeze-dried (lyophilised)Bone and soft tissue allografts/Wet processing area	**1**. Washing of bones **2.** Defating **3**. Cutting/shaping **4**.Chemical processing (dehydration)	gamma-irradiation at 25-30 kGy (must be validated)	1
	Freeze-dried (lyophilised)Bone and soft tissue allografts/Dry Processing Area	**5**. Lyophilisation **6**. Packaging **7**. Labelling **8**. Irradiation **9**. Storage at room temperature **10**. Documentation	gamma-irradiation at 25-30 kGy (must be validated)	1
	Demineralized Bone Matrix Allografts	**1**. Washing with distilled water **2**. Milling of Bones **3.** Freeze-dried and sieved **4**.Demineralized **5**. Freeze-dried again **6**. Packaged **7.** Labelled **8.** Distribution	gamma-irradiation at 25-30 kGy (must be validated)	2
	Fresh		Unprocessed tissues at hypothermic (2-8 °C) or near normothermic (~33 °C) temperatures allows maintenance of cell viability (i.e. osteochondral grafts) for a short period (1-3 months).	1

Activity	Type of processing and tissue	Critical processing parameter (CPP) / Critical Quality Attribute (CQA)	Acceptance Criteria	References *
	Autologous Chondrocyte Culture	Articular Cartilage	cells are cultured in the incubator at standard conditions (temperature 37 o C, CO2 – 5%, humidity - 95%) in culture flasks with medium (e.g. HAMF12 or DMEM, penicillin/streptomycin 1%) for period of 4-6 weeks.	3
Storage	Frozen		-40min -15max	1
	Deep-frozen		-80min -60max	1
	Cryopreservation		-196min -140max	1
	Freeze-dried		+4min +30max (room temperature 15 -25 C)	1
	Demineralized		+4min +30max (room temperature 15 -25 C)	1
	Fresh		+2min +8max	1
	Tissue culture of chondrocytes		-196min -140max	3

Activity	Type of processing and tissue	Critical processing parameter (CPP) / Critical Quality Attribute (CQA)	Acceptance Criteria	References *
Microbiological Testing(aerobic or anaerobic bacteria, yeast or fungi)	Bone and Soft Tissue Allografts	Collection of the last portion of the fluid used for washing of the tissue graft for subsequent analysis, usually following filtration.		1
	Chondrocytes	1. sampling of the transport medium should be performed parallel to the enzyme digestion process of articular cartilage, 2. in the end of a chondrocyte culture before release for the clinical use.		3
Distribution and Transport Conditions	Frozen and Deep Frozen	Container with dry ice or qualified cooling systems.		1
	Crypreserved	Dry-shipping containers	(vapour-phase nitrogen < −140 °C).	1
	Freeze-dried	Freeze-dried grafts can be carried using a container just to protect the integrity of the package system.		1
	Fresh	Fresh grafts can be carried using a container that ensures the defined storage temperature.		1

Activity	Type of processing and tissue	Critical processing parameter (CPP) / Critical Quality Attribute (CQA)	Acceptance Criteria	References *
Before graft	Thawing or rehydratation	As described in the procedure		

Abbreviations: Deep Freezing, Gamma Irradiation, Bone Allografts, Soft Tissue, Articular Cartilage

1. EDQM Guide to the quality and safety of tissues and cells for human application, 4th Ed; chapter 21.

2. AATB Guidelines

3. GTP I

7.3.2.7 Adipose Tissue

Activity	Critical processing parameter (CPP) / Critical Quality Attribute (CQA)	Acceptance Criteria	References
Procurement	Aspiration	Agreed aspiration techniques (Coleman or other)	2
Transportation to	Time and temperature in transit	Immediately at a transport	

TE		temperature of +4° C	
	Container	Specific container (for example, a Luer-lock syringe)	
Processing	Time between procurement and processing	within defined limits based on appropriate validation	1
	Microbiology - pre and post processing on the tissue and microbiology of rinsing solutions	Negative[a]	1 - 26.5
	Residual antibiotics (if used during processing)	Not defined*	
	Structural integrity / flexibility of tissue (if applicable)	Not defined*	
	Cell viability (if applicable)	Not defined*	
	Residual cryopreservative concentration (if applicable)	Not defined*	
	Storage and stability	Cryopreserved - <-80^{o}C, expiry linked to storage temp.	1
	Packaging and labelling	Sterile apyrogenic, double packaging	1 Chapter 14, 3

Autologous adipose tissue from liposuction is being used increasingly in plastic surgery for reconstructive procedures. Autologous fat transplantation in aesthetic and reconstructive plastic surgery has revolutionised surgical treatment. The challenge of banking is to preserve maximum viability, taken into account that adipose tissue is very sensitive to external treatment (centrifuge, processing methods and temperature).

Activity	Specifications (Critical processing parameter (CPP) / Critical Quality Attribute (CQA))	Adipose	*References*
	Source/type of donor	adipose aspirates / liposuction on living autologous donor	
Procurement	Infectious screening of donors	For autologous donors: Ag/AbVIH-1,2 Hepatitis B (AgHBs) and C (Ab) syphilis positive results will not prevent from storage	*EDQM T &C guide; chapter 5*
	Time between death and procurement (deceased donors)	NA	
	Technique for procurement	agreed aspiration techniques under aseptic condition	
	Characterisation of the procured tissue	Not defined - volume must be registered	*(Coleman or other)*
	-		
	Microbiology - pre processing on the tissue and microbiology of rinsing solutions	Negative or low virulent * microorganisms given a decontamination procedure is followed	*2*
	transport media	-	-
Packaging	Primary packaging	sterile packaging	-
	labelling		-

Activity	Specifications (Critical processing parameter (CPP) / Critical Quality Attribute (CQA))	Adipose	*References*
Temporary storage and transportation to TE	Temperature	immediately at a transport temperature of +1°C to 8°C	
	duration		
	Time between procurement and processing	within defined limits based on appropriate validation	
	Microbiology - pre processing on the tissue and microbiology of rinsing solutions	Not defined **	*1*
Processing			*1 - chapter 26.5*
	purity	technique should be described	
	centrifugation	Should be validated - purifying percent (blood oil) must be evaluated	
	wash or cleansing solutions	Should be validated - purifying percent (blood oil) must be evaluated	
	filtering through meshes	Should be validated - purifying percent (blood oil) must be evaluated	
	Cell viability	key criteria - Not defined*	
	Volume	should be measured	

Activity	Specifications (Critical processing parameter (CPP) / Critical Quality Attribute (CQA))	Adipose	*References*
	Cryoprotectant	validated for adipose tissue	
	Residual cryopreservative concentration (if applicable)	Not defined*	*Moscatello et al.*
	Residual antibiotics (if used during processing)	Not defined*	
	Microbiology - post processing on the tissue and microbiology of rinsing solutions	Negative	
	Primary packaging for finished product	Designed/approved for cryopreservation of human cells and placed into metal cassettes for protection during freezing, storage, transportation and shipping. [1,2]	*1*
	Labelling primary packaging	Unique identification number or code (single european code SEC) type of tissue and cells expiry date temperature range ? FOR AUTOLOGOUS USE ONLY	
Storage and stability	Temperature	under -140°C but frozen under -20°C or cryopreserved under -80°C are described	
	duration		
Distribution	Outer container packaging	Sterile apyrogenic, double packaging	*EDQM ch 14*

Activity	Specifications (Critical processing parameter (CPP) / Critical Quality Attribute (CQA))	Adipose	*References*
	Labelling outer packaging	HUMAN TISSUE Identification of originated TE identification of OHRA destination HANDLE WITH CARE DO NOT IRRADIATE (living cell)	*EDQM T&C guide, chapter 14*
Before graft	Thawing	cooling slowly / thawing fast warming	
	Washing	Not defined*	
	Rehydratation	NA	
	Microbiology	Use is not precluded but requires treatment strategy	

1 - EDQM Guide to the quality and safety of tissues and cells for human application, 4th Ed

2 - SaBTO Microbiological Safety Guidelines

3 - Directives 2004/23/EC and 2006/86/EC

[a] positive results don't necessarily preclude processing of autologous tissue. Acceptance limits for microbial load and exclusion criteria must be defined

* Where limits are not defined in the literature, they must be set and justified by the TE and validation data must be submitted to demonstrate that the specified limits are met

7.3.2.8 Pancreatic Islets

Pancreatic Islets (of Langerhans) are clusters of insulin-producing cells that located in the pancreas.

The pancreatic tissue is procured as the whole organ. Is then dissected and enzyme- digested to isolate the islets. Replacement therapy intends to restore glucose-responsive insulin secretory capacity to patients with insulin-deficient Diabetes mellitus.

What should be specified in a PPD				*What needs to be justified in case of change*		
Activity	Critical processing parameter (CPP) / Critical Quality Attribute (CQA)	Acceptance Criteria	References	*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
Procurement	Time between death and procurement (deceased donors)	Not defined*	2			
	cold ischaemia time, organ preservation methods, cold preservation fluid and shipping conditions	Not defined				
Transportation to TE	Time and temperature in transit	Pancreas maintained in preservation solution at 4°C	1			
Processing	Time between procurement and processing	Not defined*	1			

What should be specified in a PPD				*What needs to be justified in case of change*		
Activity	Critical processing parameter (CPP) / Critical Quality Attribute (CQA)	Acceptance Criteria	References	*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
	Quantification of the pancreatic islet cell mass (total islet number and the islet equivalent, known as IEQ), or of the number of insulin positive cells;	Not defined*	1			*Clinical efficacy*
	Microbiology post processing	no growth°	Ph. Eur. 2.6.12 2.6.13			
	bacterial endotoxin testing	?*	*Ph. Eur.* 2.6.14 and 5.1.10.			
	Cell viability	Not define (e.g. qualitative determination by Hoechst/propidium iodide, fluorescein diacetate/ ethidium bromide or functional assessments)defined*	1			
	pancreatic islet cell mass ((total islet number and the islet equivalent IEQ) or number of insulin-positive cells	Not defined*	1			
	beta-cell function	available only after transplantation	1, 4			

What should be specified in a PPD				*What needs to be justified in case of change*		
Activity	Critical processing parameter (CPP) / Critical Quality Attribute (CQA)	Acceptance Criteria	References	*Case of change at low risk*	*Case of change at moderate risk*	*Case of change at high risk*
Storage	Time and temperature of storage	fresh - 12-25 °C.	1			

1 - EDQM Guide to the quality and safety of tissues and cells for human application, 4th Ed

2 - SaBTO Microbiological Safety Guidelines

3 - Directives 2004/23/EC and 2006/86/EC

° Results are not available before product release - validation data must submitted to demonstrate that the specified limits are respected.

* Where limits are not defined in the literature, they must be set and justified by the TE and validation data must submitted

7.3.3 Exemples of classification of modifications

* The modifications considered as significant, i.e. likely to have an impact on the quality or safety or efficacy of a product, are the following :

1. Informations related to the quality
   - changes in the nature of the tissue retrieved, the nature of the retrieval (autologous, allogeneic), the type of donors retrieved (living, deceased, multi-organ retrieval), the retrieval procedures

- changes to the clinical and biological donor selection criteria, other than compliance with regulatory requirements
- modifications, addition or deletion of a product preparation step during the preparation process
- changes in the quality control of the harvested product, on the intermediate product or on the finished product
- changes in the quality control of the sampled product, the intermediate product or the finished product and
    - in the analytical methods when the tested parameters or the acceptance criteria are also changed
    - the tested parameters or the acceptance criteria
- changes in the quality control of critical process steps
- changes in the nature, addition or deletion of products and materials that come into contact with the tissue during the sampling and preparation stages or modification of their conditions of use
- change in the nature of an excipient or component of the finished product other than the cell part or tissue
- changes in the quality control performed on excipients, products or materials that come into contact with tissues or cells during the harvesting and preparation stages, on other components or packaging that have an impact on the quality and safety of the finished product
- changes of the qualitative and quantitative composition of the finished product
- changes in the conditions of transport and conservation (duration and temperature) of the harvested product (cells, tissues, organs), intermediate products or the finished product
- changes in the nature of the primary packaging of the finished product
- changes in the way the finished product is reconstituted/diluted before use
- change, addition or deletion of an establishment or organization (including third parties with whom an agreement is made) involved in the realization of a process step
- addition of any product of biological origin entering in the composition of the finished product or used during its preparation or change of nature of a product of biological origin entering in the composition of the finished product or used during its preparation

2. Non clinical data
    - addition of any product of biological origin entering in the composition of the finished product or used during its preparation or change of nature of a product of biological origin entering in the composition of the finished product or used during its preparation

3. Clinical data
    - addition, deletion or modification of the product's therapeutic indications

- any new data (clinical study, bibliographic data...) or modification of the data initially provided and providing new information on the efficacy and safety profile of the product
- changes in contraindications/recommendations for use

** Modification to be declared

- change in the commercial name of the finished product
- change of supplier or new supplier of a product or material that comes into contact with tissues or cells during the collection or preparation stages
- change of a third party, within the framework of a subcontracting contract, carrying out the quality control of the retrieved product (cells, tissues, organs), intermediate products or finished product when the analytical methods used for these controls are unchanged
- changes related to quality controls performed on excipients, products or materials coming into contact with products or cells during the sampling and preparation stages, on other components, or packaging when these have no demonstrated impact on their quality or that of the finished product
- changes in the quality controls performed on the sampled product (cell tissues, organs), intermediates and finished product using an analytical method when the parameters tested and the acceptance criteria are unchanged
- change, addition or deletion of a facility or organization, including third parties with whom an agreement is in place, involved in the completion of a transport stage

7.4 Reproductive tissues and cells for Medically assisted reproduction (MAR)

This part of the WP6 technical Annex concerns the definition of key quality and safety criteria for each category of cell and tissue in MAR with guidance on how to ensure that these criteria are met through in vitro validation, in process verification and clinical studies.

Critical characteristics and properties for reproductive cells and tissues are difficult to define due to the wide range of clinical / patient related factors which can impact the quality and safety of the tissues and cells. While defining criteria of acceptability for gametes is almost impossible, it is possible to define criteria for the processes used in the different preparation steps in MAR.

Another issue concerns the necessity to distinguish between the common way of assessing a change in a process and the more specific key performance indicators related to a given procedure. Thus, the document will successively consider the various processes used in MAR while specifying their key performance indicators to assess the outcome in the evaluation procedure and then will describe the common considerations about validation procedures for a change in a biological process.

7.4.1 Processes used in MAR

According to ARTHIQS and suggestions from expert sub group the following processes are considered to be used in MAR.

1. Sperm preparation for Intra-uterine insemination (IUI)
2. Conventional IVF
3. Intracytoplasmic sperm injection procedure (ICSI)
4. Cryopreservation and storage of gametes for later use (IUI or IVF/ICSI) in partner/non partner donation
5. Cryopreservation and storage of embryos for later embryo transfer in partner/non partner donation
6. Fertility preservation through cryopreservation and storage of reproductive T&C,
7. Oocyte/embryo biopsy

Critical steps and process parameter and Performance Indicators are defined for each of the parameters below

7.4.2 General considerations

1) The listed performance indicators should be monitored and verified every time a change is introduced in the procedure.

2) For sperm parameters in partner-donation, owing to: high patient variability and uncertainty of semen analysis data, variability in sperm preparation methods and the limited relevance of WHO reference values for sperm concentration, motility and vitality with respect to MAR clinical outcomes and in agreement with the Vienna consensus (Hum Reprod Open, 2017), we do not provide competence values, but concluded that each lab should define its own standards.

3) The clinical outcome, including implantation rate and live birth rate may be considered as the ultimate KPI for checking IVF clinic performance. Both parameters are largely affected by a series of clinical maternal factors pertaining to uterine receptivity and post-implantation development, and for this reason, they may not necessarily reflect the laboratory's performance.

4) Specific aspects of donor testing to prevent transmission of infectious and genetic diseases from the donor to the recipient and offspring and to protect staff while handling the patients and their gametes are covered in the EDQM T&C Guide 4th edition, section 27.5.

5) The biopsy of cells from embryos permits them to be genetically tested before transfer. This procedure is proposed to patients who are: carriers of mutations responsible for a monogenic disease (PGT-M); carriers of structural chromosomal abnormalities revealing unbalanced rearrangements (PGT-SR); and to specific categories of infertile patients in order to select embryos with a normal chromosome status (PGT-A).

Genetic analysis can also be performed on polar bodies in oocytes.

6) Changes to be considered are all changes that may impact biological processes

7) For ovarian tissue and testicular tissue, data are too limited to provide reliable values for reference indicators

7.4.3 Process specific considerations

7.4.3.1 Sperm preparation for intra-uterine insemination

7.4.3.1.1 Critical steps

- Sperm collection conditions
- Handling and processing sperm
- Insemination procedure

7.4.3.1.2 Performance indicators

- Sperm motility/morphology after sperm processing
- Clinical pregnancy rate
- Live birth rate

7.4.3.1.3 Evaluation of sperm preparation in IUI: indicators to be checked

Changes to / Indicators	**Sperm collection**	**Sperm handling and processing**	**Insemination procedure**
Sperm motility/ morphology	√	√	
Clinical pregnancy rate	√	√	√
Live birth rate	√	√	√

7.4.3.2 In vitro fertilisation

7.4.3.2.1 Critical steps

- Sperm collection
- Handling and processing sperm
- Oocyte collection

- In vitro fertilisation procedure; timing, sperm concentration, duration, media
- Embryo culture; duration, media

7.4.3.2.2 Performance indicators

- Sperm motility after sperm processing
- IVF polyspermy rate
- 1 ProNuclear (PN) rate
- IVF normal fertilisation rate (2PN)
- Embryo development rate (for different developmental stages)
- Clinical pregnancy rate
- Live birth rate

7.4.3.2.3 Evaluation of the IVF process: indicators to be checked

Changes to Indicators	**Sperm collection**	**Sperm handling and processing**	**Oocyte collection**	**In vitro fertilisation procedure**	**Embryo culture**
Sperm motility	√	√			
IVF polyspermy rate	√	√	√	√	
1 PN rate	√	√	√	V	
IVF normal fertilisation rate	√	√	√	√	
Embryo development rate	√	√	√	√	√
Clinical pregnancy rate	√	√	√	√	√
Live birth rate	√	√	√	√	√

7.4.3.3 Intracytoplasmic sperm injection procedure (ICSI)

7.4.3.3.1 Critical steps

- Sperm collection
- Handling and processing sperm
- Oocyte collection
- For these steps and parameters check the IVF section
- Preparation of oocytes for ICSI (CC removal)
- Intracytoplasmic sperm injection procedure; timing, sperm characteristics, duration, media
- Embryo culture; duration, media

7.4.3.3.2 Performance indicators

- IVF polyspermy rate
- 1 PN rate
- ICSI damage rate
- ICSI normal fertilisation rate

- Embryo development rate (for different developmental stages)
- Clinical pregnancy rate
- Live birth rate

7.4.3.3.3 Evaluation of the ICSI process: indicators to be checked

Changes to / Indicators	Preparation of oocytes	ICSI procedure	Embryo culture
IVF polyspermy rate	√		
1 PN rate	√	v	
ICSI damage rate	√	√	
ICSI normal fertilisation rate	√	√	
Embryo development rate	√	√	√
Clinical pregnancy rate	√	√	√
Live birth rate	√	√	√

7.4.3.4 Cryopreservation and storage of gametes for later use (IUI or IVF/ICSI) in partner donation

7.4.3.4.1 Sperm

7.4.3.4.1.1 Critical steps

- Sperm collection
- Handling and processing sperm
- Sperm freezing
- Storage conditions
- Sperm thawing

7.4.3.4.1.2 Performance indicators

- Sperm motility after sperm processing
- IVF polyspermy rate
- 1 PN rate
- IVF/ICSI normal fertilisation rate
- All other indicators for IUI/IVF/ICSI (mentioned in sections 1,2,3)

7.4.3.4.1.3 Evaluation of changes to the sperm cryopreservation process: indicators to be checked

Changes to / Indicators	Sperm collection	Sperm handling / processing	Sperm freezing	Storage conditions	Sperm thawing	Further use of sperm; see IUI, IVF, ICSI
Sperm motility	√	√	√	√	√	
IVF polyspermy rate	√	√	√	√	√	
1 PN rate	√	√	√	√	√	

IVF / ICSI normal fertilisation rate	√	√	√	√	√	

7.4.3.4.2 Oocytes

7.4.3.4.2.1 Critical steps

- Preparation of oocytes for cryopreservation procedure (CC removal)
- Oocyte cryopreservation procedure
- Oocyte warming procedure
- Storage conditions

7.4.3.4.2.2 Performance indicators

- Proportion of oocytes that survived after warming
- IVF/ICSI normal fertilisation rate
- All other indicators for IVF/ICSI

7.4.3.4.2.3 Evaluation of changes to the cryopreservation process: indicators to be checked

Changes to / **Indicators**	**Preparation of oocytes**	**Oocyte freezing**	**Oocyte warming**	**Further use of oocytes; see IVF, ICSI**
Proportion of oocytes survived after warming	√	√	√	
IVF polyspermy rate	√	√	√	
1 PN rate	√	√	√	
IVF/ICSI normal fertilisation rate	√	√	√	

7.4.3.5 Cryopreservation and storage of embryos for later embryo transfer in partner donation

7.4.3.5.1 Critical steps

- Embryo culture; duration, media
- Embryo freezing procedure
- Storage conditions
- Embryo warming process

7.4.3.5.2 Performance indicators

- Embryo cryosurvival rate
- Embryo development rate if cultured further
- Blastocyst cryosurvival rate

- Clinical pregnancy rate
- Live birth rate

7.4.3.5.3 Evaluation of changes to the cryopreservation process: indicators to be checked

Changes to / Indicators	Embryo culture	Embryo freezing procedure	Storage conditions	Embryo warming
Embryo cryosurvival rate	√	√	√	√
Embryo developmental rate	√	√	√	√
Blastocyst cryosurvival rate	√	√	√	√
Clinical pregnancy rate	√	√	√	√
Live birth rate	√	√	√	√

7.4.3.6 Fertility preservation through cryopreservation and storage of reproductive T&C

SPERM and OOCYTES =>refer to preceding section

7.4.3.6.1 Ovarian tissue

7.4.3.6.2 Critical steps

- Ovarian tissue (OT) collection
- Ovarian tissue processing
- Ovarian tissue cryopreservation
- Ovarian tissue warming

7.4.3.6.3 Performance indicators

- Follicular density before and after cryopreservation
- Time to return of menstruation after transplantation
- Live birth rate (spontaneous or after IVF)

7.4.3.6.4 Evaluation of changes to the ovarian tissue cryopreservation process: indicators to be checked

Changes to / Indicators	OT collection	OT processing	OT cryopreservation	OT warming
Follicular density	√	√	√	√

before and after cryopreservation				
Time to return of menstruation	√	√	√	√
Live birth rate (spontaneous or after IVF)	√	√	√	√

7.4.3.6.5 Testicular tissue

This part concerns only cryopreservation of testicular tissue for prepubertal boys, since cryopreservation of testicular tissue for pubertal boys or adult concerns spermatozoa issued from a complete process of spermatogenesis. In prepubertal boys only immature germ cells may be cryopreserved within the entire structure of seminiferous tubules and the associated intertubular compartment with Leydig cells. Up to now this concerns future clinical application, but cryopreservation is already operational.

7.4.3.6.6 Critical steps

- Testicular tissue collection
- Testicular tissue processing
- Testicular tissue freezing
- Testicular tissue warming and sperm extraction?

Performance indicators in the emerging research field of testicular tissue for fertility preservation in prepubertal boys have so far been, and remain, under study. Labs are recommended to consult recently published data to estimate performance indicators.

7.4.3.7 Oocyte and embryo biopsy

7.4.3.7.1 Oocyte biopsy

7.4.3.7.1.1 Critical steps

- Preparation of oocytes for biopsy (CC removal)
- Oocyte biopsy
- Intracytoplasmic sperm injection procedure

7.4.3.7.1.2 Performance indicators

- Successful biopsy rate (proportion of biopsied oocytes available for genetic analysis)
- ICSI normal fertilisation rate
- Embryo development rate
- Clinical pregnancy rate
- Live birth rate

7.4.3.7.1.3 Evaluation of changes to the oocyte biopsy process: indicators to be checked

Changes to / Indicators	Oocyte collection	Oocyte preparation	Oocyte biopsy
Successful biopsy rate	√	√	√
ICSI normal fertilisation rate	√	√	√
Embryo development rate	√	√	√
Clinical pregnancy rate	√	√	√
Live birth rate	√	√	√

7.4.3.7.2 Embryo biopsy

7.4.3.7.2.1 Critical steps

For previous steps and parameters, check the ICSI section

- Embryo culture; duration, media
- Embryo biopsy

7.4.3.7.2.2 Performance indicators

- Embryo development rate post biopsy
- Successful biopsy rate
- Clinical pregnancy rate
- Live birth rate

7.4.3.7.2.3 Evaluation of changes to the embryo biopsy process: indicators to be checked

Changes to / Indicators	Embryo culture	Embryo biopsy
Successful biopsy rate	√	√
Embryo development	√	√
Clinical pregnancy rate	√	√
Live birth rate	√	√

Appendix B- Organisation of the work, methods and sources

The work, supervised by ISS-CNT-CNS (Italy) and coordinated by Agence de la biomédecine (France), is the fruit of the collaboration of four groups of professionals from partner organisations, collaborating organisations and invited experts, each of them bringing expertise from their respective fields.

The work was carried out in two parts. During the first part of the project the experts identified the products in their domain, the preparation processes currently used to prepare them and the Critical Quality Attribute (CQA) s and Clinical Processing Parameters (CPP) that can be measured on the products or directly on the processes (CPP) in order to be able to evaluate or validate them.

The results of this major work are presented in Appendix A.

The second part of the work then considered how the request for the authorisation of a novel preparation process or the modification of an existing preparation process should be handled by the Competent Authority and in particular how the identified CQA and CPP should be evaluated or validated. This part of the work drew extensively upon EuroGTPII and is contextualised by the recommendations of D5.3, of which it is an Annex, and D8.3 which recommends approaches to clinical evaluation in the context of preparation process authorisation, as well as D7.1 which recommends approaches to microbiological safety and testing.

The results of part II provide the essential content of these recommendations, specifically the methods to apply guidance as to which criteria to take into account according to the situation.

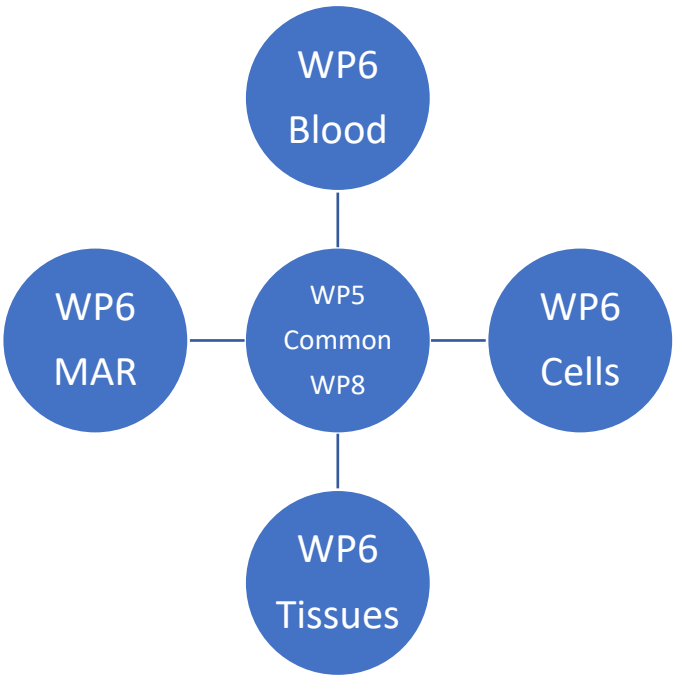


Figure 1 Structure of WP6

Work package 6 (WP6) sets out the details of the Preparation Process evaluation procedures implemented in the course of their authorisation by competent authorities. The general framework

is established by Work Package 5, extending the findings and applying the methods developed in the EuroGTPII and Vistart Joint Actions. The procedures for blood and blood products, tissues and tissue derivatives, haematopoietic stem cells and reproductive cells and tissues differ in their details. The requirements for clinical evaluation are identified in WP6, but the details of the methodologies to be elaborated are, in generic terms defined by work package 8 (WP8).

Sources and methods

The information taken into account in “identifying the key quality and safety critical characteristics for each category of blood component, tissue or cell type” is drawn from legally binding “Requirements” on the one hand and “Recommendations” on the other hand.

The sources used to identify Requirements were the applicable documents of the European Pharmacopoeia (Ph. Eur) and European Union Legislation. Applicable European Union legislation is made up of the Blood Directive and the Tissues and Cells Directive completed by their respective implementing directives.

The sources of recommendations are principally the current versions of the Council of Europe Blood Guide and Tissues and Cells Guide as elaborated and coordinated by the European Directorate for the Quality of Medicines & HealthCare’s (EDQM).

Member state legislation completes European requirements. National and European professional and scientific society, member state and regional authority guidelines complete the recommendations.

In order to ensure alignment and coherence with the results of previous European Union actions dealing with quality aspects and patient follow-up, the following current guidelines and reference documents were also taken into account:

- VISTART deliverable 5.4. This document examines the “regulatory principles for competent authorities for the evaluation and approval of clinical follow up protocols for blood, tissues and cells prepared with newly developed and validated processing methodologies”
- The Single European Code for Tissues and Cells (SEC) - Reference Compendia for the Application of a single European Coding System for Tissues and Cells
- The Notify Library – Global Vigilance and Surveillance Database for Medical Products of Human Origin
- EuroGTP II Guide - Good Practices for evaluating safety, quality and efficacy of tissue and cellular therapies and products in terms of risk levels and novelty.

Four working groups were set up for the fields of Blood and blood components, Tissues and Cells Haematopoietic Stem Cells and Medically Assisted Reproduction. Reproductive tissues are covered by the MAR expert group.

Blood Subgroup

The mention of "blood" in this document refers to blood and its components intended for transfusion.

Criteria were identified within the EU Directives, the EDQM Blood Guide, the results of Vistart WP5 and the French and UK Competent Authorities guidelines for blood.

European regulatory provisions relating to this blood and its components, in particular for quality, safety and sometimes efficacy, are available in the EU Legislation, see sotto

The 20th Edition 2020 of the EDQM Blood guide[12] for the preparation, use and quality assurance of blood components provides extensive recommendations and was the principle source of the criteria presented in these recommendations.

EU Legislation in blood and blood products

The legal framework defining the quality and safety standards for blood and its components is set out in

Directive 2002/98/EC[13],

also referred to as the European Blood Directive. It covers all steps in the transfusion process from donation, collection, testing, processing, and storage to distribution.

To help implement this main act, the European Commission proposed and adopted, in close collaboration with EU national authorities, the following additional implementing acts:

Commission Directive 2004/33/EC[14] on the technical requirements for blood and blood donation

Commission Directive 2005/61/EC[15] on the traceability requirements and notification responsibilities in case of serious adverse reactions and events

Commission Directive 2005/62/EC[16] that sets out Community standards and specifications relating to the quality system for a blood bank

Commission Directives 2009/135/EC[17], 2011/38/EU[18], 2014/110/EU[19], 2016/1214[20] address some further specific technical requirements.

It is important to note that EU countries can always choose to apply more stringent rules to the quality and safety of blood and blood products[21] than those outlined above.

The Commission is currently carrying out the first formal evaluation of the EU blood and tissues and cells legislation[22].

Table 1 EU Legislation in Blood and Blood Products

The implementing Directive 2004/33[14] defines certain technical requirements for blood and blood components identified by the Council Directive 2002/98/EC[13]; Annex IV implements Article 5 of the EC Directive and sets out storage, transport and distribution conditions for blood and blood components. Annex V implements Article 6 of the EC Directive and at the time the directive was adopted set out quality and safety requirements for blood and 18 blood components.

The EDQM Blood Guide[12] extensively elaborates and extends these quality and safety requirements (criteria) for blood and blood components. This publication is commonly used and contributed to by Member States as an established source for defined criteria. It currently lists 36 component monographs on the main blood components used and seven others for rarer products such as those used in neonatology. The monographs in Chapter 5 “Standards of blood component monographs” provide detailed criteria for:

- Whole blood components
- Red cell components
- Platelet components
- Plasma components
- White cell components

These monographs are considered as a de facto standard for blood components across Europe and adopt the following structure as used in the European Pharmacopoeia:

- Definition and properties
- Preparation
- Requirements and quality control (Parameters to be checked, Requirements, Frequency of control)
- Storage and transport
- Labelling
- Warnings

Chapter 6 of the EDQM Blood Guide[12] provides further criteria relating to standards of blood components for intrauterine, neonatal and infant use.

An EDQM survey of Members States use of the monographs and their own sources identified seven further blood components. Of these, two are not included in the current version of the EDQM Blood Guide, but five of them are, and are documented to a level equivalent to the evaluation criteria of the other blood components.

Tissues and Cells and Haematopoietic Stem Cell subgroups

Initially the work on Tissues and Haematopoietic Stem Cells was allocated to a single group. The fields of Tissues and HSC are considerably different and the specialists in the field, within the scientific societies and the Competent Authorities have and need different expertise. As such the work was divided and two separate expert subgroups were established.

The work in the subgroups started from legally binding references from the European pharmacopoeia[23]: ch 2.6.27 “Microbiological examination of cell-based preparations” and EU Legislation.

EU Legislation in Tissues and cells

The legal framework defining the safety and quality standards for tissues and cells is set out in Directive 2004/23/EC[24], also referred to as the European Tissues and Cells Directive, adopted in 2004 by the European Parliament and Council. It covers all steps in the transplant process from donation, procurement, testing, processing, preservation and storage to distribution.

To help implement this basic act, the Commission proposed and adopted, in close collaboration with EU MS, the following implementing Directives:

- **Commission Directive 2006/17/EC[25] regarding certain technical requirements for the donation, procurement and testing of human tissues and cells**
- **Commission Directive 2006/86/EC[26] concerning traceability requirements, notification of serious adverse reactions and events, additional technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells**
- **Commission Directive 2015/565[27] amending Directive 2006/86/EC as regards certain technical requirements for the coding of human tissues and cells**
- **Commission Directive 2015/566[28] implementing Directive 2004/23/EC concerns the procedures for verifying the equivalent standards of quality and safety of imported tissues and cells.**

Commission Decisions 2010/453/EC[29] and Commission Directive 2012/39/EU[30], as well as Commission Decision C(2015) 4460[31]address some further specific aspects.

It is important to note that EU countries can always choose to apply more stringent rules to the quality and safety of tissues and cells then the ones outlined above[32].

The Commission is currently carrying out the first formal evaluation of the EU blood and tissues and cells legislation[22].

Table 2 EU Legislation in Tissues and Cells

Detailed information needed to identify criteria are found in various sources of recommendations.

In the HSC field criteria were identified in guidelines published by the European Society for Blood and Marrow Transplantation (EBMT) and the Foundation for the Accreditation of Cellular Therapy (FACT) and the Joint Accreditation Committee ISCT-Europe (JACIE) international standards.

The European Eye Bank Association (EEBA) guidelines provided criteria for ocular tissues.

Extensive criteria were identified in "The Guide for quality and safety of tissues and cells" 3rd and 4th editions produced by the European Directorate for the Quality of Medicines & HealthCare's (EDQM): the EDQM T&C Guide.

The EDQM T&C guide elaborates quality and safety requirements (criteria) for tissue and cells. It includes recommendations considered to be minimum standards based on up-to-date literature reviews. Periodically updated, it is commonly contributed to and used by Member States as an established source for defined tissue specific requirements. The 4th edition lists 21 monographs that aim to be completed in the next edition: 15 monographs dedicated to the 5 main categories of tissue (ocular, amniotic, skin, cardiovascular, musculoskeletal), 4 monographs for Hematopoietic stem cells, and 2 for MAR.

The EDQM T&C monographs follow the standardised structure used in the European Pharmacopoeia:

- Definition and properties

- Preparation
- Requirements and quality control (Parameters to be checked, Requirements, Frequency of controls)
- Storage and transport
- Labelling
- Warnings

Chapters 24, 26 & 28 of the EDQM T&C guide provide further criteria relating to standards for Pancreatic Islets, Adipose Tissue and Reproductive tissues.

Tissues and Cells were divided into 9 different categories:

- Hematopoietic stem and progenitor cells
- Ocular tissues
- Amniotic membrane
- Skin
- Cardiovascular tissues
- Musculoskeletal tissues
- Pancreatic islets
- Adipose tissue
- Reproductive tissues (Reproductive tissues are covered by the MAR subgroup)

The EUROGTPII guide provided context in the use of criteria in the evaluation of novelty and associated risks.

Medically Assisted Reproduction (MAR) Subgroup

A wide range of clinical/patient related factors influence the quality of reproductive T&C. This makes the definition of criteria of acceptability for gametes almost impossible. In MAR there are not *per-se* 'products' so much as product characteristics and parameters that should be concentrated on. Since it is difficult to define gametes or embryos as products it was not considered practical to develop "product" monographs (as for blood products) and the experts agreed that it would be a better approach to look at specific IVF processes (techniques) and to define critical process parameters (CPP) by which they may be validated. A list of processes in MAR and their possible evolution has been prepared, while identifying their key steps and the ways to validate them.

Not all Specific Key Performance Indicators (KPIs) linked to procedures are adapted to assessing a change in a process. Consequently, this document will consider various preparation processes used in MAR and specify which KPIs to assess in their evaluation. It also describes the common considerations about procedures to validate changes to preparation processes.

This work was based on the following documents:

- Directive 2004/23/EC of the European Parliament and of the Council, and the associated implementing Directives (please refer to Table 2)
- The EDQM T&C Guide 3rd, 4th [7]and future editions.

The following documents were helpful to establish the initial criteria.

- The Vienna Consensus: report of an expert meeting on the development of MAR laboratory performance indicators (2017)[1].
- Revised Guidelines for good practice in IVF laboratories (2015)[2]
- The Alpha Consensus meeting on cryopreservation key performance indicators and benchmarks: proceedings of an expert meeting (2012)[3]
- ARTHIQS - Inspection guidance in Assisted Reproductive Technologies (ART) (2017)[33]
- EuroGTP II Guide (2019)[34]

Abbreviations

ABM	Agence de la biomédecine
ADM	Acellular Dermal Matrix
AG	Apheresis Granulocytes
ALK	Anterior Lamellar Keratoplasty
AM	Amniotic Membrane
ANSM	Agence nationale de sécurité du médicament et des produits de santé (French National Agency for Medicines and Health Products Safety)
AP	Apheresis Platelets
AP	Apheresis Platelets
AP AS	Apheresis Platelets, in Additive Solution
AP LD	Apheresis Platelets, Leucocyte-depleted
AP LD-AS	Apheresis Platelets, Leucocyte-depleted, in Additive Solution
AP PR	Apheresis Platelets, Pathogen Reduced
ART	Assisted Reproductive Technologies
ARTHIQS	Assisted Reproductive Technologies and Haematopoietic stem cells Improvements for Quality and Safety throughout Europe
ATMP	Advanced Therapy Medicinal Products
B&BC	Blood & Blood Components
BE	Blood Establishement
BM	Bone Marrow
CA	Competent Authority
CBU	Cord Blood Unit
CCP	Critical Processing Parameters
CCP	COVID-19 convalescent plasma
CE	Conformité Européenne
CFU	Colony Forming Units
COC	Cumulus Oocyte Complex
CPP	Critical Processing Parameters
CQA	Critical Quality Attribute
DALK	Deep Anterior Lamellar Keratoplasty
DMEK	Descemet Membrane Endothelial Keratoplasty
DMSO	Dimethyl Sulphoxide
DSAEK	Descemet Stripping Automated Endothelial Keratoplasty
EATCB	European Association for Tissue and Cell Banks
EBMT	European Society for Blood and Marrow Transplantation
EDQM	European Directorate for the Quality of Medicines & HealthCare
EEBA	European Eye Bank Association
ESHRE	European Society of Human Reproduction and Embryology
EU	European Union
EuroGTP	Good Practice for Evaluating Quality, Safety and Efficacy of novel tissues and

II	cellular therapies and products
FFP	Fresh Frozen Plasma
FFP PR	Fresh Frozen Plasma, Pathogen Reduced
FFP PR LD	Fresh Frozen Plasma, Pathogen Reduced Leucocyte-Depleted
GAPP	FacilitatinG Authorisation of Preparation Process for blood, tissues and cells
GPG	Good Practice Guidelines
HLA	Human Leukocyte Antigen
HSC	Haematopoietic Stem Cells
HSC(A)	Haematopoietic Stem Cells from Peripheral Blood Apheresis
HSC(CB)	Haematopoietic Stem Cells from Umbilical Cord Blood
HSC(M)	Haematopoietic Stem Sells from Bone Marrow
ICSI	Intracytoplasmic Sperm Injection
ISS-CNT-CNS	Istituto Superiore di Sanità - Centro Nazionale Trapianti - Centro Nazionale Sangue
IUI	Intra-Uterine Insemination
IVF	In vitro Fertilisation
JPAC	Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee
KPI	Key Perfromance Indicators
MAR	Medically Assisted Reproduction
MCV	Mean Corpuscular Volume
MHRA	Medicines and Healthcare products Regulatory Agency
MII	Metaphase II
MNC(A)	Mononuclear Cells from Unstimulated Peripheral Blood
MPV	Mean Platelets Volume
MS	Member State
ORHA	Organisation Responsible for Human Application
OT	Ovarian Tissue
PB	Polar Body
PGD/PGS (PGT)	Prenatal Genetic Diagnosis/Screening/Testing
PK	Penetrating Keratoplasty
PN	ProNuclear
PP	Preparation Process
PPA	Preparation Process Autorisation
PR SU	Platelets, Recovered, Single Unit
PR/PRT	Pathogen reduced/Pathogen Reduction Technology
PRP	Platelets, Recovered, Pooled
PRP AS	Platelets, Recovered, Pooled, in Additive Solution
PRP LD	Platelets, Recovered, Pooled Leucocyte-Depleted
PRP LD AS	Platelets, Recovered, Pooled, Leucocyte-Depleted, in Additive Solution
PRP PR	Platelets, Recovered, Pooled, Pathogen-reduced

RC	Red Cells
RC Aph	Red Cells Apheresis
RC Aph AS	Red Cells Apheresis in Additive Solution
RC AS	Red Cells in Additive Solution
RC BCR	Red Cells, Buffy Coat Removed
RC BCR-AS	Red Cells, Buffy Coat Removed in Additive Solution
RC LD	Red Cells, Leucocyte-Depleted
RC LD-AS	Red Cells, Leucocyte-Depleted, in Additive Solution
RC W	Red Cells Washed
RCF	Centrifugal Force
RT	Room Temperature
SARE	Serious Adverse Reaction and Event
SEC	Single European Code
SoHO	Substances of Human Origin
SOP	Standard Operating Procedure
SPC	Statistical Process Control
T&C	Tissues and Cells
TE	Tissue Establishment
TNC	Total Nucleated Cells
UBC	Unrelated Cord Blood
UK	United Kingdom
VISTART	Vigilance and Inspection for the Safety of Transfusion Assisted Reproduction and Transplantation
WB	Whole Blood
WB LD	Whole Blood Leucocyte-Depleted
WP	Work Package

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Glossary

All sectors

Additive solution means a solution specifically formulated to maintain beneficial properties of cellular components during storage.

Allogeneic donation means blood and blood components, tissues, cells, organs collected/donated from an individual and intended for transfusion or for transplantation to another individual, for use in medical devices or as starting material/raw material for manufacturing into medicinal products.

Cryopreservation means prolongation of the storage life of blood components, tissues, cells by freezing using a cryoprotectant.

Proficiency testing means the evaluation of participant performance against pre-established criteria by means of external quality assessment scheme, inter-laboratory comparisons by use of externally sourced samples or panels.

Specification means the description of the criteria that must be fulfilled in order to achieve the required quality standard.

Statistical process control means a method of quality control of a product or a process that relies on a system of analysis of an adequate sample size without the need to measure every product of the process.

Validation means the establishment of documented and objective evidence that the particular requirements for a specific intended use can be consistently fulfilled.

Blood

Additive solutionfor platelets components: means a solution specifically formulated to maintain beneficial properties of platelets during storage.The original platelet content in a therapeutically effective dose is suspended in a mixture of plasma (30-40 %) and an additive solution (60-70 %),

Apheresis means a method of obtaining one or more blood components by machine processing of whole blood in which the residual components of the blood are returned to the donor during or at the end of the process.

Blood component means therapeutic components of blood (red cells, white cells, platelets, plasma) that can be prepared by centrifugation, filtration and freezing using conventional methodologies in blood establishment.

Buffy coat means a blood component prepared by centrifugation of a unit of whole blood, and which contains a considerable proportion of the leucocytes and platelets.

Cryoprecipitate means a plasma component prepared from plasma, fresh-frozen, by freeze-thaw precipitation of proteins and subsequent concentration and re-suspension of the precipitated proteins in a small volume of the plasma. It contains the cryoglobulin fraction of plasma and a major portion of the Factor VIII, von Willebrand factor, fibrinogen, Factor XIII and fibronectin present in freshly drawn and separated plasma

Cryoprecipitate, Pathogen Reduced is Cryoprecipitate subjected to treatment with an approved and validated Pathogen Reduction Technique (PRT) and subsequent freezing within a period of time to a temperature that adequately maintains the labile coagulation factors in a functional state. It contains a major portion of the Factor VIII, von Willebrand factor, fibrinogen, Factor XIII and fibronectin present in freshly drawn and separated plasma

Cryopreservation for platelets components: means prolongation of the storage life of platelets by freezing using a cryoprotectant. The component is frozen within 24 hours of collection.

Granulocytes, apheresis means a concentrated suspension of granulocytes obtained by apheresis of a single donor using automated cell separation equipment.
Granulocytes, Pooled is a component that contains granulocytes obtained by pooling of an adequate number of buffy coats, suspended in either plasma or a mixture of platelet additive solution and plasma.

Haematocrit The volume of red cells in blood, after centrifugation, expressed as a percentage or as a ratio in the SI system.

Irradiation process must ensure that no part of the blood component receives a dose less than 25 Gray or more than 50 Gray.

Leucocyte depletion means the removal of leucocytes from blood and blood components.

Pathogen reduced (PR) blood component refers to a special requirement component that has been prepared following the use of PRT. The component is subjected to treatment with an approved and validated pathogen reduction technology (PRT) before storage

Pathogen reduction technologies (PRT) means procedures that irreversibly impede proliferation of pathogens, either by removal or inactivation with physical and/or chemical methods.

Platelets recovered single unit means a concentrated suspension of blood platelets, obtained by processing of a single unit of whole blood.

Platelets recovered pooled isa platelet component derived from platelet recovered single units (maximum 12 units)obtained from PRP or buffy coat.

Plasma means the liquid portion of the blood in which the cells are suspended.

Plasma, cryoprecipitate-depleted means a plasma component prepared from a unit of plasma, fresh frozen. It comprises the residual portion after the cryoprecipitate has been removed. Its content of albumin, immunoglobulins and coagulation factors is the same as that of FFP except that the levels of the labile Factors V and VIII are markedly reduced. The fibrinogen concentration is also reduced in comparison to *FFP*.

Plasma, fresh-frozen (FFP) is a component prepared either from *Whole Blood* or from plasma collected by apheresis, frozen within a period of time and to a temperature that adequately maintains the labile proteins (coagulation factors) in a functional state.

Plasma, fresh-frozen Pathogen Reduced (FFP PR)is a component for transfusion prepared from plasma derived from *Whole Blood* or apheresis plasma which is subjected to treatment with an approved and validated PRT and subsequent freezing within a period of time to a temperature that adequately maintains the labile coagulation factors in a functional state.

Quarantine FFP the FFP can be released once the donor has been re-tested, at least for HBsAg, anti-HIV and anti-HCV, with negative results after a defined period of time that is designed to

exclude the risk associated with the window period. This may be reduced if NAT testing is performed.

Red cells (RC) means the red cells from a single whole blood donation, with a large proportion of the plasma from the donation removed or the red cells obtained by apheresis of a single donor using automated cell-separation equipment.

Washing means a process of removing plasma or storage medium from cellular products by centrifugation, removing of the supernatant liquid from the cells and addition of an isotonic suspension fluid, which in turn is generally removed and replaced following further centrifugation of the suspension. The centrifugation, removing, replacing process may be repeated several times.

Tissue and Cells sector

Actual Organ Donor: Deceased or living person from whom at least one solid organ or part of it has been recovered for the purpose of transplantation.

Aseptic techniques: Procedures designed to prevent contamination from micro-organisms and spread of infection.

Banking: Processing, preservation, storage and distribution of tissues and cells for human application or other purposes, including research and training.

Brain Death: Irreversible cessation of cerebral and brain stem function; characterized by absence of electrical activity in the brain, blood flow to the brain, and brain function as determined by clinical assessment of responses. A brain dead person is dead, although his or her cardiopulmonary functioning may be artificially maintained for some time.

Cardiac Death: Death resulting from the irreversible cessation of circulatory and respiratory function; an individual who is declared dead by circulatory and respiratory criteria may donate tissues and organs for transplantation.

Cells: The smallest transplantable and functional unit of living organisms.

Cell Manipulation: Preparation of retrieved cells to make them suitable for transplantation.

Cell Migration: Movement of cells in particular directions, often in response to specific external signals, including chemical signals and mechanical signals.

Compatibility testing: Testing for the presence or absence of recipient antibodies to HLA antigens and to blood group antigens present on the transplant cells, tissues or organs.

Confidentiality: Regards the treatment of information an individual has disclosed in a relationship of trust. This relationship implies the expectation that the disclosed information will not be divulged without prior permission. Recognized exceptions in the medical context may be justified by a country's laws.

Consent to donation: Legally valid permission for removal of human cells, tissues and organs for transplantation.
Culture Expansion: In vitro, proliferation of retrieved cells for the purpose of transplantation.

Enzymes: are either produced by fermentation (like collagenase) or from animal tissues (like trypsin).

Media: solutions of inorganic salts, amino acids, vitamins and other components, like lipids and hormones.

Processing: All operations involved in the preparation, manipulation, preservation and packaging of cells or tissues intended for human applications.

Procurement: The procedure of removing cells, tissues or organs from a donor for the purpose of transplantation.

Tissue: Anatomical parts of the human body composed of different types of cells connected to each other by a connective frame. Tissue are non-vascularized. Thus, they can be stored and they do not need any revascularization step to be grafted, transplanted, or applied.

Tissue Establishment: A tissue bank or a cell therapy unit or other unit of a hospital or another body where activities of processing, preservation, storage or distribution of human tissues and cells are undertaken. It may also be responsible for procurement or testing of tissues and cells.

Haematopoietic Stem/Progenitor Cells

Haematopoietic Progenitor Cells: primitive pluripotent cells capable of self-renewal as well as differentiation and maturation into all haematopoietic lineages. They are found in bone marrow (bone marrow cells (BMC)), in the mononuclear cells of circulating blood (peripheral blood stem cells (PBSC)) and in umbilical cord blood (umbilical stem cells (USC)).

HPC extracted from Bone Marrow: HPCs are found in small numbers in bone marrow. The infused HPC(M) can originate from the recipient (autologous) or from another individual (allogeneic). They can be used as fresh unmanipulated product or can be further processed (e.g. buffy-coat preparation, cell selection, cryopreservation).

HPC extracted from Peripheral Blood:HPC(A) are procured by apheresis from the mononuclear cell fraction of circulating blood after their mobilisation from the bone marrow. The infused HPC(A) can originate from the recipient (autologous) or from another individual (allogeneic). They can be used as fresh unmanipulated product or further processed (e.g., cell selection, cryopreservation).

Mononuclear cells: Unstimulated mononuclear cells are procured by apheresis from the circulating blood. The procured cells can originate from the recipient (autologous) or fromanother individual (allogeneic). Unstimulated mononuclear cells can be used asfresh non-manipulated products or further processed (e.g., cryopreservation, cellselection, starting material for ATMPs).

HPC extracted from Umbilical Cord Blood: HPCs are found in umbilical cord blood (UCB). The infused HPC(CB) can originate from the recipient (autologous) or from another individual (allogeneic). UCB units are distributed cryopreserved as whole blood or buffy-coat enriched.

Medically Assisted Reproduction

Gamete: A reproductive cell having a single set of chromosomes. The human female produces oocytes up to 20 times larger than the spermatozoa produced by the male.

Embryo: The result of continued development of the zygote to 8 completed weeks after fertilisation, equivalent to 10 weeks of gestational age.

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FACILITATING THE AUTHORISATION OF

PREPARATION PROCESS FOR BLOOD, TISSUES AND CELLS

Technical annex 2 to overall guidance: assessing the quality and safety of donor testing, pathogen reduction and sterilisation steps as part of Preparation Process Authorisation (PPA)

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Introduction

Blood and blood components,and tissues and cells for clinical use, bear the risk of carrying a number of infectious agents. If present, an infectious agent may then be unintentionally transmitted through transfusion/transplantation, which could then lead to disease and even death in recipients. Over the years there have been numerous reports of infectious disease transmissions through blood, tissues and cells (BTC). Today, regulations, standards, improved donor selection procedures and testing are in place, all helping to minimising the risk of infectious disease transmission. However, cases of viral, bacterial, parasitical and fungal infections from BTC still occur. Moreover, new threats affecting donations or recipients have also been identified, for example prions (e.g.in variant Creutzfeldt-Jakob disease; vCJD), emerging viruses (e.g. West Nile virus, dengue virus, Chikungunya virus, Zika virus), parasites (e.g. *Plasmodium spp.* in malaria, *Trypanosoma cruzi* in Chagas disease, *Babesia* in babesiosis) and multidrug-resistant bacteria. Emergence of novel pathogens is rather unpredictable, however mathematical models suggest that every 5 years a new transfusion-transmissible infectious agent could emerge (Gallagher *et al*. 2013).The severe acute respiratory syndrome (SARS) coronavirus in 2002/2003, the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, the Zika virus in 2015/2016, and the new severe acute respiratory syndrome coronavirus (SARS-CoV-2) from 2019 onwards are good examples of how unexpectedly pathogens can emerge and spread (Kuiken *et al*. 2003;Qi *et al*. 2013;Talero-Gutiérrez *et al.* 2018; Wang *et al*. 2020). Therefore, the risk of transmission of an infectious agent through BTC remains a rare but ongoing concern.

Since the large number of cases of transfusion-transmitted human immunodeficiency virus (HIV)in the 1980s, the probability of BTC transmitted HIV, hepatitis B virus (HBV) and hepatitis C virus (HCV) infections has markedly decreased through the introduction of risk mitigation strategies: for example revised donor selection criteria, post-donation information management, improved and expanded testing strategies, including nucleic acid amplification technique (NAT) testing of donors/donations for an increasing range of infectious agents. Indeed, appropriate and reliable laboratory testing of each donation and/or donor, control of reagents, pathogen reduction, as well as, where appropriate, post-processing microbiological testing of BTC, can substantially reduce the risk of transmission, and improve the overall safety of BTC.

In this guidance, use of the word '*must*' indicates mandatory compliance in alignment with applicable EU legislation, whereas the use of the word '*should*' indicates recommended compliance in accordance with commonly accepted relevant guidance.

Aims

This annex provides high level requirements and criteria for verifying that the microbiological safety of blood, tissues and cells is in accordance with current European Blood, Tissues and Cells Directives (EUBTCDs; Directives 2002/98/EC, 2004/33/EC, 2005/61/EC, 2005/62/EC, 2011/38/EU, 2014/110/EU, 2016/1214/EU, 2004/23/EC, 2006/17/EC, 2006/86/EC, 2012/39/EU, 2015/565/EU, 2015/566/EU) and other standards and guidelines that ensure the quality and safety of BTC.

In more detail, this guidance describes aspects which the Competent Authorities (CA) of Member States (MS) should take into account when assessing:

- competence of laboratories performing donor/donation infectious disease testing and microbiological testing of BTC
- reliability of the donor/donation infectious disease marker test kits
- effectiveness of pathogen reduction during BTC processing
- effectiveness of sterilisation methods during BTC processing
- microbiological status of final BTC products

Microbiological safety will be assessed in relation to the potential presence of bacteria, viruses, fungi, parasites and prions in BTC (as defined by GAPP).

Scope

The content of this document only applies to BTC and their applications as regulated in EUBTCDs, and all novel BTC that are not currently covered by other regulations.

BTC that are subject to *substantial manipulation* or that are *not intended to be used for the same essential function or functions in the recipient as in the donor* (as defined in Advanced Therapy Medicinal Product (ATMP) Regulation 1394/2007/EC), BTC products classified as Medical Devices and other Medicinal products (such as plasma-derived medicinal products), are not part of the scope of the GAPP Joint Action. Donation, procurement and testing of BTC intended for ATMP manufacturing do fall under the scope of the GAPP Joint Action.

The procedures of BTC donor and product monitoring and quality control testing themselves are not in the scope of this guidance.

Furthermore, this guidance does not extend to the assessment of activities such as aseptic working methods, clean room maintenance or environmental monitoring, which are assessed by CAs during the Blood Establishment/Tissue Establishment (BE/TE) inspections. Health and safety issues for staff are also out of the scope of this guidance.

1. General validation requirements

Performance validation is required fordonor/donation infectious disease marker test kits, pathogen reduction and sterilisation, and thus, the general validation requirements described here apply to chapters 3, 4 and 5, respectively.

Validation is usually split into two components: qualification and process or method validation. Each part of the process, and individual items (including facilities, equipment, computer systems, materials and staff), should be qualified before they are first used in a process, and then re-qualified at predetermined intervals, or when significant changes are made. Process or method validation should only be performed once all the items used have been qualified and before a new process or method is used routinely. (Adapted from EDQM T&C2.16.1.) Retrospective validation is no longer an acceptable approach (Directive (EU) 2016/1214 Art. 1: Good Practice Guidelines/GPG Blood 4.4.1.2).Process validation of new BTC should cover all intended processes and sites of preparation. A scientific and risk-based validation approach could be justified for new blood components based on extensive process knowledge from the development stage in conjunction with the appropriate ongoing statistical process control (SPC)(GPG Blood 4.4.1.3), and for new tissues and cells, if applicable.

The key elements of the site qualification and validation programme should be clearly defined and documented in a validation master plan or equivalent document (GPG Blood 4.3.2.3-4).

The process or method to be used, as well as acceptance criteria should be documented in a validation plan and approved by suitably qualified and competent organisation management before qualification or process/method validation begins. The results of the validation are compared with the acceptance criteria, and any deviation from the expected results or from the validation plan should be recorded and fully investigated during the validation and documented in the validation report. Following validation, the acceptance or rejection of the process by designated organisation management should be documented. (Adapted from EDQM T&C 2.16.1.)Equipment, facilities, systems and processes should be evaluated at an appropriate frequency to ensure that they are still operating appropriately (GPG Blood 4.4.1.6).

If processes are outsourced to external service providers it is required that responsibilities between BE/TE and service provider are clearly defined, and specifications for the whole process are produced. External service providers should meet the requirements of EUBTCD (Directive 2005/62/EC Annex, paragraph 8; Directive 2004/23/EC Art. 24). Data supporting qualification and/or validation studies obtained from sources outside of the establishment may be used provided that this approach has been justified and there is adequate assurance that controls were in place throughout the acquisition of such data (GPG Blood 4.3.1.4).

In general, the process or method validation needs to be performed once by each organisation. If the process or method has been successfully validated by any organisation, it may be transferred between organisations. In this case the receiving organization should repeat the validation to a reduced extent, guided by the sending organisation, if in accordance with any relevant national regulations. This on-site validation should focus on “worst case” conditions. (Adapted from WHO guidelines on transfer of technology in pharmaceutical manufacturing, Annex 7.)

Details concerning specificity of validation of donor/donation testing, pathogen reduction and sterilisation will be described in the chapters 3, 4 and 5.

2. Requirements and criteria for laboratories performing donor/donation infectious disease testing and microbiological testing of BTC

BE/TEcan perform infectious disease testing of BTC donors themselves or they could outsource this work to an appropriately qualified and competent external laboratory selected by the BE/TE (Directive 2002/98/EC Art. 3; Directive 2004/23/EC Art. 3;Directive 2006/17/EC Annex; Directive 2005/62/EC Annex 8;GPG T&C ch. 8).Such a laboratory may be part of a hospital or private clinic, but may also be an independent enterprise offering the appropriate testing services. In addition to donor testing, the laboratory can examine preparations of BTC to determine, measure or otherwise describe the presence or absence of various micro-organisms (see chapter 6) (EDQM T&C ch. 10). Whether the laboratory performing these activities is part of the BE/TE or a third party offering its services to BE/TE, it must meet requirements laid down in the EUBTCD (Directive 2002/98/EC Art. 2; Directive 2004/23/EC Art. 24.2).

2.1. Testing and screening of donors/donations

In this document, the word 'testing' is used to refer to the investigations performed on either donor or donation sample to determine any infectious disease risk associated with the donation. Although some MS may use the word 'screening' to describe this activity, 'testing' has been used because of the wide range of practices in MS, including the different establishments/laboratories involved in provision of blood, tissue and cells, for broad clarity, and for consistency with the wording in the relevant EU directives (Directive 2006/17/EC; Directive 2002/98/EC). The testing performed is to look for the presence of specific markers of infection for a range of infectious agents.

This document is intended to cover the testing activities performed to identify evidence of the presence of infectious agents which may be present in blood, tissue and cell donations. The basic testing process and procedures are the same for blood, tissues and cells, although there may be some differences in the specific testing requirements. Most donations are collected from selected, low risk donors, the expectation being that the majority have no evidence of infectious disease risk (except for e.g. partner donations in MAR or autologous donors). The one key difference between the testing activities is that for blood donation, it is a sample from the donation itself that is tested, whereas for tissue and cell donation the sample to be tested is taken from the donor(the exception being cord blood donation, when a sample of the cord blood may be tested as well as the maternal sample).

2.2. Quality system

Based on the EUBTCDs, any laboratory undertaking the testing of donors/donations must have a well-managed quality system (Directive 2002/98/EC Art. 11; Directive 2004/23/EC Art. 16). As any structure or body, that is responsible for any aspect of the testing of human blood or blood components is determined to be a Blood Establishment (except hospital blood banks) (Directive 2002/98/EC Art. 3), laboratories testing blood donations and performing microbiological testing of

blood components must develop and maintain a quality system that is based on EU Good Manufacturing Practices (GMP) (Directive 2003/94/EC), and meet the requirements identified in Directive 2005/62/EC (Art. 2), as amended by Directive (EU) 2016/1214 and the Good Practice Guidelines (GPG Blood). Similarly, the quality system of tissue and cell donor and microbiological testing laboratories must meet the requirements laid down in the Directive 2004/23/EC (Art. 16 and 24).

Furthermore, standards and specifications of quality systems for laboratories testing blood donations and performing microbiological testing of blood components are defined in GPG Blood (ch.1.2), the application of which are mandatory in MS. Even though no similar legal requirement exists for tissue and cell donor testing laboratories and microbiological testing laboratories, it is recommended that these laboratories follow the general requirements regarding quality systems and quality management as described in Good Practice Guidelines for TEs (GPG T&Cch.2).

2.3. Standard

The EUBTCD are the minimum standards for laboratories performing donor infectious disease testing and microbiological testing of BTC. The EDQM Guide to the preparation, use and quality assurance of blood components is an additional standard for blood donor testing laboratories, and the EDQM Guide to the Quality and Safety of Tissues and Cells for Human Application could be used for tissues and cells, respectively. In addition to the EUBTCD, laboratories must meet the relevant national legislation and national standards which apply to those specific activities.

Many medical laboratories in EU follow EN ISO standards, either voluntarily or if required by national legislation. EN ISO 15189, the international standard for medical laboratories specifying requirements for quality and competence is internationally and within the EU the most used (Zima 2017;Boursier*et al.* 2016;Buchta*et al.* 2018). In some EU MS, other national or international standards which have adopted essential contents of EN ISO 15189 are used, whereas medical laboratories in some EU MS use EN ISO 17025, which outlines general requirements for the competence of testing and calibration laboratories, as an alternative or additional standard (Zima 2017). Furthermore, a laboratory using an in-house test for BTC donor infectious disease marker testing must be compliant with standard EN ISO 15189 (Regulation (EU) (2017/746 Art. 5). If a laboratory follows ISO standard(s), it must ensure that in addition the relevant requirements within the EUBTCD are met.

2.4. Accreditation, designation, authorisation or licensing of laboratory by Competent Authorities

Based on the EUBTCDs, any laboratory undertaking donor, blood component, tissue or cell testing must be accredited, designated, authorised or licensed by a relevant CA (Directive 2002/98 Art. 5, Directive 2006/17 Annex II 2.1). Designation, authorisation and licencing by CA mean that the laboratory has been identified and given official permission to perform testing. Accreditation means an attestation by a National Accreditation Body - officially recognised by their national government - when a laboratory meets the requirements set by harmonised standards and, where

applicable, any additional requirements including those set out in relevant sectoral schemes, to carry out a specific activity (Regulation (EC) No 765/2008;https://european-accreditation.org/).

Where the national legislation and fundamentals of permission vary between MS, accreditation is based on harmonised standards. Accreditation according to standards is an effective way to prove competence of the laboratory, and it further facilitates accurate and reliable outcomes and reduces errors in the laboratory processes (Allen 2013). Furthermore, accreditation increases harmonisation and transparency (https://european-accreditation.org/). Whether laboratories are accredited, designated, licensed or authorised by the CA, this information should be shared, in addition to the other requirements set out above for laboratories, to increase mutual trust, especially when BTC are distributed to other EU MS.

2.5. Additional requirements for testing laboratories

If BE/TE outsources the donor/donation testing or microbiological testing of BTC, it must establish a written contract with the laboratory performing testing (Directive 2004/23/EC Art. 24;Directive 2005/62/EC Annex 8). Any contract between BE/TE and an external testing laboratory should describe the roles and responsibilities of all parties, and specify detailed procedures (Directive 2004/23/EC Art. 24;GPG Blood 8.1.2). Good Practice Guidelines describe the general principles regarding a written contract (GPG T&C 3.1; GPG Blood 8.1), as well as requirements for contract giver, the service/product provider and the contract itself (GPG T&C 3.2.-3.4; GPG Blood 8.2.-8.4).

Donor testing laboratories should use appropriate algorithms to ensure that their testing procedures have maximum sensitivity without loss of specificity (EDQM T&C 5.4). The algorithms should be defined in writing (i.e. standard operating procedures) to deal with initially reactive specimens, and to resolve discrepancies in results after retesting (GPG T&C 9.14; GPG Blood 6.4.7). It is recommended that donor testing algorithms would be defined nationally taking into account the epidemiology of infectious agents in the national donor population, and enabling the appropriate and consistent investigation and resolution of test reactivity (EDQM Blood ch.9). As such algorithms are often specific to the individual MS, no model algorithm has been included in this guidance. An example of a widely used algorithm for infectious disease marker primary testing and confirmatory testing is presented in the EDQM Blood Guide (ch.9).

3. Requirements for selection, validation and performance of donor/donation infectious disease marker test kits

Blood transfusion, as well as tissue and cell transplantation, and reproductive cell transfer, may result in transmission of infectious diseases. In order to prevent such transmission and to ensure an equivalent level of safety for all donation types, each donor/donation must be tested in accordance with the requirements laid down in EUBTCDs(Directive 2002/98/EC Annex IV;Directive 2006/17/EC Annex II and III).

As a minimum requirement, all donors/donations must be tested for HIV, HBV and HCV (as summarised in Table 1). In addition to the minimum requirements, testing of donors/donations for additional infectious agents or infectious markers may be required for specific blood components, tissues or cells. Additionally, differences in endemicity of infectious agents in different MS or regions, together with the emergence and spread of transmissible infectious agents, may, in some MS, require testing for a number of other infectious agents (Directive 2002/98/EC Annex IV;Directive 2006/17/EC Annex II 1 and Annex III 2-3;EDQM T&C 5.5).Furthermore, national legislation may result in additional variation between the EU MS.

Table 1. Summary of infectious disease markers required to be tested, as a minimum, for BTC donors/donations.

Donor type	Mandatory tests within the EU	Directive	Additional tests
Blood donors	HIV 1/2 (anti-HIV 1/2) Hepatitis B (HBs-Ag) Hepatitis C (anti-HCV)	2002/98/EC Annex IV	Based on e.g. the donor's history, the characteristics of the BTC donated, national epidemiological situation, requirements in national legislation, guidance by European Centre for Disease Prevention and Control (ECDC) and recommendations by WHO, additional testing may be required e.g. *Treponema pallidum,*HTLV-1, Cytomegalovirus (CMV), malaria, toxoplasma, Epstein-Barr virus (EBV), *Trypanosoma cruzi*, Hepatitis E virus.
Tissue and cell donors	HIV 1/2 (anti-HIV-1,2) Hepatitis B (HBsAg, anti-HBc) Hepatitis C (anti-HCV-Ab) *Treponema pallidum*	2006/17/EC Annex II	
Reproductive cell donors	HIV 1/2 (anti-HIV-1/2) Hepatitis B (HBsAg, anti-HBc) Hepatitis C (anti-HCV-Ab) *Treponema pallidum* (non-partner donors) Chlamydia (non-partner sperm donors; urine sample NAT testing)	2006/17/EC Annex III	

Effective testing for the detection of transmissible infectious agents can reduce the risk of transmission to a very low level (EDQM Blood 2.3.3.;WHO TTI guidelines 2009). In addition to effective laboratory testing of donors/donations for a range of markers of specific infectious agents, the choice of test kits or platforms together with the quality management systems in place are crucial to maximise the microbiological safety of transfusion and transplantation. Requirements for selection, validation, and performance of infectious disease marker test kits for the testing of BTC donors/donations are summarised below.

3.1. Selection of infectious marker test kits

The selection of appropriate test kits is a critical part of the donor/donation testing. Numerous commercial infectious marker test kits are available. These are based on various types of assays which detect antibodies, antigens or the nucleic acid of the infectious agent (EDQM T&C 5.5;WHO TTI guidelines2009 3.1-3.2). Different types of assays include(WHO TTI guidelines 2009 3.1.):

- Immunoassays
    - Enzyme immunoassays (EIAs);
    - Chemiluminescent immunoassays (CLIAs);
    - Haemagglutination (HA)/particle agglutination assays (PAs);
    - Rapid/simple single-use assays (rapid tests);
- NAT assays.

However, not all test kits are suitable in all situations and each testing system may have specific advantages and/or limitations that should be taken into consideration when selecting infectious marker test kits (WHO TTI guidelines2009). As a minimum requirement the following factors should be considered in selecting the most appropriate test kits.

Test kits used *in vitro* for the testing of BTC donors/donations are considered as *in vitro* diagnostic medical devices which must be *Conformité Européenne* (CE) -marked before placing on the market within the EU (Regulation (EU) 2017/746 Art. 2). Therefore, infectious disease marker testing of BTC donors/donations should be carried out using CE-marked test kits, where appropriate.

Test kits should be suitable for the detection of the required markers in the sample types being tested (EDQM T&C5 5.3; JPAC 2013 9.2). Typically infectious-disease marker test kits specifically intended for the testing of donors/donations are designed to be used with samples from a living or deceased heart-beating donors (i.e. donor after brain death) (EDQM T&C 5.3.3). If there is a need for collection of post-mortem samples (from deceased non-heart beating donor), the test kit should have been validated for this purpose, either by the manufacturer, or by the user (EDQM T&C Appendix 19). Additionally, ideally only test kits specifically designed and validated for donor/donation testing should be selected. Test kits and systems specifically intended for use for diagnostic purposes could be selected after the appropriate validation for use for testing purposes (EDQM T&C 5.4; WHO guidelines 2011 7.4).

In selecting a specific test kit for the testing of BTC donors/donations, both sensitivity and specificity should be as high as possible (WHO TTI guidelines2009 3.3;EDQM T&C 5.1). High sensitivity ensures identification of infection and high specificity decreases rates of non-specific

reactivity, which could result in the wastage of donations and unnecessary deferral of donors(WHO TTI guidelines 2009).

3.2. Validation of infectious marker test kits

All infectious marker test kits must be validated for their intended use in accordance with current scientific knowledge (Directive 2006/17/EC Annex II 2.1). Furthermore, all testing procedures related to blood donor/donation testing must be validated before use (Directive 2005/62/EC Annex 6.3.1).

Chapter 1 (General validation requirements) applies also to this chapter 3.

All CE-marked donor/donation infectious disease marker test kits have undergone performance evaluation (see section 3.3) by manufacturers (Regulation (EU) 2017/746Art.56). The IVD manufacturer is responsible for the performance evaluation of the CE-marked donor/donation infectious disease marker test kit. This implies an assessment and analysis of the data used to establish or verify the scientific validity, the analytical and, where applicable, the clinical performance of a device (Regulation (EU) 2017/746, Directive 98/79/EC. Note: 2017/746 will be fully applied from 26.5.2022 onwards).

All IVD devices are further required to undergo conformity assessment, the process of demonstrating whether the requirements relating to a device have been fulfilled. For high risk devices (e.g. mandatory donor/donation infectious disease marker test kits), conformity assessment always requires assessment by a Notified Body. After full application of the IVD regulation in 2022, all IVD devices for the detection of infectious disease markers will require assessment by a Notified Body. Before 26.5.2022, based on the IVD Directive (98/79/EC), some infectious disease markers may fall out of the scope of Notified Body assessment, and conformity assessment is the responsibility of the manufacturer.

For the highest risk class (D), the Notified Body assessing the device/test kit may request the European Union reference laboratory(ies) designated by the Commission to verify the performance claims and compliance with common specifications, where they exist (Regulation (EU) 2017/746 Art. 48). Infectious disease test kits intended for testing of BTC donations/donors will fall into class D according to the IVD regulation (for respective classification rule, see Regulation (EU) 2017/746 Annex VIII rule 1, as well as Medical Device Coordination Group Guidance on classification of IVD devices, under development in 2020).

However, depending on the intended use of the test kit, because of variation in the performance of CE-marked test kits, and differences in populations and the background disease prevalences in different EU MS, additional laboratory evaluation and validation work may be required by the individual MS.

An on-site validation of the CE-marked donor/donation infectious disease marker test kit should be required prior to its routine use in each laboratory. On-site validation should demonstrate, in addition to qualification, that the basic performance specifications of the assay established by the kit manufacturer are met in the laboratory (WHO guidelines 2011 7.4;GPG Blood 6.3.3).

Additionally, donor/donation testing laboratories are required, by their quality system and/or regulation, to demonstrate that in routine use, the performance specifications of the test kits/assays are constantly maintained (WHO guidelines 2011 7.4). The means by which this could be demonstrated are a combination of, for example:

- appropriate reactivity with manufacturers' and any internal and external quality control materials with every series of tests (WHO guidelines 2011 7.4; JPAC 2013 9.1);
- statistically monitoring trends in control measurements on defined control material (WHO guidelines 2011 7.4; JPAC 2013 9.1);
- successful participation in external quality assessment schemes (proficiency testing) by all qualified members of staff (WHO guidelines 2011 7.4;Directive 2005/62 Annex, 6.3.5).

When the testing laboratory intends to use in-house tests instead of CE-marked kits, the performance of each in-house test must be validated by the laboratory itself before being brought into routine use. This means that the laboratory must demonstrate conformity with the relevant general safety and performance requirements set out in Annex I of Regulation (EU) 2017/746 which apply to it, taking into account its intended purpose. In addition to these, the conditions listed in point 5 of Article 5 of Regulation (EU) 2017/746 must be met (e.g. manufacture and use of the test under appropriate quality management systems, laboratory compliance with standard EN ISO 15189, a justification of their manufacturing, modification and use etc.).Before application of the IVD Regulation (EU) 2017/746 in 2022, laboratories must follow respective national legislation.

User validation of CE-marked test kits and in-house tests for use with post-mortem samples should be undertaken in accordance with any EDQM guidance (e.g. Example of validation of screening: infectious disease assays of blood from deceased donors in EDQM T&C Appendix 19).

3.3. Performance of infectious marker test kits

The performance of an infectious marker test kit means the assessment of its ability to achieve its intended purpose as claimed by the manufacturer. This consists of the analytical and the clinical performance (Regulation (EU) 2017/746 Art. 2), as well as scientific validity. The analytical performance means the ability of a donor/donation test kit to correctly detect a particular analyte (adapted from Regulation (EU) 2017/746 Art. 2). Characteristics describing the analytical performance include(Regulation (EU) 2017/746 Annex I 9.1.a; WHO guidelines 2011 7.3):

- analytical sensitivity
- analytical specificity
- trueness (bias)
- precision
    - repeatability (replicates of series)
    - reproducibility, variation by operator, by day or by lot of reagents
- accuracy (degree of closeness of measurements to the true value, resulting from trueness and precision)
- lower and upper limits of detection (serial dilution) and quantitation
- measuring range, linearity, cut off
- determination of appropriate criteria for specimen collection and handling

- control of known relevant endogenous and exogenous interference(e.g. haemolytic sera, lipemic sera)

The clinical performance means the ability of a test kit to yield results that are correlated with a particular pathological state in accordance with the target population (Regulation (EU) 2017/746 Art. 2). Specifically, characteristics of the clinical performance include (diagnostic) sensitivity, (diagnostic) specificity, positive predictive value, negative predictive value, likelihood ratio, and expected values in normal and affected populations (Regulation (EU2017/746Annex I 9.1.b).

CE-marked donor/donation infectious marker test kits (which have undergone a performance evaluation by a manufacturer and demonstrated conformity) should meet these above mentioned general performance requirements (Regulation (EU) 2017/746 ch. II Art. 5). These general performance requirements also apply to in-house donor/donation tests and therefore these tests should also meet these requirements (Regulation (EU) 2017/746 Art. 5.5).

In addition to general performance requirements, CE-marked donor/donation test kits are compliant with the common technical specifications for the detection, confirmation and quantification in human specimens of markers of HIV infection (HIV 1 and 2), HTLV 1 and 2, and hepatitis B, C, D (Commission Decision 2009/886/EC Annex, 3). Specifically the requirements for sensitivity and specificity of these test kits are set out in Table 1 of the Commission decision 2009/886/EC. It is recommended that the minimum evaluated (diagnostic) sensitivity and (diagnostic) specificity levels of all donor/donation infectious disease marker test kits should be as high as possible and preferably not less than 95 - 99.5% (Commission Decision 2009/886/EC).

3.4. Donor/donation testing for emerging infectious agents

New and emerging infectious agents, or those that have moved to infect a new geographical area can pose a significant risk of transmission via transfusion/transplantation (EDQM Blood 2.3.3; EDQM T&C 16.4.1.1). Even though transmission of infectious agents can be minimised by donor deferral, there are situations where donor/donation testing is the main tool to reduce the risk of transmission. Donor/donation testing becomes especially important when donor deferral may reduce BTC supply e.g. in the newly affected area. In addition, a possibility of asymptomatic infection or existence of a carrier state may increase need for donor/donation testing (EDQM Blood 2.3.3). Thus, reliable donor/donation infectious disease marker testing may be vitally important to maintain the safety and sustainability of BTC supply.

As with mandatory donor/donation infectious disease marker testing, CE-marked kits should be used, if available. However, in the presence of an unexpected outbreak caused by a new agent, new test kits may become available in the market without following the standard procedures for CE mark (self-certification of the producer). Therefore it is recommended that the guidance of European Commission and ECDC on BTC donor/donation infectious disease marker testing is followed (EDQM T&C 16.4.1.1). It is also important to define, in accordance with the professionals involved, the minimum acceptable specifications of the new test kits based on the scientific information available at that time.

In-house tests developed for the detection of rare or new emergent diseases can be used when commercial CE-marked test kits are not available on the market in the EU. However, they must

meet the general performance and validation requirements as set in Regulation (EU) 2017/746 and summarised above.

4. Criteria for validation of pathogen reduction steps

Even with sensitive and specific testing, there remains a residual risk of transmission of infectious agents during the window period, when the pathogen is present but undetectable by the test in use. It is also possible that a pathogen could mutate in a way that makes it undetectable by the NAT-based testing, or, in the case of newly identified threats such as emerging viruses and prions, there may not be a suitable test available. BTCcan also be contaminated by bacteria and fungi during procurement or processing, and those stored at or close to room temperature are more likely associated with bacterial or fungal growth (for example platelets).

One way to address these concerns and further enhance the safety of BTC is to introduce pathogen reduction technologies (PRT), if possible.PRT have been demonstrated, through validation studies, to inactivate pathogens or decrease their number, using physical and/or chemical methods, without significantly compromising the safety of the BTC (see chapter 4.4). Currently available systems can inactivate or decrease the number of a wide range of viruses, bacteria and parasites but they do not reduce infectivity associated with prion proteins such as the causative agent of vCJD (EDQM Blood 4.4.4). PRT could also represent a more generalised approach against emerging pathogens.

This section relates to the MS CA assessment of validation packages that demonstrate the performance of PRT.

Chapters 1 (General validation requirements) and 6.3 (Methods for microbiological control) also apply to chapter 4.

4.1. Validation requirements depend on the type of PRT

According to the Blood Directive 2005/62/EC (Annex, 6.4), the processing of blood components must be carried out using appropriate and validated procedures including measures to prevent contamination and microbial growth in the final blood products. Also according to the Tissues and Cells Directive 2004/23/EC (Art. 20), all processes that affect quality and safety of tissues and cells need to be validated and carried out under controlled conditions. Thus, PRT need to be validated before they are introduced into the processing procedures for BTC, to provide evidence that a chosen PRT process can reliably inactivate or decrease the number of pathogens in a given BTC without compromising the quality, safety and effectiveness of final BTC products.

A range of PRT are already established and in widespread use (see Table 2). Others are under development or were developed as in-house PRT systems, meaning that each method was developed and used only in the BE/TE/laboratory which developed it. For blood components, established PRT are in many cases commercially available products authorised by the CA. At the time of writing this guidance, an entire portfolio of PRTs suitable for all blood components was not available, but the sector has been steadily progressing: PRT systems for red cells and whole blood were in development but not currently in use in Europe (EDQM Blood 4.4.4). For tissues, established PRT are likely to be established protocols rather than commercially available products. Validation requirements in these two cases are different and described below:

- **On-site validation of established PRT systems.** A reduced validation strategy is usually sufficient when using a PRT system/device that has already been authorised by a relevant CA and recognised in the EU (CE-marked devices for e.g. platelets or routinely used systems for e.g. plasma components). Validation of PRT systems in accordance with published methods, or following long-established practices using the same materials and equipment, may rely on ongoing quality control and periodic reviews to confirm that the method has the intended outcome (EDQM T&C 2.16.1). For example, the performance of spiking studies (see later) is not mandatory. Both data from the PRT supplier as well as relevant literature can be referred to. A comprehensive assessment of the relevance of these data by the BE/TE is required to ensure it is directly applicable to the treatment process to be used and the operational conditions at the site. However, possible changes in sample processing procedures, instruments and equipment or the BTC itself should be partially validated according to a risk-based approach.
- **Validation of novel or in-house PRT systems.**The use of an in-house PRT requires an extensive validation, covering parameters of a primary validation study (*Ph. Eur* 5.1.1; EMA/CHMP/CVMP/QWP/850374/2015). Elements such as the degree of pathogen reduction, capacity, specificity and robustness should be addressed. The PRT systems should be validated using “worst case” scenarios. This will usually involve spiking the material with a larger-than normal level of the target pathogens or suitable model organisms, and demonstrating their effective removal, or reduction to acceptable levels, by the process. See Section 4.2.

Table 2. Examples of existing PRT.

PRT mechanism	BTC for which is used	Specific considerations when assessing a validation study
Blood		
Amotosalen + UVA light (320-400 nm)	Platelets (whole blood or apheresis derived) Plasma (whole blood or apheresis derived)	CE-marked. Evaluation of platelet concentration loss (< 10%), *in vitro* platelet function (swirling, pH etc.), and *in vivo* post-transfusion platelet recovery (post-transfusion platelet count increment). Include effectiveness of

		removal of the active agent. For pathogen inactivation effectiveness, see Schlenke (2014), Tables 3 and 6.
Riboflavin + UVB light (280-360 nm)	Platelets (whole blood or apheresis derived) Plasma (whole blood or apheresis derived)	CE-marked. Does not require removal of the active agent. For pathogen inactivation effectiveness, see Schlenke (2014), Tables 3 and 6.
UVC light Filtration + Methylene Blue + visible light (400-700 nm)	Platelets Fresh frozen plasma	CE-marked. No toxicological assessment necessary. For pathogen inactivation effectiveness, see Schlenke(2014), Table 3.
Solvent/Detergent	Large-pool of plasma (whole blood or apheresis derived)	At the time of writing this guidance, authorised in several European countries (e.g. AT, BE, BG, CZ, DE, DK, EE, ES, FI, FR, HR, HU, IE, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK). (EMA List of nationally authorised medicinal products)
Solvent/Detergent	Single donation or mini-pool of plasma (whole blood or apheresis derived)	CE-marked.
Tissues		
Antibiotic/anti-mycotic treatments	Amniotic membrane tissue, musculoskeletal tissue, adipose tissue, cardiovascular tissues, ocular tissues, skin tissue	Allowed residual concentration, or removal of antibiotics should be described.
High concentrate glycerol	Skin tissue, amniotic membrane tissue, ocular tissue	Glycerol solutions used should be sterile and of high quality (e.g. see *Ph.Eur.* monograph 0497 – Glycerol 85 %)
Decellularisation	Skin tissue, cardiovascular tissues, amniotic membrane tissue	All solutions used for decellularisation should be prepared from sterile and high quality products whenever possible; or sterility filtered (<0.22µm).
Chemical decontamination (e.g. peracetic acid, iodophors, ethanol)	Musculoskeletal tissue	Possible residue issues should be justified.

Low dose irradiation (e.g. 15 kGy)	E.g. musculoskeletal tissue, amniotic membrane	E.g. when using a combination of PRTs.
Supercritical carbon dioxide treatment	Musculoskeletal tissue, pericardium tissue	Does not require removal of the active agent.

(EDQM T&C monographs)

4.2. Aspects of PRT validation

The application should describe all relevant information that the CA requires to undertake its review:

- **Starting material**. The effectiveness of a PRT should be shown in the BTC preparation itself and not only in an aqueous solution (EDQM T&C 8.8.2).
- **Specification of reduction capacity.** Prior to the PRT validation it is necessary to assess the bioburden usually present in the BTC material as well as defining worst case scenarios. The latter can be critical for a successful pathogen reduction and should be also addressed in the study.
- **Target organisms**. Appropriate model organisms for the spiking studies include typical contaminants likely to be found in the BTC material as well as micro-organisms that might represent a challenge for the PRT. In addition, model organisms should be stable in the presence of the matrix. Ideally, known and well characterised reference organisms should be used (Spindler-Raffel et al. 2017: WHO Bacterial reference strains; EDQM T&C 2.16.9 and 8.6.1.2; *Ph. Eur* 2.6.1; CPMP/BWP/268/95). The applicant should justify the choice of micro-organism in accordance with the aims of the validation study.
    - Suitable spike stocks. To demonstrate high magnitude reduction ability, BE/TE or contracted testing laboratory should source representative high titre stocks of pathogens (JPAC Validation on Plasma and Platelet Pathogen Inactivation). A panel with relevant characteristics should be included. Where WHO bacteria reference strains are available they should be used. The quantitation range of the assay should cover the bioburden concentration range expected in the BTC.
    - Key bacteria against which PRT should demonstrate effective reduction: see Table 1 in the JPAC guidance “Validation of Plasma and Platelet Pathogen Inactivation”.
    - Strains of micro-organism that are known to be resistant to antimicrobial treatment, e.g. spore-forming, heat-resistant bacteria, may be used for spiking (EDQM T&C 2.16.9).
    - Viruses that may contaminate BTC vary considerably in their size, physical properties and genomic material. In addition, the pathogenicity of a virus may depend on the patient group and on the BTC being administered. To demonstrate effectiveness against known viruses and emerging risks, PRT validation data should demonstrate removal or inactivation of a wide range of enveloped and non-enveloped viruses, including viruses of concern and/or established models. Typically, validation studies involve several virus types.

Guidance is available for the selection and assay of model viruses(CPMP/BWP/268/95 Table 1).

- **Interfering factors.** Factors which might have an effect on the reduction capacity have to be considered in the validation study (e.g. hemoglobin concentration in UV inactivated platelet concentrates). Monitoring the levels of these factors should be in place to ensure levels are within an acceptable and valid range.
- **Critical process parameters (CPP).** CPPs are used to measure the performance of the PRT treatment unit, and relate to the reduction performance of the target pathogen (PRT treatment effectiveness). Continuous monitoring of CPPs provides assurance that the system is under control and alerts operators and control systems if PRT treatment effectiveness is reduced to an unacceptable level.
- **Quantitative assays for each model pathogen.** To determine the reduction capacity accurately, validated quantitative assays for each model pathogen have to be in place at the BE/TE or contracted testing laboratory. These should detect live pathogen. NAT testing will not differentiate between live and inactivated pathogens but can be used in the validation of removal processes.
- **Model process.** If a scaled-down model of the PRT process is used during validation (e.g. to conserve material, virus stocks, or protect the usual processing environment), the validation documentation should verify the PRT scale model and its comparability with the proposed/current preparation process.
- **Controls.** Suitable sample controls should be collected during the validation to demonstrate the mechanism of pathogen reduction.

Additional aspects for the CA to consider:

- Critical reagents and materials must be CE-marked, when applicable (Directive 2006/86/EC, Annex I, C.6; GPG Blood 4.1.9).
- PRT should be carried out at appropriate interval after BTC donation (in many cases, as short as possible). If commercial PRT kit is used, manufacturer gives instructions on the maximum interval and these should be followed. If PRT is carried out after the maximum recommended interval, any bacteria present may have multiplied, and the level of bacteria may be significantly higher. Additionally, growth of bacteria may lead to the formation of pyrogenic agents and endotoxin whose immunological activity is not diminished by the PRT.(JPAC Validation of Plasma and Platelet Pathogen Inactivation).
- The product matrix and its components might have a significant effect on the model organisms and their behavior (e.g. complement killing of bacteria). Bacteria can start to grow in the product after spiking thereby altering the initial spiking concentration. A non-inactivated control should be performed in parallel.
- The PRT validation process requires BTC to be deliberately spiked with known and defined micro-organisms, so that the reduction achieved by the PRT can then be demonstrated. Certain requirements (e.g. EU GMP Guidelines chapter 5.18) might restrict the deliberate use of potential contaminants in the production facilities. For validation purposes, the sharing of equipment and facilities that would be used in BTC processing should be avoided due to the risk of cross-contamination. Exemptions can be made in cases in which validation procedures are performed in closed systems.
- Re-validation should be performed in case of change of facility, change of process or any relevant new knowledge.

4.3. Validation criteria

The methodology for the statistical assessment of PRT assays and limitations of such studies have been described previously (CPMP/BWP/268/95; CPMP/ICH/295/95).

In summary, the validation will result in a set of data for each pathogen or representative model used in the spiking study.

The titre of the spiked test material before undertaking the scale model PRT can be compared to the titre of the sample(s) collected from the test material when the scale model process has been completed, in order to determine the overall pathogen reduction achieved. Sample titres and reduction figures achieved are normally reported on a logarithmic scale. The reduction achieved for each pathogen or appropriate model should be reported and include the 95% confidence intervals wherever possible.

Although it is considered that the level of bacterial contamination in blood donation which may result in clinically significant levels of bacteria in stored platelet components is below 100 cfu/unit, a higher minimum proven level of pathogen reduction should be demonstrated: PRT should reduce anybacterial contamination by the amount specified i.e. 10^4(4 $\log_{10}$) to ensure maximum effectiveness (JPAC Validation of Plasma and Platelet Pathogen Inactivation; Murphy *et al.* 2008; Pearce *et al.* 2011). However, this also depends on the time when the PRT takes place: the later in the process the PRT takes place, the higher the necessary effectiveness. PRT should also be able to remove or inactivate substantial amounts of virus, typically 4 $\log_{10}$ or more, although, the log number reduction should not be used as the single, absolute measure of the effectiveness of PRT (CPMP/BWP/268/95ch. 6.1).

Validation reports should include a discussion of the suitability of the scale model system, taking into consideration the results from appropriate assay control samples, and the degree to which these support the proposed mechanism of pathogen reduction.

4.4. Effect of PRT on BTC properties

PRT should not change the properties of the BTC in such a way to make it unacceptable for the clinical use. However, depending on the PRT method the functionality and quality of the resulting BTC can become reduced. The selection of recipients in whom treatment with these BTC might be relevant should therefore be taken into account for safety reasons. The benefits of PRT in reducing microbiological risk should be balanced against any loss of potency or effectiveness of the BTC and this should be assessed as part of the validation (JPAC Validation of Plasma and Platelet Pathogen Inactivation). A framework to assess this will be provided in the GAPP *Technical Annex 1 to overall guidance: authorisation of changes in donation, procurement and collection, processing, preservation, storage and distribution*.

5. Criteria for validation of sterilisation methods

Essential step for microbiological and viral safety of BTC is the confirmation of validated processes for pathogen reduction (see chapter4 of this guidance) or sterilisation, where applicable. The sterilisation methods and criteria described here apply primarily for bacteria and fungi. If a risk assessment points out a viral contamination possibility, it is necessary to demonstrate the process capability of removing/inactivating relevant viruses during the process.

Sterilisation is defined as a process that results in the state of complete absence of all cell-based micro-organisms capable of replication (sterility) (*Ph. Eur* 5.1.1; EDQM T&C 8.6.1). According to Directive 2006/17/EC (Annex IV, 1.3), sterile, wherever possible CE marked, instruments and devices must be used for tissue and cell procurement. Where possible, single-use instruments for procurement are recommended. When re-usable instruments are used, a validated cleaning, disinfection, packaging and sterilisation process for removal of infectious agents has to be in place (Directive 2006/17/EC Annex IV 1.3.9).

Consistently, Directive 2005/62/EC sets the standards for using sterile CE-marked blood bag systems for the collection and processing of blood and blood components(Directive 2005/62/EC Annex 6.2.2).

The conventional test for sterility is described in *Ph. Eur* 2.6.1. Additionally, use of a validated automated culture system may be advantageous if available (*Ph. Eur* 2.6.27). If sterility test is not feasible, sterility needs to be assured by the use of suitably designed, validated and controlled processes.

Chapters 1 (General validation requirements)and 6.3 (Methods for microbiological control)apply also to this chapter 5.

5.1. Uses of sterilisation

Tissues (e.g. bone and amniotic membrane) can in some cases be subject to sterilisation methods (EDQM T&C 1.3).Sterilisation should be applied to tissue grafts in their final packaging without subsequent exposure (JPAC General guidelines for tissue processing, 21.5.3.2). Sterilisation is not applicable to cells, blood components and most tissues. Wherever possible, sterilisation methods should be applied to instruments, procurement devices and materials (e.g. raw materials, reagents, excipients, single-use components, containers, gowning and cloth) which are in contact with starting materials, process intermediates or final products (Directive 2006/17/EC Art. 2, section 7 and Annex IV 1.3.8).

5.2. Sterilisation methods

The sterilisation method used should be shown to be suitable to remove or destroy the type and number of contaminants in the source material. Whenever possible, sterilisation should be done

using methods described in the European Pharmacopoeia (5.1.1), the main points are also presented in European Medicines Agency guideline (EMA/CHMP/CVMP/QWP/850374/2015).These methods are based on moist heat (steam), dry heat, gas, irradiation or membrane filtration. Selection of the sterilisation method should be based on the characteristics of the object of the sterilisation and its associated bioburden and justified (see Table 3). Modifications or combinations of the described methods may be used, provided that the procedure(s) is validated.

Table 3. Sterilisation methods according to *Ph. Eur* 5.1.1 "Methods of preparation of sterile products"

Sterilisation Method	Application examples	Reference conditions
Steam	Instruments, materials, cloth and media	Terminal steam sterilisation at ≥121 °C for 15 min
Dry Heat	Glass and metal instruments/ Tools	Terminal dry heat sterilisation at ≥160 °C for ≥2 h
Ionisation radiation (irradiation)	Musculoskeletal tissues (EDQM T&C 21.4.3), skin (EDQM T&C 19.4.3), amniotic membrane (EDQM T&C 18.4.3) (Singh *et al.* 2016). Containers, equipment and gowns	Terminal ionising radiation of absorbed dose ≥ 25 kGy(IAEA 2007)
Gas (chemical agent) (acceptable only if no other sterilisation methods are feasible; EMA/CHMP/CVMP/QWP/850374/2015)	Containers and equipment	Depends on chemical, no general conditions predefined
Membrane filtration	Fluid or gas products that are not amenable to other sterilisation methods	Nominal pore size ≤0.22 µm

5.3. General validation requirements for sterilisation

Validation should be performed in order to demonstrate the consistent effectiveness of the method chosen and to provide the assurance of sterility. Whenever a sterilisation step is introduced, the following general validation requirements need to be addressed (*Ph. Eur* 5.1.1; JPAC General guidelines for tissue processing, 21.5.3).

5.3.1. Sterility Assurance Level (SAL)

For sterilisation processes with a well-defined dose/kill relationship, a very high level of sterility assurance can be achieved(EDQM T&C 8.6.1). This is quantified by the SAL value which is an experimentally-derived number expressing the likelihood of a contaminant to survive the process. In order to determine the SAL, the bioburden of the respective matrix should be known. Frequently, sterilisation processes are validated to assure the SAL ≤ 10^{-6} for sterile products or equipment. To validate the sterilisation technique, SAL of 10^{-6}should be achieved for the most resistant micro-

organism (often bacterial spores). This is a “worst-case” validation and will guarantee a significant overkill for more sensitive microbes. SAL means that the likelihood of non-sterile item is 1 in 1 million. The SAL 10^{-6} cannot be applied to membrane filtration method or to quantify the effectiveness of virus inactivation/removal. (EDQM T&C 2.16.9; *Ph. Eur* 5.1.1; JPAC General guidelines for tissue processing, 21.5.3; EDQM T&C 8.6.1.2, 10.3.6).

5.3.2. Biological indicators

Biological indicators are test systems (e.g. inoculated carriers) containing viable micro-organisms (usually spores of bacteria, e.g. *Bacillus*or *Clostridium* sp.) that provide a defined worst case challenge to verify the required effectiveness of a specified sterilisation process. Commercially available biological indicators intended for specific sterilisation processes are recommended, but if suitable ones are not available, custom-made may be used.(EDQM T&C 2.16.9; *Ph.Eur* 5.1.2)

Bioburden (and where relevant, bacterial endotoxins) should be specified prior to sterilisation. Bioburden is usually expressed as a measure of the numbers and identification of the species of micro-organisms in the material to be sterilised (EDQM T&C 10.3.6, 10.4.3; *Ph. Eur* 2.6.12 and 2.6.13).Validation of sterilisation potency requires that the maximum predicted level of microbiological contamination can be eliminated by determining the elimination capacity as the number of log scale reductions of the spiked micro-organism. The micro-organisms should verify the required effectiveness of the selected sterilisation method by covering all relevant micro-organisms commonly found on the object including, for example, vegetative Gram positive and negative bacteria, vegetative fungi, fungal and bacterial spores, and viruses, if applicable (EDQM T&C 10.3.6; *Ph.Eur* 5.1.2;EMA/CHMP/CVMP/QWP/850374/2015; CPMP/BWP/268/95).

Viral indicators should be chosen to resemble viruses which may contaminate the donation. Further detailed recommendations of viral safety (*Ph. Eur* 5.1.7) as well as examples of the used virus indicators are listed in CPMP/BWP/268/95*Virus validation studies: the design, contribution and interpretation of studies validating the inactivation and removal of viruses.*

5.4. Specific validation criteria for sterilisation methods

Depending on the sterilisation method in question, more specific data on the effectiveness of the method may need to be evaluated. As a main principle, validation of the effectiveness of the method should be undertaken using a combination of physical indicators (e.g. thermo-couples in moist heat sterilisation) and biological indicators, which should be placed at the locations where sterilising conditions are most difficult to achieve (e.g. cold spots when using heat, difficult to penetrate areas when using gas, minimum/maximum load) (*Ph. Eur* 5.1.2). (This principle is not applicable to membrane filtration). Parameters to achieve the required SAL and examples of the most widely accepted biological indicators are described under the relevant sterilisation methods below.

Conditions of the sterilisation methods should be developed and validated in compliance with *Ph. Eur* 5.1.1 and 5.1.2. In addition, guidelines for validation of sterilisation methods are explained e.g. in the publication by European Medicines Agency (EMA/CHMP/CVMP/QWP/850374/2015).

5.4.1. Steam sterilisation (Autoclaving)

Steam (moist heat) sterilisation is performed in saturated steam under pressure in autoclaves (Directive 2014/68/EU for pressure equipment) and the critical parameters are pressure, time and temperature. When using the method, equal distribution and adequate penetration of steam should be verified. The reference cycle for steam sterilisation is 15 min at 121 °C. Depending on the product and load, another combination of time and temperature may be adopted based on cycle validation, with a minimum acceptable temperature of 110 °C. The sterilisation effectiveness may be calculated by F0 concept. F0 is the time in minutes for the specified temperature that causes the same lethality as one minute at 121 °C, with minimum F0 not less than 8 min. (Ph.Eur5.1.5)

- Suitable test micro-organism: *Geobacillusstearothermophilus* (e.g. strains ATCC 7953, NCTC 10007, CIP 52.81, NCIMB 8157, ATCC 12980)
- Additional information can be found in: ISO 17665-1:2006*: Sterilization of health care products* - Moist heat - Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices.

5.4.2. Dry heat

For dry heat, the critical parameters are time and temperature. Reference conditions are minimum of 160 °C for at least 2 h. Other combinations may be used if validated and SAL ≤ $10^{-6}$is demonstrated. Validation should be done using a combination of temperature mapping and biological indicator.

- Suitable test micro-organism: *Bacillus atrophaeus* (e.g. strains ATCC 9372, NCIMB 8058, NRRL B-4418, CIP 77.18), at temperatures between 160 °C and 180 °C.
- Additional information can be found in:ISO 20857:2010 *Sterilization of health care products* — Dry heat — Requirements for the development, validation and routine control of a sterilization process for medical devices

5.4.3. Irradiation

Sterilisation by irradiation is achieved by gamma rays, accelerated electron beams or x-rays. The reference absorbed dose is 25 kGy (*Ph. Eur* 5.1.1; IAEA 2007). In practice, to maintain the properties of the tissues, some TE prefer low irradiation dose (e.g. 15 kGy) and generally the given dose varies ranging from 15 kGy to 35 kGy (Nguyen et al. 2013). The irradiation dose is selected depending on the bioburden and it should result in SAL of ≤10^{-6}. Depending on bioburden, ≥ 25 kGy irradiation dose may be required for sterilisation of bacteria and fungi. Quite often ≥ 34 kGy may be required for virus inactivation, since many viruses are resistant to irradiation. Viral inactivation data should be supported by appropriate marker viruses (EDQM T&C 8.6.2.1). Validation is usually performed by using dosimeters placed throughout the load.

- Suitable test micro-organism: *Bacillus pumilus* (e.g. strains ATCC 27142, NCTC 10327, NCIMB 10692, CIP 77.25).For this method, biological indicators are not always necessary, but may be required for the validation of irradiation sterilisation of tissues (*Ph. Eur* 5.1.2).

- Additional information can be found in:ISO 11137-2: *Sterilization of health care products* -- Radiation -- Part 2: Establishing the sterilization dose
  ISO 11737-2:*Sterilization of medical devices* -- Microbiological methods -- Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process

5.4.4. Gas sterilisation

Multiple gas sterilisation processes are currently used and they are divided in two categories: alkylating agents (e.g. ethylene oxide) and oxidising agents (e.g. hydrogen peroxide and peracetic acid). With all options, sufficient gas and moisture penetration is essential and thus gas concentration, exposure time, temperature and humidity are the parameters to follow. It is the responsibility of the user to define the suitability of the biological indicator for reactive chemical in question. It should be noted that the levels of residual toxic substances after sterilisation should be minimised (e.g. residual ethylene oxide in the product should not exceed a limit of 1 ppm, CPMP/QWP/159/01).

- Suitable test micro-organisms:
  Ethyleneoxide: *Bacillus atrophaeus* (e.g. strains ATCC 9372, NCIMB 8058, NRRL B-4418, CIP 77.18); Hydrogen peroxide: *Geobacillusstearothermophilus*
- Additional information can be found in: ISO 11135:2014: *Sterilization of health care products* - Ethylene oxide - Requirements for the development, validation and routine control of a sterilization process for medical devices

5.4.5. Filtration

In contrast to other methods, the principle of membrane filtration is not inactivation but removal/reduction of micro-organisms. If filtration is used as a sterilisation method, the nominal pore size of the microporous membrane should not be greater than 0.22 µm. The sterilisation capacity of single use filters are usually validated by the manufacturers. Before filtration, filter capacity should be evaluated by the user and the method should retain microbial challenge of at least 10^7cfu/cm^2 on filter surface using suitable micro-organism (*Ph. Eur* 5.1.2). It should be noted that filtration is not suitable sterilisation method for viruses and mycoplasma.

- Suitable test micro-organism: *Brevundimonasdiminuta*as single cells suspension(for filters with nominal pore size ≤0.22 µm) (ATCC 19146, NCIMB 11091, CIP 103020). In addition, if possible, a suspension of vegetative bacterial cells representing the natural flora in question.
- Additional information can be found in: GMP Guide, Annex 1

5.5. Information on sterilisation validation

Validation should be planned and reported. Plan/report should include the following relevant information:

- The object(s) to be sterilised.

- The sterilisation method used, together with the justification for selection of the particular method. Method selection should be based on the properties of the object(s) to be sterilised.
- Selected biological indicator with which SAL is determined.
- Validation procedure to be followed, appropriate to ensure the sterility of the object(s) to be sterilised, and including e.g. maximum/minimum loads, package instructions for the sterilisation process and effect of it, special requirements of the objects, worst case approach and risk assessment/evaluation.

5.6. Effect of sterilisation on tissue properties

It should be noted that, to ensure the required SAL is achieved, the sterilisation method used may have an effect on the mechanical and biological properties of the tissues. Sterilisation should not render tissues clinically ineffective or harmful to the recipient nor should it adversely affect the essential properties. (JPAC General guidelines for tissue processing 21.5.3.2; see also GAPP *Technical Annex 1 to overall guidance: authorisation of changes in donation, procurement and collection, processing, preservation, storage and distribution*)

6. Requirements for assessing microbiological safety of the final BTC product

The microbiological safety of BTC is based on donor selection, donor/donation testing and minimisation of initial contamination, with protocols to control and monitor contamination during procurement and processing (adapted from GPG T&C 13.2.1).Even if BTC collection and processing procedures are intended to produce non-infectious final BTC products for the recipients, in some cases microbiological contamination may still occur. The risk of microbiological contamination of BTC depends on for example the origin, collection and procurement methods and processing steps of the BTC (EDQM Blood 4.1.8).As an example, causes of bacterial contamination in blood products include occult bacteraemia in the donor, inadequate or contaminated skin preparation at the phlebotomy site, coring of a skin plug by the phlebotomy needle and breaches of the closed system from equipment defects or mishandling.

Release is the act of certifying compliance of specific BTC or batch of BTC with the predefined requirements and specifications. Before any BTC are released for clinical use, all relevant records(including donor records, test results, processing and storage records, and BTC post-processing quality-control test results) should have been reviewed, approved and documented as acceptable by an authorised and trained person according to the relevant standard operating procedure (SOP) and/or national regulations. Microbiological quality criteria form part of final release criteria for some, but not all, BTC.

Requirements and criteria for microbiological safety of the final BTC product differ according to the level of microbiological quality achievable, by any method:

- For some tissues (e.g. musculoskeletal tissues and amniotic membrane), terminal sterilisation can be applied and the aim is to reach sterile tissue grafts. Parametric release with acceptance criteria for the control of identified process parameters can replace microbiological testing of the tissue grafts. Validated procedures for all critical production steps (procurement of tissues, transportation, all processing steps, packaging and storage) and a fully validated sterilisation method should be applied (see chapter 5) (EDQM T&C 10.3.5.2).
- Some BTC will not require and do not tolerate further disinfection or sterilization after procurement and/or processing(e.g. reproductive cells, embryos, other cells).
- Many BTC cannot be sterilised and in those cases, aspects of microbiological testing of BTC need to be considered in order to ensure the microbiological quality of the final BTC product. Those aspects are described in chapters below.

BTC collection/procurement and processing should be performed using aseptic techniques and in aseptic environment. Requirements for these and for environmental microbiological monitoring are not in scope of this guidance (additional information can be found e.g. in EU GMP Annex I;JPAC General guidelines for tissue processing, 21.5.1).

6.1. Common requirements

Differences in BTC make it difficult to establish a general rule for microbiological testing requirements (see Table 4). Therefore, for each procedure, risk assessment should be applied to determine the quality control strategy to be followed through the whole process and to identify critical steps to reduce the possibility of contamination and cross-contamination.

Microbiological safety of BTC can be demonstrated by microbiological testing using validated methods of known sensitivity and specificity. Currently such methods are primarily compendial microbiological methods of the European Pharmacopoeia (*Ph. Eur*). Microbiological testing of final BTC products should be performed by an authorised testing laboratory (see chapter 2) and in compliance with *Ph. Eur* requirements (see chapter 6.3).

In general, testing, when applicable, is recommended to be performed for both pre-processing samples of the procured BTC and on post-processing samples of final BTC products. Based on a risk analysis, some steps of the process can be identified as critical for the quality and safety of the final BTC product and samples may need to be tested. Sampling should be conducted immediately before packaging or as late as possible during the procurement or processing. (EDQM T&C 10.3.1).

Wherever possible, representative samples of BTC should be removed and tested for bacterial and fungal contamination using validated protocols . Swabs, contact solutions or other validated non-destructive sampling methods should be used where it is impossible to remove samples without damaging the BTC graft. (EDQM T&C 10.3.1, JPAC General guidelines for tissue processing, 21.5.2).Aseptic techniques to obtain samples are required in order to minimise the risk of false positive cultures due to contamination at the time of sampling or upon inoculation in culture.

For some BTC, pathogen reduction can be applied (see chapter 4).Validated PRT may offer alternative approaches to assuring the bacterial safety of BTC (EDQM Blood 4.4.2).Further processing after the PRT should be conducted without antimicrobial agents. Methods for testing of final BTC products should be evaluated carefully with respect to possible inhibition of microbiological growth due to decontaminating agents or their residues (EDQM T&C 10.3.5.3).

BTC with a short shelf-life may be released based on negative-to-date results. In this context, implementation and documentation of sufficient assurance of the microbiological quality of the final BTC product when released is essential. This will include in-process microbiological tests that have been established on the basis of risk analysis, usually including sterility testing of the starting material and/or of samples from the intermediate product at critical steps, if applicable, in combination with final results of in-process controls (EDQM T&C 13.2.2.10).Final testing is still ongoing after the BTC is released and will be completed. Procedures for handling positive results after release should be in place, including potential recall, notifying the clinician caring for the recipients and identification of the microbial species and resistogram (EDQM T&C 10.4.2.1).

Whenever the analysis indicates data that is outside of specified control limits, an investigation into potential causes of contamination should be undertaken and, where appropriate, the strain should be identified and collection and processing procedures should be revalidated (adapted from EDQM Blood 4.4.2).In this case the final BTC product should not be used for clinical application unless a risk–benefit analysis indicates that it is the best option for the recipient.

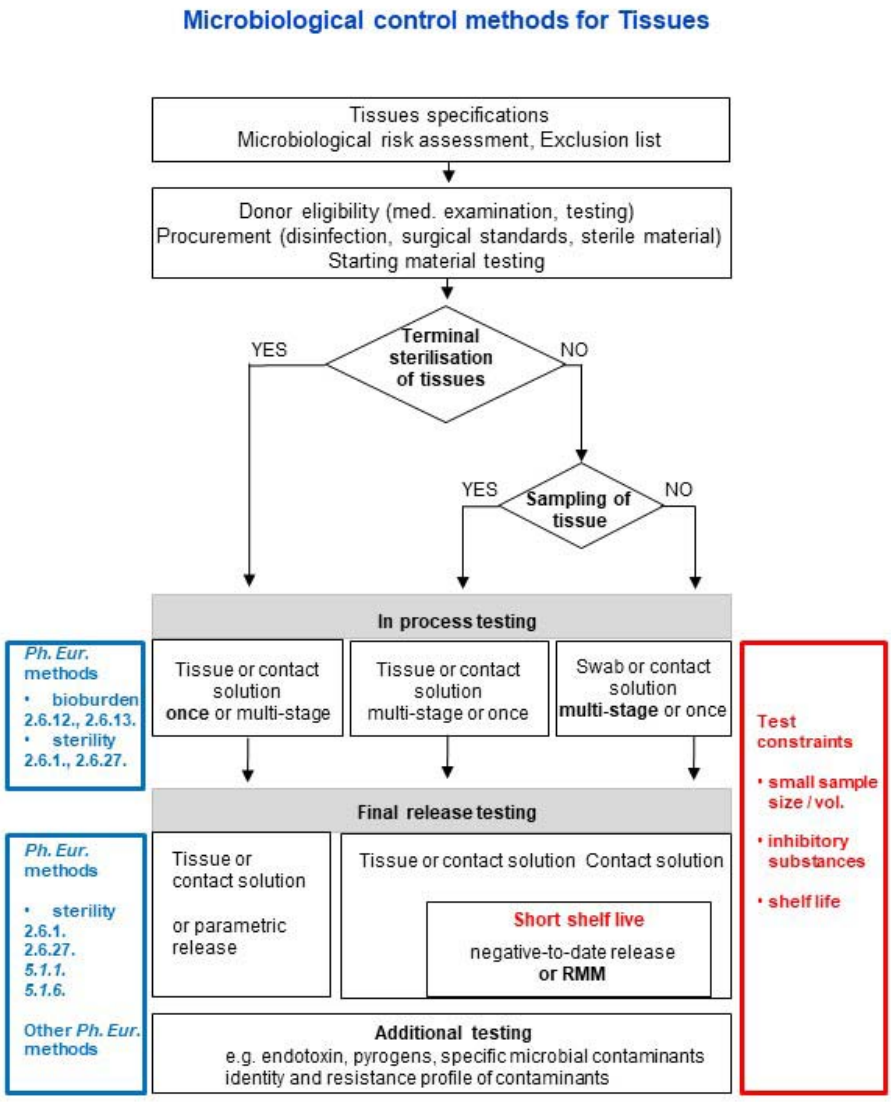
Table 4. Factors affecting microbiological safety that should be considered when determining the microbiological testing protocol (sample types, sampling times, analyses) (modified from EDQM T&C Table 7.2).

Phase	Risk factors	Examples/information
Procurement	BTC type	BTC type specific micro-organisms should be taken into account when validating the microbiological analyses.
	Procurement environment	Funeral home, operating theatre etc. Skin disinfection prior to venepuncture.
Processing	Contamination during processing; open *vs* closed processing	Closed processes are less prone to contamination during processing than processes where BTC are exposed to the environment. Tissues that are minimally processed, cellularised, or contain blood, blood vessels and lipids are more likely to support microbiological contaminants than those that are blood- and cell-depleted.
	Effectiveness of the PRT to remove contaminants	Some BTC can be treated with PRT which reduces the risks of transferring any microbiological contamination (see chapter 4).
Sampling	Suboptimal detection of contaminants due to the sampling method	If the only option for final microbiological sampling is swabbing or testing of unrepresentative samples, the risk that contaminants will be undetected is higher than in processes where 5-10 % destructive testing of final BTC products can be performed.
	Sampling of preservation method	Validation of storage using a sterile barrier test: samples from preservation media can be tested to

		validate storage method (materials).
	Use of antibiotic/antimycotic agents during processing	Culture media for some BTC contains antibiotics/antimycotics which, if not inactivated properly in samples, might inhibit microbial growth during testing, leading to possible false-negative results.
	Number of samples	The amount of samples to be tested depends on batch size, e.g. *Ph. Eur* 2.6.1, table 2.6.1-2. Not based on statistical process control approach.
Storage	Storage method of the final BTC product	Room temperature *vs* cooling.
	Packaging	Appropriate packaging for BTC in question should be used. If tissue is sterilised, it should be sterilised in its final packaging and its packaging should be compatible with sterilisation method used.
	Shelf-life of the final BTC product	Limited time for testing; Preparations of BTC with a short shelf-life may be released based on an intermediate readout of the test before the test period is completed (negative-to-date result).
Application/ transfusion	Transfer of contaminants at application/transfusion	Method of application/transfusion (e.g. permanent *vs* temporary) and application site both affect the risk of transfer of contaminants.

The microbiological control methods are not identical for all BTC. Whereas blood and haematopoietic progenitor cells are collected and processed in closed systems, most tissues and for example reproductive cells are collected in open systems. PRT may be applied to some BTC, but not all. Whilst some tissues can be sterilised, most BTC cannot be. As an example, microbiological control methods for tissues are schematically presented below (Figure 1).

Figure 1. Microbiological control methods for tissues.



Ph. Eur. 2.6.1. Sterility
Ph. Eur. 2.6.12. Microbiological examination of non-sterile products: microbial enumeration tests
Ph. Eur. 2.6.13. Microbiological examination of non-sterile products: test for specified micro-organisms
Ph. Eur. 2.6.27. Microbiological examination of cell-based preparations
Ph. Eur. 5.1.1. Methods of preparation of sterile products
Ph. Eur. 5.1.6. Alternative methods for control of microbiological quality

6.2. Specific requirements depending on the type of BTC processing

Different requirements for testing of microbiological safety of BTC apply for cases where BTC has been procured and processed in closed or open systems. BTC procurement systems can either be closed, with equipment designed and operated in such way that the BTC are not exposed to the environment, or can be open, exposing the BTC to the environment.

Chapter 6.3 Methods for microbiological control apply to both cases.

6.2.1.BTC with processing in closed systems

Use of closed systems is strongly recommended for all steps in blood component processing. Open systems may exceptionally be necessary due to local constraints and should be undertaken in an environment specifically designed to minimise the risk of contamination (GPG Blood 6.6.3).Processing in closed systems are generally used also for haematopoietic progenitor cells and mononuclear cells procured by apheresis (EDQM T&C 22.3).

For BTC which are processed in closed systems, repeated testing steps do not yield additional information on the microbiological status of the BTC and are thus not required. In such cases, a reduced testing strategy that relies on single testing of samples taken at an appropriate time point may be applicable. (EDQM T&C 10.3.5.1)

According to the Directive 2004/33/EC(Annex V, 2.2),appropriate microbiological control of the collection and processing of blood products must be performed.Bacterial cultures of platelet components provide the best indication of the overall rate of contamination of whole blood donations, provided that the samples for culture are obtained in a suitable volume and at a suitable time after collection. Data on routine bacterial monitoring should be analysed using statistical process control techniques to ensure that the process remains in control. (EDQM Blood 4.4.2).

6.2.2.BTC with processing in open systems

Most tissues and cells, including those for which PRT has been applied to, are exposed to the environment at certain processing stages between procurement and packaging. If terminal sterilisation cannot be used, the contamination risk during open processing should be avoided to the greatest possible extent. The requirements for microbiological sampling and testing are expected to be most stringent in these situations (EDQM T&C 10.3.5.4).

Sampling and microbiological assessment should include the starting material, the transport solution, any solutions used to wash BTC(EDQM T&C 10.3.5.4) and critical steps identified on a risk-based analysis, if applicable.

Microbiological testing of tissues and cells should be performed according to the tissue-specific requirements in Part B of EDQM T&C Guide and general criteria described in chapter 10.3. Tissue-specific requirements describe the minimum standards to control microbiological safety of each BTC type and microbial contaminants that should result in BTC discard, if applicable.

6.3. Methods for microbiological control

The conventional method for control of microbiological quality in relation to the absence of micro-organisms in BTC is described in *Ph. Eur* 2.6.1. For cell-based preparations, compendial method 2.6.27 can be applied. For quantification of microbiological contamination (bioburden testing) of starting material or of preparations during processing before sterilisation/decontamination, the appropriate method is described in *Ph. Eur* 2.6.12 whenever bioburden limits need to be ensured. The method 2.6.12 should be used together with 2.6.13 if the risk assessment applied to the BTC requires the absence of specific highly pathogenic micro-organisms.

The samples for sterility testing should be representative of all types of the components, but if this is not possible, surrogate testing may be performed (EDQM T&C 10.4). This testing may require use of validated methods employing special media and/or conditions to enable growth of such micro-organisms and their detection.

Highly virulent micro-organisms should be predefined in order to exclude BTC if these micro-organisms are detected at any stage of processing.

Several BTC derived preparations are short lived and of small quantity. Conventional compendial methods, e.g. growth based microbiological methods (*Ph. Eur* 2.6.1, 2.6.27), are now increasingly outperformed by alternative rapid microbiological methods (RMM) in terms of sensitivity, speed and width of information. Use of RMM may mean that final test results are available much faster, allowing a timely and often more substantiated final BTC product release. (EDQM T&C 10.4)

The use of RMM for testing of BTC preparations is still limited. One reason is the considerable effort for the control laboratory to validate new methods with respect to method performance in comparison to the compendial reference method. *Ph. Eur*5.1.6 "Alternative methods for control of microbiological quality" and 2.6.27 "Microbiological examination of cell-based preparation" provide the current EU framework for RMM validation. EDQM provides an online resource (see Bibliography) in which information on exemplary RMM validation procedures for a particular application are made available to control laboratories. This resource is currently regarded as a starting point for users although not peer-reviewed and not exhaustive.

Based on risk assessment, tests for absence of mycoplasma (*Ph. Eur* 2.6.7) and bacterial endotoxins (*Ph. Eur* 2.6.14 and *Ph. Eur* 5.1.10) should also be performed, where required.

Any deviations from the *Ph. Eur* standards should be justified, and alternative test methods should be validated in accordance with *Ph. Eur* 5.1.6.

Different practices are in place among BE/TEs in the MS in terms of percentage of testing, methods, sample volumes, time of sampling, shelf life and residual risk. Microbiological testing is performed using culture-based or rapid detection devices. In order to support harmonisation of the microbiological strategies among EU MS, recommendations for microbiological testing should be taken into account, for example:

- detection of a broad range of (transfusion/transplantation-relevant) bacteria,
- applicability of test procedure with a late sampling time point,
- quality controlled testing procedure.

7. Final considerations

Most of the recommendations described in this guidance apply to all types of BTC: blood, tissues and cells. They share same requirements and recommendations for laboratories performing donor/donation infectious disease testing and microbiological testing of BTC, donor/donation infectious disease marker test kits, and validation of pathogen reduction technologies and

sterilisation. In this respect, harmonization of the blood, tissue and cells sectors is already taking place.

Throughout GAPP, in particular within the technical annexes to the Guidance to CA, extensive reference has been made to existing requirements and recommendations, the applicable European Union legislation and the publications of the Council of Europe: the EDQM T&C Guide, the EDQM Blood Guide and the European Pharmacopeia. The authors are aware that the guidance provided at the time of publication will require regular updating as the practices in science and medicine change, to take into account the evolution of research and of available therapeutics and technologies. This can be observed by the constant evolution of the EDQM guides themselves.

It is also of note that the means of making information available are being revolutionised by the profound changes that information technology has brought about and will continue to bring, to the ease of access to information and the ability to target it. Thus, rarely published and quickly out of date reference books can be succeeded by knowledge bases, such as that proposed by the European Pharmacopoeia, which provide up to date information, customised to the profile of the user.

The work carried out in GAPP WP9 developing the concept of an information system may bring solutions to how to keep the GAPP guidance up to date, provide the users with the particular guidance they require, and wherever needed, make specific national regulations easily accessible and transparent.

EUDAMED, the database under development by the EC to implement Regulation (EU) 2017/745 on medical devices and Regulation (EU) 2017/746 on *in vitro* diagnosis medical devices, will improve transparency and coordination of information (e.g.device registration, clinical investigations and performance studies) regarding CE-marked infectious disease marker test kits available on the EU market (EC website concerning EUDAMED). When IVD device data will become available in EUDAMED in 2022, it will help both BEs/TEs and CAs to ensure the appropriate test kits for donor infectious disease marker testing will be selected.

Some topics and part of guidance in this Annex 2 cover borderline activities, also falling under other regulatory frameworks (e.g. medicinal products, medical devices).For example, issues related to authorisation, accreditation, designation, licensing of laboratories, infectious disease marker test kits and sterilization may be under a mandate of some other authorities than BTC CAs. Relevant authorities should take into account regulatory requirements of BTC oversight. Therefore, in addition to the effective communication between authorities of different sectors within MS, clarity and transparency across regulatory borderlines should be achieved through a revision of the European Union legislation.

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Acronyms

Ab	antibody
Ag	antigen
ATMP	Advanced Therapy Medicinal Product
BE	Blood Establishment
BTC	Blood, Tissues and Cells
CA	Competent Authority
CE	*ConformitéEuropéenne*
cfu	colony-forming unit
CLIA	chemiluminescent immunoassay
CPP	Critical Process Parameter
CMV	cytomegalovirus
EBV	Epstein-Barr virus
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
EIA	enzyme immunoassay
EMA	European Medicines Agency
EUBTCD	European Blood, Tissues and Cells Directives
GAPP	Facilitating the Authorisation of Preparation Process for blood, tissues and cells
GMP	Good Manufacturing Practices
GPG	Good Practice Guidelines
HA	haemagglutination
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HTLV	human T-cell leukaemia virus
IAEA	International Atomic Energy Agency
IVD	*in vitro* diagnostic
JA	Joint Action
JPAC	Joint United Kingdom Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee
MERS	Middle East Respiratory Syndrome
MS	Member State
NAT	nucleic acid amplification technique
PA	particle agglutination
Ph. Eur.	European Pharmacopeia
PPA	Preparation Process Authorisation
PRT	Pathogen Reduction Technology
RMM	rapid microbiological methods

SAL	Sterility Assurance Level
SARS	severe acute respiratory syndrome
SOP	standard operating procedure
SPC	statistical process control
TE	Tissue Establishment
UV	ultraviolet
vCJD	variant Creutzfeldt-Jakob disease
WHO	World Health Organization
WP	Work Package

Definitions

Accreditation An attestation by a national accreditation body that a conformity assessment body meets the requirements set by harmonised standards and, where applicable, any additional requirements including those set out in relevant sectoral schemes, to carry out a specific conformity assessment activity (Regulation (EC) No 765/2008)

Analytical sensitivity The limit of detection, i.e. the smallest amount of the target marker that can be precisely detected (Official Journal of the European Union L 318/ Commission decision 2009/886/EC)

Analytical specificity The ability of the method to determine solely the target marker (Official Journal of the European Union L 318 /Commission decision 2009/886/EC)

Bioburden Total number of viable micro-organisms or total microbial count present, on or in BTC or in the environment, usually measured before the application of a decontamination or sterilisation process (adapted from EDQM T&C)

Biological indicators Test systems containing viable micro-organisms (usually spores of bacteria) that provide a defined challenge to verify the required effectiveness of a specified sterilisation process (Ph.Eur. 5.1.2.)

CE-marked kit Test kit marked by a manufacturer to indicate that the test kit is in conformity with the applicable requirements set out in Regulation (EU) 2017/746 on *in vitro* medical devices and other applicable Union harmonisation legislation providing for its affixing (modified from Regulation (EU) 2017/746).

Closed system A procurement/processing system with equipment designed and operated such that the cells are not exposed to the environment (adapted from EDQM T&C)

Conformity assessment The process demonstrating whether the requirements of the Regulation (EU) 2017/746 relating to a test kit have been fulfilled(modified from Regulation (EU) 2017/746).

Critical process parameter (CPP) A process parameter whose variability has an impact on a critical quality attribute and which therefore should be monitored and controlled to ensure the process produces the desired quality (Directive (EU) 2016/1214 Art. 1, GPG Blood)

Deceased donor A person declared to be dead according to established medical criteria and from whom cells, tissues and organs have been recovered for the purpose of human application (EuroGTP II Guide)

Diagnostic specificity The probability that the test kit gives a negative result in the absence of the target marker (adapted from Official Journal of the European Union L 318/Commission decision 2009/886/EC)

Diagnostic sensitivity The probability that the test kit gives a positive result in the presence of the target marker (adapted from Official Journal of the European Union L 318/Commission decision 2009/886/EC)

Donation (the process of) Donating human blood, tissues or cells intended for human applications (adapted from Directive 2004/23/EC)

Donation (types of biological material) The blood, tissues, and cells collected from the donors

Donor A living or deceased human being, who donates BTC for another human being or for him/herself

Effectiveness Presence of desired functionality proven by *in vitro* analytics (adapted from the EDQM T&C)

Evaluation See 'Validation'

F_0 The time in minute for the specified temperature that causes the same lethality as one minute at 121 °C (*Ph.Eur* 5.1.5)

In-house Manufactured and used within an organisation (for example BE/TE/laboratory) and not distributed outside facility/organisation (adapted from Regulation (EU) 2017/746)

In-process control Checks undertaken during processing to monitor and, if necessary, to adjust the process to ensure that a product conforms to its specification. Control of the environment or equipment may also be regarded as a part of in-process control. (EDQM T&C)

***In vitro* diagnostic medical device** Any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, intended by the manufacturer to be used *in vitro* for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information on one or more of the following: (a) concerning a physiological or pathological process or state; (b) concerning congenital physical or mental impairments; (c) concerning the predisposition to a medical condition or a disease; (d) to determine the safety and compatibility with potential recipients. (Regulation (EU) 2017/746)

Kit A set of components that are packaged together and intended to be used to perform a specific *in vitro* diagnostic, or a part thereof (Regulation (EU) 2017/746)

Likelihood ratio The likelihood of a given result arising in an individual with the target clinical condition or physiological state compared to the likelihood of the same result arising in an individual without that clinical condition or physiological state (Regulation (EU) 2017/746)

Microbiological quality Fulfilment of a specific set of microbiological standards, characteristics and criteria. Microbiological quality may also be seen as an indicator of the microbiological safety of the BTC. (adapted from EDQM T&C)

Microbiological safety Approach to minimize the risk of contamination by viable micro-organisms or micro-organism derived toxic substances. Microbiological safety of BTC results from the management of donor selection, procurement of BTC, testing and the preparation processes. (adapted from EDQM T&C)

Musculoskeletal Tissues that are part of the skeleton and muscular system, including muscles, bones, cartilage, tendons and ligaments, which function in the support and movement of the body (EDQM T&C)

National accreditation body The sole body in a Member State that performs accreditation with authority derived from the State (Regulation (EC) No 765/2008)

Negative-to-date release The release of BTC for clinical use before completion of testing for bacterial or fungal cultures. The cultures are negative at the time of release. (adapted from EDQM T&C)

Negative predictive value The ability of a donor test kit/test to separate true negative results from false negative results for a given attribute in a given population (adapted from Regulation (EU) 2017/746)

Open system A procurement/processing system that exposes the BTC to the environment (adapted from EDQM T&C)

Partner donation The donation of reproductive cells between a man and a woman who declare that they have an intimate physical relationship (Directive 2006/17/EC)

Pathogen reduction technologies Procedures that irreversibly impede proliferation of pathogens in BTC, either by removal or inactivation with physical and/or chemical methods (EDQM Blood)

Performance evaluation An assessment and analysis of data to establish or verify the scientific validity, the analytical and, where applicable, the clinical performance of a donor testing kit/assay(adapted from Regulation (EU) 2017/746)

Performance study A study undertaken to establish or confirm the analytical or clinical performance of a donor test kit/test (modified from Regulation (EU) 2017/746)

Positive predictive value The ability of a donor testing kit/assay to separate true positive results from false positive results for a given attribute in a given population (adapted from Regulation (EU) 2017/746)

Predictive value The probability that a person with a positive test result has a given condition under investigation, or that a person with a negative test result does not have a given condition (adapted from Regulation (EU) 2017/746)

Proficiency testing The evaluation of participant performance against pre-established criteria by means of external quality assessment scheme, inter-laboratory comparisons by use of externally sourced samples or panels (EDQM Blood)

Qualification As part of validation, means the action of verifying that any personnel, premises, equipment or material works correctly and delivers the expected results (Directive 2005/62/EC)

Quality system The organisational structure, defined responsibilities, procedures, processes, and resources for implementing quality management and includes all activities which contribute to quality, directly or indirectly(Directives 2005/62/EC, 2006/17/EC).

Rapid test Qualitative or semi-quantitative *in vitro* diagnostic medical devices, used singly or in a small series, which involve non-automated procedures and have been designed to give a fast result (Official Journal of the European Union L 318/25)

Reproductive cells All tissues and cells intended to be used for the purpose of medically assisted reproduction (adapted from Directive 2006/17/EC)

Spiking The addition of a known amount of a mixture to a standard, sample or placebo, typically for the purpose of confirming the performance of an analytical procedure(adapted from WHO guidelines on transfer of technology in pharmaceutical manufacturing, Annex 7)

Standard The requirements that serve as the basis for comparison (Directive 2005/62/EC)

Sterilisation Any process that eliminates or inactivates transmissible infectious agents (pathogens) containing nucleic acids, e.g. vegetative and spore forms of bacteria and fungi, parasites or viruses, present on a surface, in a fluid, in medication or in a compound such as biological culture media. Sterilisation can be achieved by applying the proper combinations or conditions of heat, chemicals, irradiation, high pressure and filtration. (EDQM T&C)

Sterility The absence of viable microorganisms, as defined by a sterility assurance level (SAL) equal to or less than 10^{-6} (*Ph.Eur* 5.1.1.)

Sterility assurance level(SAL) Represents the expected probability of a micro-organism surviving on an individual unit of product after exposure to a sterilisation process. SAL 10^{-6} has been established as the standard for allografts and indicates a probability of one chance in a million that one unit of product will be contaminated with a single organism after a sterilisation process, and grafts are then considered sterile. (EDQM T&C)

Terminal sterilisation A process in which the product is sterilised in its final container (*Ph.Eur* 5.1.1)

Validation Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product

	meeting its predetermined specifications and quality attributes; a process is validated to evaluate the performance of a system with regard to its effectiveness based on intended use. This evidence may include laboratory assessment of test kit performance. In the context of this document, the term 'evaluation' of test or method performance, can be considered to be part/all of any 'validation'. (modified from Directive 2006/17/EC)
Validation plan	A document describing the activities to be performed in a validation, including the acceptance criteria for the approval of a process or method for routine use (adapted from WHO guidelines on transfer of technology in pharmaceutical manufacturing, Annex 7)
Validation report	A document in which the records, results and evaluation of a completed validation program are assembled and summarized (adapted from WHO guidelines on transfer of technology in pharmaceutical manufacturing, Annex 7)

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FACILITATING THE AUTHORISATION OF PREPARATION PROCESS FOR BLOOD, TISSUES AND CELLS

Technical Annex 3 to overall guidance: assessing clinical data as part of Preparation Process Authorisation (PPA)

1. Introduction

Significant scientific and technological developments in the blood, tissue and cell (BTC) sector enable improved or novel processing and testing protocols, and novel and innovative applications of BTC. Such advancements, however, may pose a quality and safety risk and have a direct or indirect impact on the clinical outcome of the recipients, into which BTC are transfused, transferred, injected, grafted or implanted[1,2]. Furthermore, the wide distribution of these innovations can increase safety risks when their clinical efficacy is insubstantially claimed[2]. Therefore, it is of vital importance to evaluate the potential risk consequences andclinical efficacyapplyingto clinical use of BTC. Systematic collection and evaluation of clinical data validates the clinical safety and efficacy of novel BTCand provides valuable informationfor Competent Authorities (CAs) as part of the preparation process authorisation (PPA).

Serious Adverse Reaction (SAR) reporting is required by the European Blood, Tissues and Cells Directives (EUBTCDs)[3,4] for all BTC, not only for novelties. SARs are unintended responses associated with the procurement or human application of BTC that are fatal, life threatening, disabling, incapacitating or which result in, or prolong, hospitalisation or morbidity, such as the transmission of infectious agents (bacterial, fungal, viral or parasitical). However, apart from SAR reporting, the current EUBTCDs do not cover clinical assessment nor clinical follow-up before or after authorisation, nor the follow-up of offspringborn as a result ofMedically Assisted Reproductive (MAR) techniques using donor gametes or donated embryos. Even though Directive 2006/86/EC[5] Annex II B1 mentions the importance of retrospective evaluation of the clinical outcome for tissue and cells application, there is no explicit requirement in the EU Blood Directives (EUBDs)[3,6–8] or in the EU Tissue and Cell Directives (EUTCDs)[4,5,9] to demonstrate clinical efficacy of the BTCwith respect to recipients. All the same,someCAsreview detailed dossiers and require clinical outcome data as part of the PPA. However, other CAs only apply a minimal approach with less stringent national requirements. Moreover, data is collected and presented differently in the different Member States (MS). These divergent approaches to PPAoccasionally lead to a lack of mutual acceptance of authorisations between MS and pose significant barriers for the exchange of BTC within the EUMS and patients' access to BTC[2]. As there is consensus that human applications of certain novel BTC require assessment of clinical efficacy/effectiveness[2,10], both Blood Establishments (BEs)/Tissue Establishments (TEs) and authorities agree that clinical data should be collatedto support the PPA[1], and that it should also include requirements to confirmthe clinical outcome data[2].In order to fully support this purpose, guidance on evaluation of quality and safety as well as clinical efficacy of novel BTC is needed.

A standardised assessment of clinical data as part of PPA aims to facilitate:

- promotion of the evaluation ofthe clinical efficacy and safety of BTC applications;
- implementationof consistent requirements and the equal possibility for all stakeholders to distribute their BTC;
- comparison of data between different types of BTC for similar processes, stakeholders or MS;
- harmonisation of CAs evaluation and authorisation practices;
- mutual acceptance of authorisation amongst MS;
- inter-MS exchanges of BTC;
- access of patients to novel BTC therapies.

Aim

This document aims to define *a methodological framework to evaluate clinical data requested for authorisation processes upon introduction of innovation to the current processing and testing protocolsfor human BTC therapeutics*, as defined in the GAPP Grant Agreement.

The aim of this document is to provide CAs with key principles as to:

- which factors should be considered by CAs when assessing the clinical component of a Preparation Process Dossier (PPD) for completeness and suitability;
- when a Clinical Follow-up Plan (CFUpP)or a Clinical Investigation Plan (CIP)should be requested in order to support the authorisation of a new BTC preparation process and/or therapeutic application;
- what elements should be included in the CFUpP or CIP;
- what type of clinical data would be required to determinethe safety and efficacyof human BTC applications for therapeutic use in recipients.

Scope

The content of this document only applies to BTC and their applications as regulated by EUBTCDs[3–9], and all other novel BTC that are not currently covered by other regulations.

BTC that are subject to *substantial manipulation,* or those that *are not intended to be used for the same essential function or functions in the recipient as in the donor* (as defined in Advanced Therapy Medicinal Product Regulation 1394/2007/EC[11]), or products classified as medical devices or medicinal products (such as plasma-derived medicinal products), are not part of the scope of the GAPP Joint Action.

Furthermore, this annex focuses on BTC recipients (and their offspring in the case of MAR),not donors (except in the case of autologous donation). Another project called TRANSPOSE (TRANSfusion and transplantation: PrOtection and SElection of donors) has constructed risk-based guidelines for the selection and protection of donors.

The guidance provided does not consider additional requirements defined in relevant national/ regional/local regulations that should be taken into account by the CAs and the applicants.

2. The extent of the planfor collecting clinical data should bebased on risk assessment

The level of risk associated with the clinical use of BTC is determined by factorsspecific to the origin, collection/donation/procurement, processing, storage, handling and clinical applicationprocedures of BTC. Therefore, an applicant/BE/TE should perform the risk assessmentfor any BTC intended for clinical use whenever a significant change in one of the aforementioned factors takes place. This assessment should identify the relevant risk factors, the potential risk consequences for recipients, and estimate the level of risk associated with the clinical use of the BTC.The risk assessment exercise should also consider all pre-clinical and clinical evaluations, and the possible risks and adverse reactions anticipated based on prior experiences. Other relevant data such as scientific literature or data generated by other BE/TEs or the clinical use of similar BTC, may also be considered during the risk assessment exercise.Examples of risk assessment methodologies available are described in the *Good practice guideline to authorisation on preparation processes in blood, tissues and cells*.

The risk assessment results should be presented to the CA as a part of the PPD (Figure 1).The CA should assess whether the risk assessment takes into account all relevant and up-to-date information regarding the BTC in question and whether the final estimated risk level has been determined correctly.

VISTART Joint Action has defined the "*Principles for Competent Authorities for the evaluation and approval of Clinical Follow-up Protocols for BTC prepared with newly developed and validated processing methods"*[1], which determine the correlation between risk level and the extentof clinical data to be required for the clinicalcomponentof PPD. According to VISTART,if the application of the BTC does not pose any risk for recipients (or offspring in the case of MAR),only the Serious Adverse Reactions and Events (SARE) reporting that is mandatory for all BTC would be required[1]. With regard to novel BTC preparation processes, a minimum information part of the PPD, including the results of the risk assessment performed, should always be provided for the CA. However, when the human application of the BTC poses any risk(low, moderate or high), a plan for collecting clinical data should be requested to support the PPA. The extent of the plan for collecting clinical data required as part of PPD should be proportional to the risk level[1,10](see Figure 1). In the case of low risk, in addition to the mandatory continuous SARE reporting, the applicant should develop a clinical follow-up plan (CFUpP; see section 5). For moderate risk, in addition to the SARE reporting and CFUpP, the applicant should develop a clinical investigation plan (CIP; see section 6). In the case of high risk, in addition to the SARE reporting and CFUpP, the CIP should be designed so as in order to compare the novel BTC to a standard/conventional therapy, if available (see section 7).

EuroGTP II project has defined the "*Good Practices for evaluating quality, safety and efficacy of novel tissue and cellular therapies and products*"[10] (EuroGTP II Guide), including some of the requirements for Clinical Evaluation Protocol. In the context of this current guidance, these procedures were further specified and defined as CFUpP and CIP.

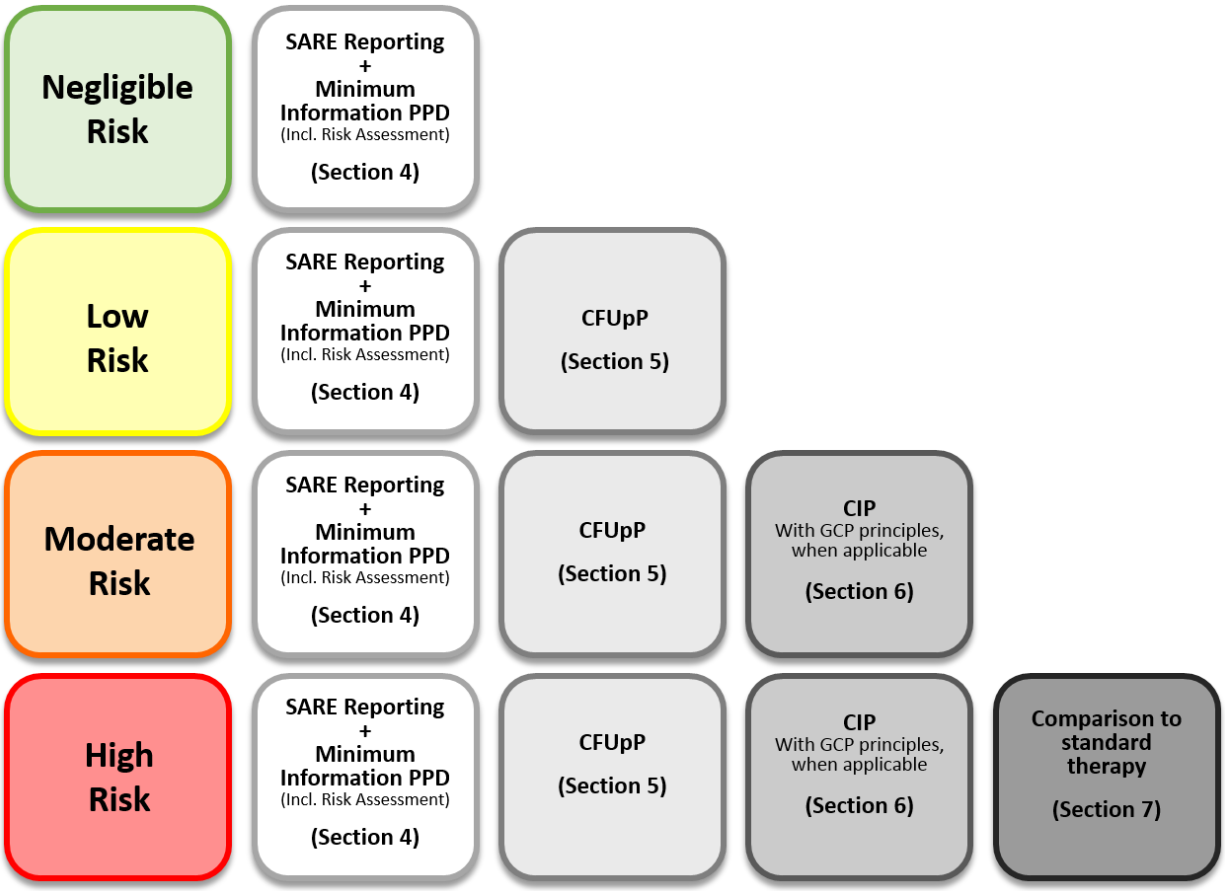

Figure 1. The extent of plan for collecting clinical data included in the clinical component of the PPDis based on the risk level.

3. Clinical data sources and types

Clinical data that the applicantuses in the clinical evaluation and provides to support the clinical component of PPD can be obtained from various sources and in different forms. Relevant data may include clinical investigation(s) of the BTC concerned, or it may be available from scientific literature or from Real-World Data (RWD)[1,12]. Factors to be considered when assessing clinical data for completeness and suitability will be presented in the sections below.

3.1 Clinical data generated and held by the BE/TE and clinicians

Clinical data may have been generated by collaborating BE/TE(s)and clinicians, alsoin other MS(s) or in third country(ies). Data may include unpublished data by the applicant and some clinical investigations carried out on behalf of BE/TE.

All data generated and held by the BE/TE, whatever their trends,should be identified and made available for CA evaluation. Documentation related to results and conclusions of the investigation

needed for the clinical evaluation (as well as the independent ethics committee opinionsand CAapprovals) should be provided by the applicant.

3.2 Clinical data in scientific publications

Clinical data derived from scientific literature can be used toaugment data not held by the applicant that are needed for the clinical evaluation. For some BTC, clinical data generated usingliterature searcheswill represent the greater part (if not all) of the clinical evidence available. Clinical data may not necessarily relate only to the BTC under evaluation, but also to similar BTC.

There are different sources of scientific literature that can be utilisedfor clinical evaluation. Important sources include scientific literature databases, internet searches and citation referenced in scientific literature. A comprehensive search strategy is recommended, generallyinvolving multiple databases. The search strategy should be thorough and objective, i.e. it should identify all relevant favourable and unfavourable data. Therefore, the search strategy should be documented and justified. The literature search protocol and the literature search report form a key part of the clinical evidence and should be included in theclinical component of the PPD.(Adapted with modifications from MEDDEV[12])

It is important to consider the quality and reliability of the data.For example a large scale clinical investigationpublished in a high impact, peer-reviewed journal would be considered of high quality and reliability, whereas unpublished clinical data with limited follow up in a small number of recipients less so.[10]

3.3 Real-World Data

The CIP or the CFUpP should be supplemented where possible by Real-World Data (RWD) either at national level or, if possible, at international level[1].So-called RWD are data related to recipient health status and/or the delivery of health care collected from a variety of sources. Examples of RWD include data derived from electronic health records (EHRs), data from registries, and recipient-generated data, including from in-home-use settings.

Electronic health record (EHR) systems, which are electronic platforms containing individual patient health records, are generally maintained by health care providers, health care organisations, and health care institutions, and are used to deliver care. A typical individual EHR may include for examplea patient's medical history, diagnoses, treatment plans, pharmacy records, and laboratory and test results[13].

The large European registries in the field of BTC - maintained for example by ESHRE, EBMT, and ECCTR - gather the most relevant clinical indicators which have been agreed upon by experts of the sector in question. The registries collect clinical indicators in order to promote scientific knowledge and to assess the efficacy of the different therapies amongst the stakeholders. In addition to BTCregistries, there are also disease specific registries, which contain data of clinical care and outcome of a defined patient population. These include rare disease registries initiated by many organisations, such as patients' advocacy groups, private foundations, clinicians and national health systems. Most disease registries are used to support care management for groups of patients with one or more diseases.

The fitness for using registry data requires sufficient processes, such as the ability to gather recipient follow-upinformation when needed, to ensure data quality, and to minimisemissing or incomplete data.

Registriesmay not capture all data elementsneeded to answer everyquestion of interest. They generally collect major events and as such, other changesin medical status may not be reliably and consistently documented,if at all. Additionally, data related with the quality of the BTC is very limited orinexistent in the majority of the registries.

Registries and the clinical information of the recipients are not currently available for all BTC, and applicants may need to establish alternative methodologiesto provide and structure the required data.

Quality of life measures and patient reported outcome measures (PROM) are increasingly being used to understand patient experiences and preferences. These may be particularly important when well-defined widely accepted clinical outcomes are not available. The use of PROM is justified when the number of affected patients is small and therefore often results in limited clinical experience.

With regard to registry and EHR data quality, CA should consider that:

- Information collected in BTC registries is typically based on voluntary submissions by the stakeholders. Therefore retrieval of information about outcomes may be incomplete and unreliable. For instance, they may offer limited coverage of a MSand all recipients are not considered;
- The registry or EHR may also lose contact with recipients if they change healthcare providers or residence[13];
- The way the data elements are entered in the EHR may limit their accessibility. For example, recipient's symptoms may be documented in unstructured data in the clinician's note without the use of standardised language or a standard symptom scale.

There are several potential advantages of the use of RWD in clinical evaluations that CAs should consider:

- Registries and EHRs may facilitate clinical investigators and study personnel to have access to many types of data that can be combined, aggregated, and analysed;
- PROMmay have the potential to provide clinical investigators access to real-time data;
- Registries and EHRs can facilitate follow-up on recipients to assess long-term safety and efficacy of BTC;
- There are opportunities for long-term follow-up of large numbers of recipients, which may be of particular importance in studies where the outcome of interest occurs rarely[13].

In the future, there will probably beincreasing interest in using RWDtogenerate evidence to support CA decisions about the efficacy of novel BTC. If such data will be provided for CA for assessment, the CA should consider whether the RWD are fit for use, and whether the RWD canprovide adequate scientific evidence to answer or help answer theregulatory question.

Examples from other sectors include the European Medicines Agency's (EMA) *Regulatory Science to 2025*[14] strategy which includes consideration of how to use RWD in decision-making while the EUnet HTA Joint Action is developing standards for the use of patient registry data for health technology assessment (HTA) purposes.[15]

4. Minimum information of the clinical component of the PPD

4.1 General information

In the context of the authorisation request for the clinical application of a novel BTC or preparation process, applicants should always provide CAs witha minimum set of information, including at least the following:

- A clear characterisation and definition of the BTC under evaluation (defined in*Good practice guideline to authorisation on preparation processes in blood, tissues and cells* and *Technical Annex 1 to overall guidance: authorisation of changes in donation, procurement and collection, processing, preservation, storage and distribution*);
- Risk assessment results (section 2);
- Justification of the changeor the innovation, including the key benefits;
- Alternative therapies or BTC, if any;
- Relevant bibliographyused as clinical evidence including a description of literature search protocol (names of databases, search terms etc.) and the literature search report (section 3.2.).

4.2 Clinical indications

The disease(s)/condition(s) and/or population that a clinical use of BTC is intended to treat should be clearly described, for example:

- Pathologies/conditions that can be treated or prevented with the novel BTC;
- The scientific rationalebehind the proposition of a new clinical indication (if applicable);
- Potential contra-indications.

4.3 Application/administration methods

Application methods and procedures, as well as any particular requirement associated with the novel BTC therapy/BTC resulting from novel preparation process should be described, namely:

- Administration form(s), concentration(s) and dosage(s) of the BTC(if applicable);
- Immediate pre-implantation preparation procedures (e.g. adding solutions/reconstitution procedures, cutting, thawing, auxiliary devices required, if any);
- Application/implant methods (e.g. infusion, surgery, laparoscopy, insemination, etc.);
- Special skills or training required (depending on the level of novelty and/or complexity of the clinical application procedure(s)).

5. Assessment of Clinical Follow-UpPlan (CFUpP)

Clinical follow-up of BTC recipients should be required whenever clinical application of a BTC, resulting from a novel preparation process, poses any risk (low, moderate or high) to recipients or to MAR offspring. Even so,the clinical follow-up shouldbe proportionate in terms of scale, complexity and durationto the level of residual/unknown risk[1]. The extent of the clinical follow-up could also be adjusted in the light of previous clinical experience with a similar BTC[1,10].

To confirm the adequacy of the clinical follow-up of recipients or MAR offspring, the CA should request the applicant to present a CFUpP[1]. The CFUpPshould be planned in close cooperation with the BE/TE and the clinicians responsible for the clinical application of the BTC. The CFUpP should include at least:

- the number of BTC applications/recipients for follow-up;
- the type and duration of clinical follow-up, includinginformation onfollow-up procedures (for example samples, imaging);
- the methodology for clinical follow-up data collection (examples in section 6.7);
- the parameters identified to prove safety and/or efficacy of the specific BTC (sections 5.1 and 5.2);
- data consistency assessment and/or data analysis including biometrics, statistics.

(Adapted from Vistart[1] and EuroGTP II[10])

According to the risk level, the CFUpP may differ from the standard follow-up in clinical practice to a more structured plan for active collection of a specific set of data related to the safety and efficacy of the BTC[1,10]. Moreover, in case of moderate or high risk level, CFUpP should be sent for CA assessment once clinical investigation according to the CIP is concluded (sections 6 and 7), and may be updated or amended according to its results (section 8).More specific examples of aspects which could be considered when assessing the CFUpP provided by an applicant are presented the following sections.

5.1 Clinical safety data

Clinical safety data to be collected should be based on risk factors related to the process (donation, procurement, processing, storing, transport, product or clinical application) identified during the risk assessment that cannot be mitigated to negligible risk level by *in vitro* or pre-clinical studies and therefore may have consequences once BTC is applied to recipients. In particular, the collection of data on the potential risk consequences associated with the clinical application of the BTC (see Table 1) should be considered.

TABLE 1: Examples of potential risk consequences of the clinical use of BTC[1,10]
- Unexpected immunogenicity - Implant failure/engraftment failure/pregnancy loss - Disease transmission (incl. disease transmission to offspring in case of MAR) - Toxicity/carcinogenicity - Other potential risks (associated with specific BTC)

While the safety concerns are closely linked to the specific characteristics of the BTC, the critical assessment of safety should consider the following issues (non-exhaustive list):

- findings from pre-clinical studies and/or results from clinical investigations that affect, or could affect, the evaluation of safety in clinical use;
- the nature of the recipient population (e.g.demographics) and the number of recipients required to obtain statistically significant data[16–19], where applicable. If the number needed is too high because the disease concerned is a rare disease, then alternative solutions could be proposed;
- detection of common and non-serious adverse events, focusing on events of relatively high frequency and those that are known to occur with similar BTC (for example, adverse events possibly related to the BTC administration process, surgical procedures or other).

5.2 Clinical efficacy data

Clinical efficacy data should be collected to determine the therapeutic effect of any BTC resulting from novelty in the preparation process. As with clinical safety data, the applicant should propose the plan for collection of efficacy data.

Clinical efficacy data should be adequate to demonstrate efficacy in the recipient population after a predefined period of time, to demonstrate results of the optimal therapeutic effect, to evaluate the duration of the therapeutic effect of the administered BTCand to allow for a benefit – risk assessment that takesinto account the existing therapeutic alternatives for the target population.

The CA should be provided with a plan that proposes to collect all relevant data, whether positive or negative, and the applicant should explain how the data is intended to support the application of BTC for the proposed indications.

While assessing the plan to collect clinical efficacy data the CA might consider the following issues:

- relevant features of the recipientpopulations, including demographic features, disease stage, and any other potentially important covariates;
- the nature and scale of expected clinical benefit and the basis for these expectations;
- statistical methods and any issues that could affect the interpretation of the results;
- summary of patient reported outcome measures,if collected by the applicant.

5.3 Duration of the clinical follow-up

The length of clinical follow-up will depend on the expected shelf-life and characteristics of the BTC in question, as well as on the clinical indication. The use of a previously validated or generally accepted follow-up period is possible, provided that a correlation between the duration of clinical follow-up and safety and efficacy can be established[20]. If the efficacy is dependent on the long-term persistence of the BTC, a long-term clinical follow-up of the BTC recipients(and/or offspring) should be requested. However, if the follow-up period is very long then alternative solutions, e.g. at shorter follow-up period, might be acceptable, if suitably justified[14]. The duration of the clinical follow-up should always be justified and scientifically sound.

6. Assessment of Clinical InvestigationPlan (CIP)

If the end result of the risk assessment performed by the applicant ismoderate or high risk level, the applicant should plan for a clinical investigation for evaluating the novel BTC. Clinical investigationshould be the primary way forevaluating if a novel BTC is safe and effective in recipients.A Clinical Investigation Plan (CIP) is a document that describes how the clinical investigation will be conducted (the objective(s), design, methodology, statistical considerations and organisation of a clinical investigation) and ensures the safety of the novel BTC recipients and integrity of the data collected.

The depth and extent of CIP should be adaptable and appropriate to the nature, intended purpose, and risks of the BTC in question.It should be presentedto the relevant CA for assessment and approval before starting clinical application of the novel BTC.

The CIP provided to CA should define (at least):

- Objectives and purpose of the clinical investigation;
- Recipient inclusion and exclusion criteria;
- Number of BTC recipients planned to be included in the clinical investigation;
- Alternative therapies or BTC, if any;
- Control treatment (if applicable);
- Recruitment procedures and informed consent protocol for the recipients;
- Planned follow-up visits and procedures (incl. tests, samples, imaging etc.) and duration of the clinical investigation;
- Data collection methodology;
- Safety and efficacy parameters;
- Endpoints defined by the applicant and end users to assess safety and efficacy;
- Statistical protocols, data handling, record keeping and methodology for data analysis;
- Discontinuation/termination criteria (safety signals defined; if these were reached, the clinical application of the BTC were to be discontinued/terminated);
- Predicted timing for periodic or final reports of the CIP.

The type of clinical investigation selected depends on a number of considerations and should be justified according to:

- Remaining level of risk;
- The availability of a suitable control treatment, if applicable(section 7);
- The length of time that recipients need to be monitored will depend on the BTC in question and its indication. If a long term follow-up is required, a controlled investigation may not be practical, and a registry approach may be considered[10].

The CIP design, and the eventual execution of the clinical investigation, should take into consideration and follow the principles of Good Clinical Practices (GCP)[21], where applicable (Appendix I).

After completion of the clinical investigation, the applicant should report the results of parameters assessed, as well as the conclusions.

Specific aspects of CIP are described in sections below.

6.1 GCP principles

For CIPs with moderate or high levels of risk, the principles of GCP[21] should be adhered to, when applicable (see Appendix I - Good practices of clinical setting for BTC [adapted from GCP principles]).

In addition to a conclusive statement on compliance with GCP principles, the information provided in the PPD should allow the assessment of the adhesion and implementation to GCP principles. Where the nature of the BTC does not permit full compliance with GCP principles, applicants should justify the reasons for non-compliance and describe the alternative practices adopted.

6.2 Independent Ethics Committee (IEC) decisions/opinions

Local/regional/national Independent EthicsCommittees (IECs) are bodies designatedto review and approve biomedical research involving humansubjects. IECs should safeguard the rights, safety, and well-being of the participants under clinical investigation. In particular, special attention needs to be paid to clinical investigations that may include vulnerable subjects.[16]In some MS, the IEC's favourable decision/opinion of the CIP could be mandatory before commencing the clinical investigation on humans. The IEC may review informed consent forms (ICF; section 6.3), including the information provided for the possible recipients of the novel BTC, participant recruitment procedures, available safety information, and investigator's qualifications (section 6.14.2) and any other documents that the IEC may need to fulfil its responsibilities.[21] If IEC opinions/decisions are given, these should be included in the application and reviewed by the assessor.

6.3 Recruitment procedures and informed consent process of the recipients

The role of informed consent is crucial in maintaining the trust of the general public in health professionals. Therefore, it is important that the limits of the consent are clearly established (and subsequently, accurately respected). As a result, the informed consent form (ICF) should be as clear and concise as possible and written in simple and easy to understand terms comprehensible to the intended clinical investigation participant.

Clinical investigation of a novel BTCcan be carried out only afterthe person concerned (BTC recipient) has given informedconsent to it.[22] This person should make a free choice as participation to CIP is voluntary. Beforehand, participants need to be given appropriate information of certain aspects of the CIP, see examples listed below. In some MS, the IEC assesses the contents of the ICF and the information given to the novel BTC recipients, in some other MS the CA assessor needs to assess the those. The ICF should give information on:

- the therapy, as well as its consequences and risks;
- alternative therapies available;
- how long the participation in the clinical investigation is likely to last, and what type of follow-up procedures are involved;
- approximately how many other recipients are taking part, and the probability for random assignment to each group (if applicable);

- compensation or treatment available in case something goes wrong;
- the circumstances under which their participation (or the investigationin its entirety) may be terminated;
- theright of the person concerned to refuse to participate or withdraw their consent, at any time, without penalty or loss of standard treatment to which they are otherwise entitled to.

If the clinical investigation involves children or adults who lack the capacity to consent, there shouldbe more than one ICF – each tailored to the sub-group in question. For example, one aimed at children and the other for the parent/guardian(s).

CIP should describe the BTC recipient recruitment process. For example, the following details should be given:

- How will potential clinical investigation participants be identified (e.g. advertising the clinical investigation or via existing recipient lists);
- What resources will be used for recruitment (description of the format of the resources, e.g. letters to possible participants, in the clinic, through social media or through newspapers);
- Who will be approaching potential participants and who will be obtaining informed consent (description of the professionals' role and whether there is a prior clinical relationship with potential participants);
- How will it be assured that potential participants (or their legal representative) have understood the information and that their consent is informed.

(Adapted from Recruitment and Informed consent procedure template of European Commission[23])

6.4 Insurance

It must be ensured that there is an adequate insurance coverage for the recipients of novel BTC, in accordance with applicable regulatory requirements. Proof of insurance should be requestedwhen this is stipulated by national legislation.

6.5 Inclusion and exclusion criteria

The target population needs to bedescribedin the CIP, specifying the inclusion and exclusion criteria for participating in the clinical investigation.Inclusion criteria are characteristics that the prospective participantsmust have if they are to be included in the clinical investigation. Exclusion criteria are those characteristics that disqualify prospective participantsfrom inclusion in the clinical investigation. Inclusion and exclusion criteria may include factors such as age, gender, type and stage of disease, the participant's previous treatment history, and the presence or absence of other medical conditions.Defining clear-cut inclusion and exclusion criteria increases the likelihood of producing reliable and reproducible results, minimises the likelihood of harm to the participants, and guards against exploitation of vulnerable persons.

6.6 Clinical endpoints

An endpoint is the primary outcome that is being measured by clinical investigation. A clinical endpoint is an outcome that represents clinical benefit (such as survival), the absence of disease or

onset of symptoms. Endpoints can also be subjective, as for example improving symptom score or health-related quality of life score.

Endpoints should be selected to address the objectives of the clinical investigation and should be clinically relevant, practical and affordable to obtain, and measurable in an unbiased manner.

6.7 Planned follow-up procedures, samples and/or visits of the recipients

The CIP should contain all the detailsrelevant for the clinical investigation, for example:

- The expected duration of BTC recipient participation;
- A description of the sequence and details of all investigative procedures (including tests, samples, imaging etc.);
- The methods and timing for assessing, recording, and analysing safety and efficacy parameters;
- The type and duration of the follow-up of participants after (serious) adverse reactions.

6.8 Methods for data collecting

The CIP should be designed to collect high-quality, reliable and meaningful data. Methods for data collecting should be specified and justified, including for example:

- Patient reported outcome measures (PROM)(for example questionnaire surveys and participant diaries; in paper or electronic format)shoulduse standardised instruments, where possible, to promote the collection of uniform high-quality data and allow for meaningful comparisons. If standardised instruments are not available, investigator-invented scales can be used but should be carefully designed and piloted before using in clinical investigation.Electronic PROM systems providebetterquality of data and could allow for immediate intervention if problems or deviations occur.
- Review of EHRsmay be used either as the sole source of data, or complementary to other methods used to collect information. EHRs can be important sources of information that can document participants' medical history, clinical or laboratory profile at varying time points in a cost-efficient manner.
- Investigation report forms (paper or electronic) can be designed specifically for data collection regarding the clinical investigation in questionso that all the data needed to answer the research question will be captured. All the data on each individual taking part in a clinical investigationwill be held in the investigation report forms.
- Collection of biological material/samples and various imaging technologies can be used to obtain informationonanatomical, pathological and biological mechanisms involved in the development of disease, its prognosis, or response to treatment. Biological data can serve as clinical endpoints but obtaining samples can burden participants. Biological data need to be collected under standardised conditions with considerable attention to detail.

6.9 Multicentre investigations

A multicentre investigation is an investigation conducted by more than one organisation responsible for human application (ORHA). Multicentre investigationscan be conducted in one MS, at multiple MS, or they can include centres from third countries. Multicentre investigationsbenefit from a larger number of participating recipients, the possibility of including a wider range of population groups, and the ability to compare results among centres. Multicentre research promotes networking by bringing together different groups of investigators who can also share resources, expertise and ideas. Multicentre investigationsare recommended, whenever possible, in order to reduce any potential bias.

In multicentre investigations, the ORHAs (incl. countries), as well as numbers of recipients planned for each centre should be specified in the PPA application.

6.10 Data protection and data integrity

All data handling must comply with the international and national data protection requirements[24]. There should be organisational and technical arrangements in place to avoid unauthorised access, disclosure, dissemination, alteration or loss of information and personal data processed. There should be measures in place to ensure confidentiality of records and personal data of the BTC recipients(including data gathered in the context of CFUpP and SARE reporting). All these arrangements and measures should be described in the CIP.

All data regarding the clinical investigation should aim to be complete and accurate, and consistent between recipients and different ORHAs (in multicentre investigations). Achieving high-quality data can usually only be proven via audits, inspections or assessment of the results.

6.11 Analysis of the clinical data

The plan for analysing the clinical data should be specified in the PPA application, should use sound methods and should include:

- a description of the statistical methods to be used, including timing of any planned interim analysis/analyses;
- the number of recipients planned;
- reason for choice of sample size;
- the level of significance to be used.

In general, data that are not methodologically sound (such as single recipient reports) should not be acceptedfor demonstration of adequate clinical safety and efficacy of a BTC (adapted from MEDDEV[12]).

The assessor should identify if additional clinical follow-up or other measures are necessary in order togenerate any missing data.

6.12 Discontinuation/termination criteria

The CIP should outline the discontinuation and termination criteria for the clinical investigation. For example, individual participant(s) must have the possibility to discontinue the clinical investigation in the event of:

- withdrawal of consent at any time;
- circumstances that would endanger the health of the participant;
- non-compliance with clinical investigation procedures.

Premature termination of the clinical investigation might be necessary, for example for safety reasons, if the IEC terminates its approval/favourable opinion of the clinical investigation, or if the clinical investigation proves to be impossible or difficult to conduct in practice. Applicants should inform the CA of premature termination.

6.13 Periodic and final reports

When clinical investigations are very large or long in duration, when the interventions have associated serious safety concerns, or when the disease being studied is very serious, then interim data monitoring and periodic reporting should be considered.

The CIP should determine the time point, or number of treated recipients reached, when the periodic and final reporting should be conducted. The periodic and final analysis process can be described in a separate document.

6.14 Appendices required to support PPA

The CA should also consider some additional aspects when performing the PPA. These are reviewed in the following sections.

6.14.1 Agreements

A written and signed agreement should be formulatedbetween:

- the clinician(s) performing the recipients' clinical investigation (also institution/ORHA, if applicable)
- andthe BE or TE that is responsible for the novel BTC therapy/BTC resulting from novel preparation process.

The agreement should:

- take into account relevant national/local requirements for these agreements
- list responsibilities of the participants, for example regarding
    - data collection and data analysis;
    - communication with relevantCAs;
- detail who owns, has access to, has the right and the responsibility to process, has the right to publish, and stores the generated data;
- definethe period of validity of the collaboration;
- refer to data protection requirements (for example EU's General Data Protection Regulation[24]);
- be signed by all relevant parties.

6.14.2 Experience of investigators

The clinicians responsible for performing the clinical investigation of BTC recipients (investigators) must collect and report investigation-related data in addition to the standard clinical practice.

Investigators should:

- be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation;
- meet all the competencesspecified by the applicable regulatory requirement(s);
- provide evidence of such competences through an up-to-date curriculum vitae (CV) and/or other relevant documentation as required by the BE/TE, the IEC, and/or the CA;
- be thoroughly familiar with the appropriate applicationof the BTC;
- be aware of, and comply with,relevant national/local regulatory requirements, and principles of GCP;
- permit inspection by appropriate CAs, as and when applicable.
  (Adapted from GCP[16])

It is recommended to appoint one of the investigators in a Principal Investigator(PI) role. The Principal Investigator will be the lead investigator with responsibility forfollowing the CIPand for the proper conduct of the data collection and reporting.The PI should have the required competence according to relevant legislation.

7. Control treatments for BTC with high risk level

Details related to the definition, performance and evaluation of control treatment(s) should be included as part of the CIP, at least for those BTC with high levels of risk.

In most cases, the standard/conventional BTC is recommended to be used as control, if available. If ethical considerations prevent using establishedBTC in parallel with the novelty or if the effect of the novelty is expected to be major, based on preliminary data, already existing comparison data of standard/conventional BTC could be used. Reasons for not using a control group should be justified in the CIP.

When applicable, alternative therapies/procedures, other than standard/conventionalBTC can also be considered as control treatment(s).

Randomisation into novelty and control treatment groupingsshould always be considered as a good practice. Randomisation is used to prevent allocation bias into the treatments groups by creating balanced investigationdivision.Known and unknown recipient characteristics that may influence the investigated outcome parameters should be balanced, asideally the treatment intervention is the only difference between the investigation groups. Randomisationis considered a critical element in establishing acausal relationship between treatment and clinical outcomes. Treatment assignment based upon investigator'sjudgment, rather than randomisation, creates a challenge for proving treatment efficacy that must be addressed. However, for several reasons (including ethical and practical considerations), the administration of BTC can in many cases not be subjected to a

randomised, controlled investigation. In this case, the reason for not using randomisation should be justified in the CIP.

8. Updates and amendments

The CFUpP and CIP resultant from the risk assessment should be updated by the applicant throughout the BTC life cycle, as and when necessary[20].

Applicants should inform the CA, in a timely fashion, when there is a need to change and/or update the initial CIP and/or CFUpP, based on:

- New clinical data available for the BTC under evaluation;
- Identification of potential new risks and risk consequences;
- Changes concerning current knowledge/the state of the art, such as changes to applicable standards and guidance documents, new information relating to the medical condition managed with the BTC and its natural course, or therapeutic alternatives available to the target population;
- Other aspects identified during clinical follow-up/post authorisation.

9. Final considerations

These guidelines indicate that a common framework and harmonised approach can be suitable to assess the clinical component of the PPD for the different BTC.

The good practices proposed in this document are aligned with the views of CAs and stakeholders, and reflect the contents of precedingEU initiatives. Nevertheless, appropriate levels of flexibility should be considered during the implementation of these guidelines as the assessment of clinical data (beyond the reporting of serious adverse reactions) is not included in the scope of the current EUBTCDs, and at present clinicians/end users are not obliged to provide clinical data to BE/TE. Additional challenges may arise considering the structure and limited resources of many CAs and BE/TEs, the anticipated number of recipients lost to follow-up due to the nature of the BTC therapies, and the absence of formal registries for all BTC.

Despite the foreseen challenges, this document should be considered an integral part of the generic guidance produced by the GAPP technical WPs, and interpreted as an important milestone for the improvement of practices and the safety of BTC recipients in Europe.

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Acronyms

BE	Blood Establishment
BTC	Blood, Tissues and Cells
CA	Competent Authority
CFUpP	Clinical Follow-Up Plan
CIP	Clinical Investigation Plan
CV	Curriculum vitae
EBMT	European Society for Blood and Marrow Transplantation
ECCTR	European Cornea and Cell Transplantation Registry
EHR	Electronic health record
EMA	European Medicines Agency
ESHRE	European Society of Human Reproduction and Embryology
EUBD	European Blood Directives
EUBTCD	European Blood, Tissues and Cells Directives
EUnetHTA	European Network for Health Technology Assessment
EuroGTP II	Good Practices forevaluating quality,safety and efficacyof novel tissue andcellular therapiesand products (EuroGTP II Guide)
EUTCD	European Tissues and Cells Directives
GAPP	Facilitating the Authorisation of Preparation Process for blood, tissues and cells
GCP	Good Clinical Practice
GvHD	Graft versus Host Disease
ICF	Informed Consent Form
IEC	Independent Ethics Committee
JA	Joint Action
MAR	Medically Assisted Reproduction
MS	Member State
ORHA	Organisation Responsible for Human Application
PI	Principal Investigator
PPA	Preparation Process Authorisation
PPD	Preparation Process Dossier
PROM	Patient Reported Outcome Measures
RWD	Real-World Data
SAR	Serious Adverse Reaction
SARE	Serious Adverse Reactions and Events
TE	Tissue Establishment
VISTART	Vigilance and Inspection for the Safety of Transfusion, Assisted Reproduction and Transplantation
WP	Work Package

Definitions

Applicants– European Blood/Tissue Establishments (BE/TE) that request Competent Authorities for authorisation for the clinical application of blood, tissues or cells (BTC).

Blood, Tissues and Cells– Substances of Human Origin included in the scope of the European Directives 2002/98/EC[3] and 2004/23/EC[6].

Clinical benefit - The positive impact of (a) BTC therapy(ies) on the health and quality of life of an individual, expressed in terms of a meaningful, measurable, recipient-relevant clinical outcome(s), including outcome(s) related to diagnosis.(adapted from [25])

Clinical data - Information concerning safety or efficacy that is generated from the use of a BTC and is sourced from the following: clinical investigation(s) of the BTC concerned; clinical investigation(s) or other studies reported in scientific literature of the BTC in question; reports published in peer reviewed scientific literature on other clinical experience of the BTC in question; clinically relevant information coming from post authorisation surveillance. (adapted from[25])

Clinical Investigation Plan (CIP) - A document that describes the rationale, objectives, design, methodology, monitoring, statistical considerations, organisation and conduct of a clinical investigation[25], prepared by the applicant(s) in the context of the authorisation request for clinical use of novel BTC therapies/BTC resulting from novel preparation process.

Clinical Follow-up Plan(CFUpP) –The plan for monitoring the novel BTC recipient for a given time after clinical application/administration; may comprise of medical visits,tests, diagnostic procedures, samples etc. (adapted from[1])

Efficacy - Presence of desired (clinical) effects/patient outcomes depending on the mode of action of the BTC[1,26].

Follow-up - Subsequent evaluation of the health of a recipient for the purpose of monitoring the results of the BTC application, maintaining care and initiating post-application interventions.(adapted from [26])

Informed consent - A person's voluntary agreement, based upon adequate knowledge and understanding of relevant information, to donate, to participate in research or to undergo a diagnostic, therapeutic or preventive procedure.[26]

Randomised controlled study - A study in which subjects are allocated at random into groups, called the "investigation" and "control" groups, to receive or not receive an experimental therapeutic intervention. (adapted from[26])

Recipient - Person to whom human BTC are applied. (adapted from[26])

Third countries - Countries that are not members ofthe EU.

Appendix I -Good practices of clinical setting for BTC

(Adapted from GCP principles[16])

1. Clinical investigation should be conducted in accordance with the ethical principles in the Declaration of Helsinki and the applicable regulatory requirement(s).
2. Before clinical investigation is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual novel BTC recipient and society. A clinical investigation in recipients should be initiated and continued only if the anticipated benefits justify the risks.
3. The rights, safety, and well-being of the BTC recipients involved in the clinical investigation are the most important considerations and should prevail over interests of science and society.
4. The available nonclinical and clinical information on an investigational BTC should be adequate to support the proposed clinical investigation.
5. Clinical investigation should be scientifically sound, and described in a clear, detailed plan.
6. Clinical investigation should be conducted in compliance with the plan that has received prior independent ethics committee (IEC) approval/favourable opinion.
7. The medical care given to, and medical decisions made on behalf of, BTC recipients should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
8. Each individual involved in conducting a clinical investigation should be qualified by education, training, and experience to perform his or her respective task(s).
9. Freely given informed consent should be obtained from every BTC recipient prior to participation in the clinical investigation.
10. All information associated with the clinical investigation should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
11. The confidentiality of records that could identify BTC recipients should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12. Investigational BTC should be donated, analysed, processed/prepared, handled, stored and distributed in accordance with good practices described in current versions of the Guide to the quality and safety of Tissues and Cells for human application[26]and Guide to the preparation, use and quality assurance of blood components[27]of the Council of Europe. They should be applied/transplanted/transfused in accordance with the approved plan(s).
13. Systems with procedures that assure the quality of every aspect of the clinical investigation should be implemented.

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	Ministry of Health – Croatia (WP3 Leaders)	Tihana Cikač Vanja Nikolac
	Ministry of Health, Government of Malta (MHM) – Malta	Fewzi Teskrat
	AsociaciónEspañola de Bancos de Tejidos (AEBT) – Spain	Anna Vilarrodona Antonia Álvarez Marquez Elba Agustí Lydia Padró
	Finnish Medicines Agency – Finland	Karri Penttilä
	LietuvosSveikatosMokslųUniversitetoLigoninės Kauno Klinikos (HLUHSKKA) – Lithuania	Domas Vaitiekus
	Viesoji Istaiga Vilniaus Universiteto Ligonine Santaros Klinikos (VULSK) – Lithuania	Rita Cekauskiene
	Romanian National Registry of Hematopoietic Stem Cells Voluntary Donors – Romania	Aurora Dragomiristeanu
Collaborating Partners & Invited Experts	European Blood Alliance (EBA)	Peter Van Den Burg
	European Eye Bank Association (EEBA)	Gary Lloyd Aubrey Jones Iva Dekaris
	European Society for Blood and Marrow Transplantation (EBMT)	Eoin McGrath
	European Society of Human Reproduction and Embryology (ESHRE)	Cristina Magli Nathalie Vermeulen Veerle Goossens
	Regea Cell and Tissue Center – BioMediTech – Finland	Tiia Tallinen
	Hellenic National Blood Center (E.KE.A) – Greece	Anthi Gafou

	Finnish Red Cross Blood Service – Finland	Kari Aranko
	Common representation of SoHO's Associations (CoReSoHO)	Akila Chandrasekar
	Agence nationale de sécurité du médicament et des produits de santé (ANSM) – France	Caroline Matko
	Invited Expert– Sweden	Mona Hansson
MS CA representatives	Austrian Agency for Health and Food Safety (AGES) – Austria	Stephanie Fritz
	Agence nationale de sécurité du médicament et des produits de santé (ANSM) – France	Imad Sandid
	Federal Agency for Medicines and Health Products – Belgium	Evelyne Van Gastel
European Commission DG SANTE	Unit D4 – Substances of Human Origin	Stefaan Van Der Spiegel Deirdre Fehily