Overall Guidance (GAPP): Good practice guideline to authorisation on preparation processes in blood, tissues and cells establishment

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Conflitto di interessi

La sottoscritta Ursula La Rocca, in qualità di Relatore,

dichiara che

- nell'esercizio della sua funzione e per l'evento in oggetto, **NON È** in alcun modo portatore di interessi commerciali propri o di terzi;
- dichiara inoltre che gli eventuali rapporti avuti negli ultimi due anni con soggetti portatori di interessi commerciali **non sono tali da permettere a tali soggetti di influenzare** le sue funzioni al fine di trarne vantaggio.

CENTRO NAZIONALE SANGUE

Obiettivi GAPP

- Facilitare e promuovere lo sviluppo di un approccio comune ed ottimale per valutare ed autorizzare i **processi di preparazione nei Blood and Tissues and Cells Estabilishments**
- Contribuire **all'implementazione della legislazione europea** nel settore di sangue, emocomponenti, cellule e tessuti
- Fornire strumenti per incrementare l'**armonizzazione delle attività** degli stati membri che riguardano la trasfusione di sangue, il trapianto di cellule e tessuti e la riproduzione assistita

WP Tecnici

WP5: DEVELOPMENT OF OVERALL GUIDANCE ON ORGANIZATION OF PPA SYSTEM

WP6: AUTHORIZATION OF CHANGES IN DONATION, PROCUREMENT AND COLLECTION, PROCESSING, PRESERVATION, STORAGE AND DISTRIBUTION

WP7: AUTHORIZATION OF CHANGES IN DONATION, PROCUREMENT AND COLLECTION, PROCESSING, PRESERVATION, STORAGE AND DISTRIBUTION

WP8: ASSESSING CLINICAL DATA AS PART OF PPA

WP9: KNOWLEDGE SHARING ON PPA BETWEEN EU CAS

WP10: TRAINING COURSES AND MANUAL FOR TRAINING

CENTRO NAZIONALE SANGUE

Risultati principali GAPP

- **Linea guida** per un approccio comune all' autorizzazione di nuovi prodotti e processi derivati da sostanze di origine umana (blood, tissues and cells), basate sui concetti di valutazione del rischio, adeguate evidenze cliniche, autorizzazione condizionata

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

- **Technical Annexes:**
  - **Technical annex 1:** Authorization of changes in donation, procurement and collection, processing, preservation, storage and distribution (including labelling and package inserts)
  - **Technical annex 2:** Assessing the quality and safety of donor testing, pathogen reduction and sterilisation steps as part of Preparation Process Authorisation (PPA)
  - **Technical annex 3:** Assessing clinical data as part of PPA

- **Risk assessment tool** per sangue e componenti del sangue;
- **Knowledge sharing platform** per valutatori e autorità competenti;
- **Manuale per il training** dei valutatori

Linea guida: Good practice guideline to authorization on preparation processes in blood, tissues and cells establishments

Definire l'approccio comune alla autorizzazione di nuovi prodotti e processi derivati da sostanze di origine umana

RACCOMANDAZIONI per CA

ambito normative

- DE 2002/98/CE
- DE 2004/23/CE

Dispositivi medici, Farmaci o ATMPS

SURVEY WP5

Valutazione dello **stato dell'arte presso le CA dei diversi SM**, per conoscere le modalità di **gestione del cambiamento di processi** e **prodotti** nell'ambito delle **sostanze di origine umana**

CENTRO NAZIONALE SANGUE

DELIVERABLE 5.2

REPORT ON THE OUTCOME AND CONCLUSIONS OF THE SURVEY, DESK-BASED REVIEW OF PREPARATION PROCESS AUTHORISATIONS IN OTHER FIELDS AND THE MULTI-COUNTRY WORKSHOP

Rispondenti: 24

CA Nazionali (23) Regionali (1)

Ambito di competenza dei rispondenti	
Blood	19
Tissues and Cells	20
MAR	18
Medicinal products	11
Medical device	8
Veterinary medicines	8

L'autorizzazione è correlata ad ispezioni?	Risposta
Yes	18
No	5
Not applicable	1

Che tipo di autorizzazione viene concessa?	Risposta
Autorizzazione definitiva (senza date di scadenza/rinnovo)	12
Autorizzazione condizionata	10
Autorizzazione temporanea	16
Altro	3

La tua CA dispone di un sistema per gestire l'autorizzazione di nuovi/nuove	Risposta
Attività	17
Prodotti	12
Processi	14
Indicazioni cliniche	2
Non disponibili	4
Altro	5

Disomogeneità in termini di **tipologia di autorizzazione concessa**, **modalità di erogazione**, l'eventuale **ricorso ad ispezioni**, la **disponibilità di sistemi per gestire le autorizzazione**

CENTRO NAZIONALE SANGUE

DELIVERABLE 5.2
REPORT ON THE OUTCOME AND CONCLUSIONS OF THE SURVEY, DESK-BASED REVIEW OF PREPARATION PROCESS AUTHORISATIONS IN OTHER FIELDS AND THE MULTI-COUNTRY WORKSHOP

Rispondenti: 24
CA Nazionali (23) Regionali (1)

La tua CA dispone di un sistema per la categorizzazione del rischio	Risposte
Richiesta di modifiche ad autorizzazioni esistenti	5
Richieste di autorizzazione per nuove attività, prodotti, processi, indicazioni cliniche	2
Valutazioni del rischio non disponibili	**15 (75%)**
Respondenti 20	

Disomogeneità tra le CA degli Stati Membri in termini di:

- ***Requisiti per l'autorizzazione di SoHo***
- ***Risorse (personale, competenze e supporto scientifico)***
- ***Normativa da considerare***

- **Guidance for authorization of changes in preparation processes** — **GAPP**
- Guidance in risk assessment — **EuroGTP**
- **Guidance/ help in assessing new/novel activities, processes, products** — **GAPP**
- ***"Network" between CA´s for knowledges sharing*** — **GAPP**

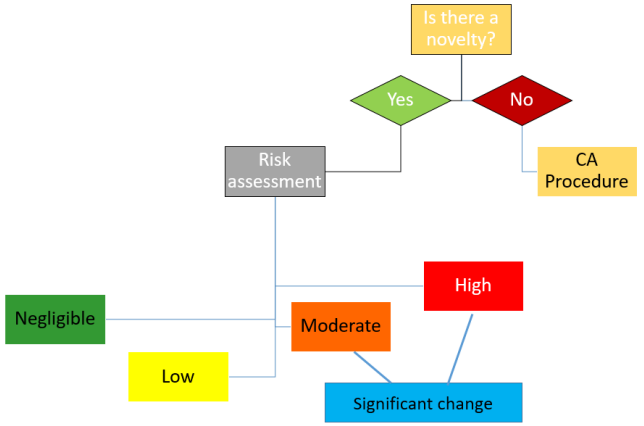
CENTRO NAZIONALE SANGUE

Linea guida: Good practice guideline to authorization on preparation processes in blood, tissues and cells establishments

- **Novità:** qualsiasi **cambiamento** che possa influire sulla **qualità e/o sulla sicurezza di sangue, cellule e tessuti e/o sulla sicurezza dei riceventi**. Ciò può essere **determinato dall'introduzione di un nuovo prodotto** (sangue, cellule o tessuti), **una nuova procedura** definita da BE o TE, **una nuova procedura adottata da un altro centro che ne ha dimostrato evidenza scientifica** o **l'applicazione di un prodotto già esistente per** il trattamento di **una nuova indicazione clinica.**

- **Cambiamento significativo:** cambiamento con conseguenze significative sulla **qualità e/o sulla sicurezza del prodotto e/o la sicurezza del ricevente**, valutato come **rischio moderato o alto**.

Un cambiamento significativo sarà identificato come **novità** e **successivamente valutato** in termini di **rischio** mediante **lo strumento fornito da EuroGTPII.**



Linea guida: Good practice guideline to authorization on preparation processes in blood, tissues and cells establishments

APPLICATION PROCESS

L'iter inizia con la **preparazione di un dossier (PREPARATION PROCESS DOSSIER - PPD) per il processo da autorizzare,** che comprende 6 moduli, **volti a valutare i CAMBIAMENTI** che implicano una **NOVITÀ** (sec. **EuroGTPII**) **ed i rischi correlati.**

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.

Module 4: Quality	Module 5: Preclinical studies	Module 6: Clinical information
• Updated SOPs. • Validation.	• *In-vitro/In-vivo* studies • Performed studies. • Bibliography.	• General clinical information. • Clinical indication. • CIP. • CFUpP

PREPARATION PROCESS DOSSIER (PPD)

LE INFORMAZIONI DA FORNIRE SONO CORRELATE **ALL'ENTITÀ DEL CAMBIAMENTO**

APPLICANT INFORMATION

Informazioni BE/TE

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	

PREPARATION PROCESS DOSSIER (PPD)

NOVELTY

*Definita **la tipologia di sangue-emocomponenti/cellule/tessuti**, il richiedente dovrà valutare **il rischio utilizzando il tool EuroGTPII***

Utilizzato strumento EuroGTPII, progettato inizialmente per tessuti e cellule, poi esteso a sangue, che fornisce una relazione di sintesi dei rischi individuati

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):

*Le **attività** in cui le specifiche **innovazioni possono essere introdotte***

*Per facilitare revisione e valutazione delle CA sono presenti **domande che possano guidare nella valutazione delle novità***

CENTRO NAZIONALE SANGUE

PREPARATION PROCESS DOSSIER (PPD)

RISK ASSESSMENT

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

***Valutazione del rischio**, tenendo conto anche di **fonti di informazione esterne**, quali **dati di letteratura** sottoposti a peer reviewed, dati non ancora pubblicati, **pareri ed informazioni di esperti esterni**, dati relativi ad esiti clinici*

Final Risk Score *secondo **EuroGTP II:***

- *trascurabile (N)*
- *basso (L)*
- *moderato (M)*
- *alto (H)*

*Se rischio **basso, moderato o alto***

- *strategie di riduzione del rischio*
- *necessità di estensione della valutazione clinica.*

CENTRO NAZIONALE SANGUE

PREPARATION PROCESS DOSSIER (PPD)

Quality

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

Il modulo qualità contiene le informazioni relative alle SOP ed alla validazione delle attività in cui verrà implementata l'innovazione

CENTRO NAZIONALE SANGUE

PREPARATION PROCESS DOSSIER (PPD)

Pre-clinical study

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

Il richiedente fornirà alla CA informazioni riguardo eventuali studi in vitro/in vivo eseguiti, con relativa sintesi dei principali risultati e bibliografia.

CENTRO NAZIONALE SANGUE

PREPARATION PROCESS DOSSIER (PPD)

Clinical Information

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*

*In relazione **al grado di rischio individuato***

- *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 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

VALUTAZIONE DEL PPD

Step 1: Applicant Information

- **COMPLETEZZA INFORMAZIONI**

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

CENTRO NAZIONALE SANGUE

VALUTAZIONE DEL PPD

Step 2: Novelty Questions and Risk assessment

- **VALUTAZIONE RISPOSTE AI QUESITI SULLE INNOVAZIONI INTRODOTTE, ANCHE IN TERMINI DI COMPLETEZZA DELLE INFORMAZIONI**
- **ESAME RISCHIO RESIDUO, CHE PUO' ESSERE VALUTATO SOLO CON DATI DI FOLLOW UP O VALUTAZIONE CLINICA, CON L'OBIETTIVO DI VALUTARE L'APPROVAZIONE PER L'INTRODUZIONE PER USO CLINICO, IN RELAZIONE AL RISCHIO RESIDUO**

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
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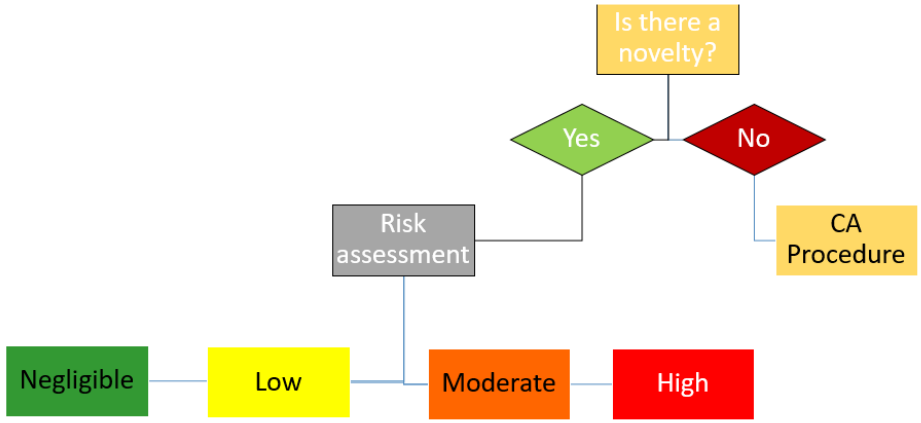
Has your establishment provided this type of BTC for a same clinical indication or applied/infused into a same anatomical site?			10 and 11
If the answer to any of the novelty questions above is 'NO'; the applicant must provide the information described in the corresponding section. For new applicants, 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.			



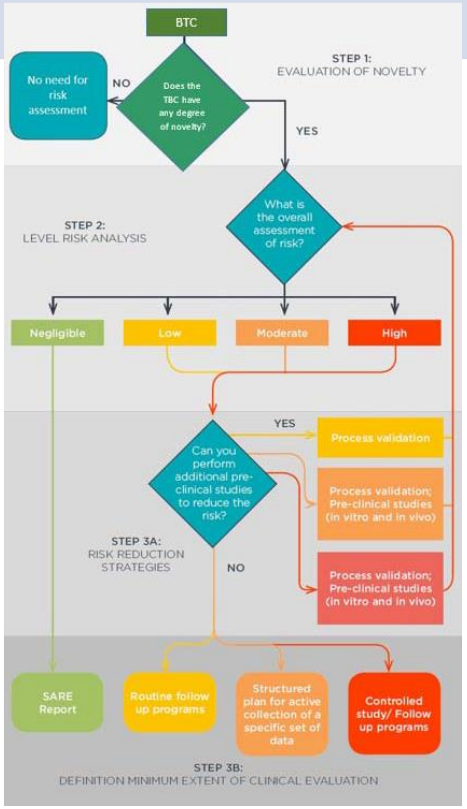
VALUTAZIONE DEL PPD

Step 2: Novelty Questions and Risk assessment

- VALUTAZIONE RISPOSTE AI QUESITI SULLE INNOVAZIONI INTRODOTTE, ANCHE IN TERMINI DI COMPLETEZZA DELLE INFORMAZIONI
- ESAME RISCHIO, CON L'OBIETTIVO DI VALUTARE L'APPROVAZIONE PER L'INTRODUZIONE PER USO CLINICO

LA DETERMINAZIONE DEL RISCHIO STABILIRÀ QUALI INFORMAZIONI DI SUPPORTO SONO NECESSARIE

Mediante strumento EuroGTPII



VALUTAZIONE DEL PPD

INDICAZIONI SU COME VALUTARE
E MITIGARE IL RISCHIO QUANTIFICATO

Elenco degli studi necessari in base al livello di rischio individuato.

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.

CENTRO NAZIONALE SANGUE

VALUTAZIONE DEL PPD

Step 3:

CA confirm appropriate information received

ESITO

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.

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.

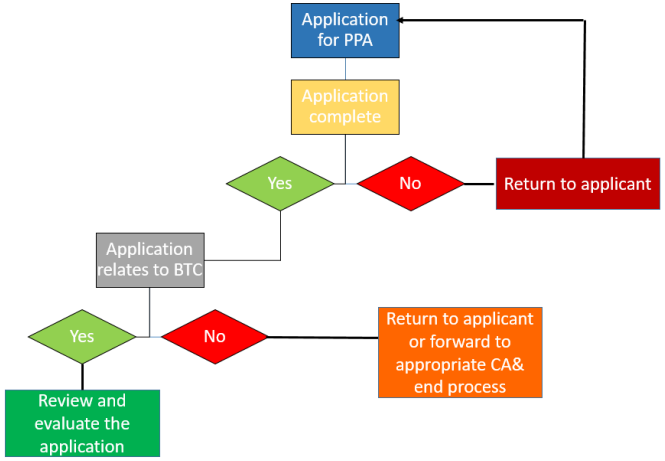
CENTRO NAZIONALE SANGUE

VALUTAZIONE DEL PPD

Step 3:

CA confirm appropriate information received

ESITO



Informazioni incomplete ?

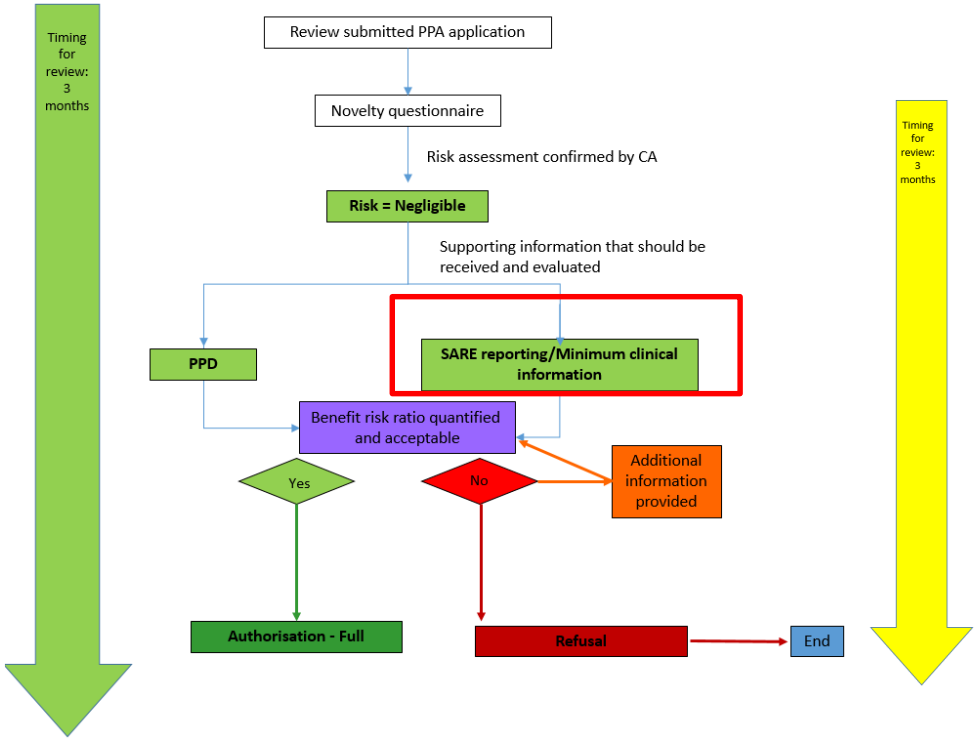
Ulteriori info

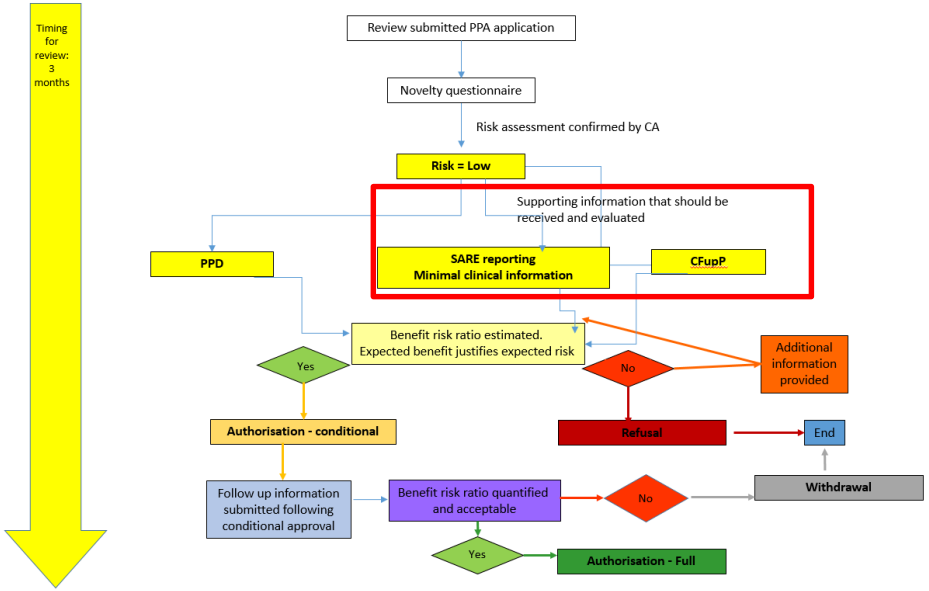
VALUTAZIONE DEL PPD

Step 4:

Flow of Evaluation of the Application according to the risk assessment

PROCEDURE DA SEGUIRE A SECONDA DEL LIVELLO DI RISCHIO



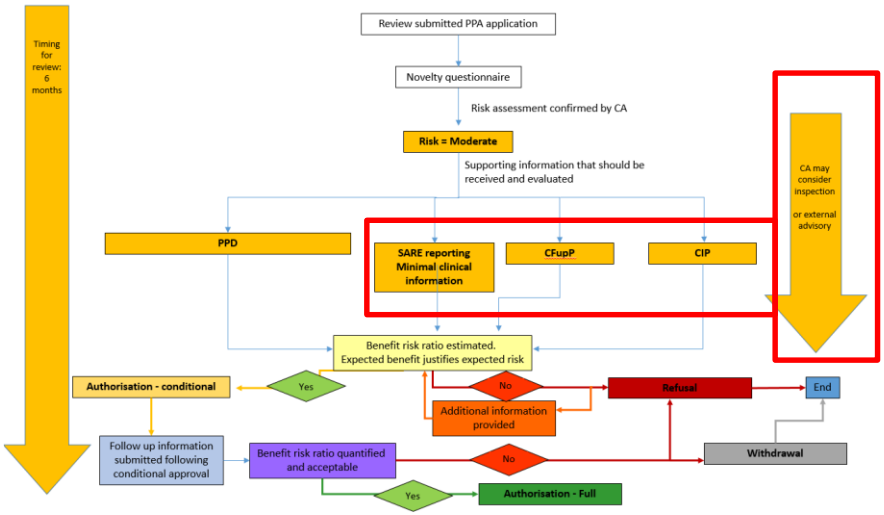


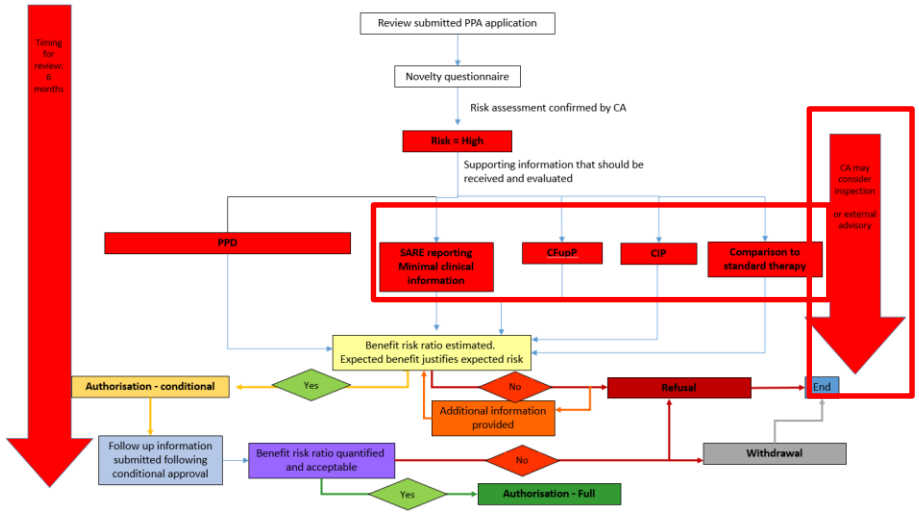
VALUTAZIONE DEL PPD

Step 4:

Flow of Evaluation of the Application according to the risk assessment

PROCEDURE DA SEGUIRE A SECONDA DEL LIVELLO DI RISCHIO

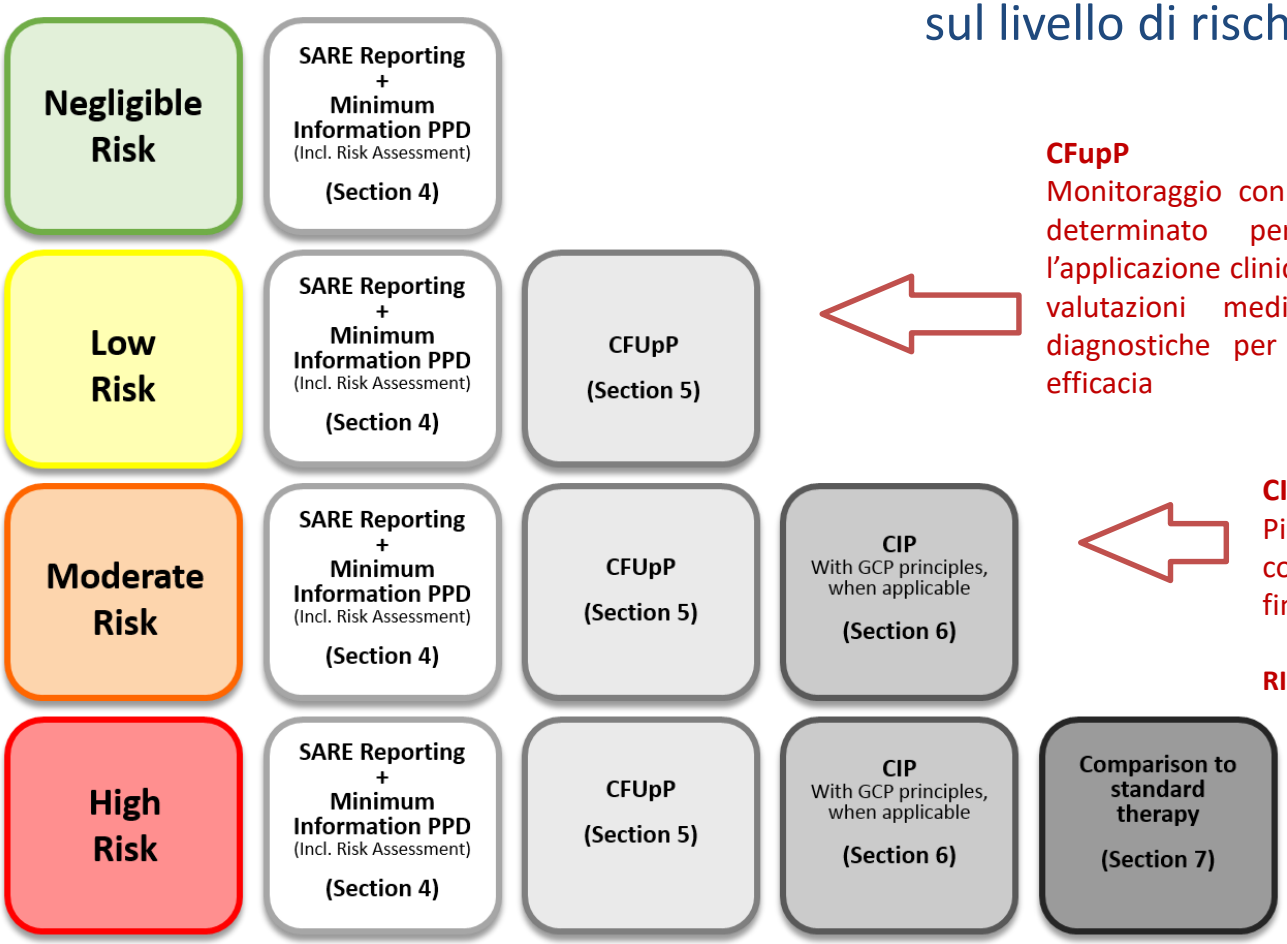




CENTRO NAZIONALE SANGUE

SCALE FOR NOVELTY AND ASSOCIATED RISK

L'estensione dei dati clinici richiesti per la valutazione del PPD è basata sul livello di rischio



CFupP
Monitoraggio con Follow Up Clinico per un determinato periodo di tempo dopo l'applicazione clinica, con richiesta di eventauli valutazioni mediche, test e procedure diagnostiche per fornire dati di sicurezza, efficacia

CIP
Pianificazione di uno studio clinico, con razionale, obiettivi, endpoints finali, dati di sicurezza ed efficacia

RICORSO AD ISPEZIONI/EXPERT BOARD

CIP con valutazione comparativa con la ST

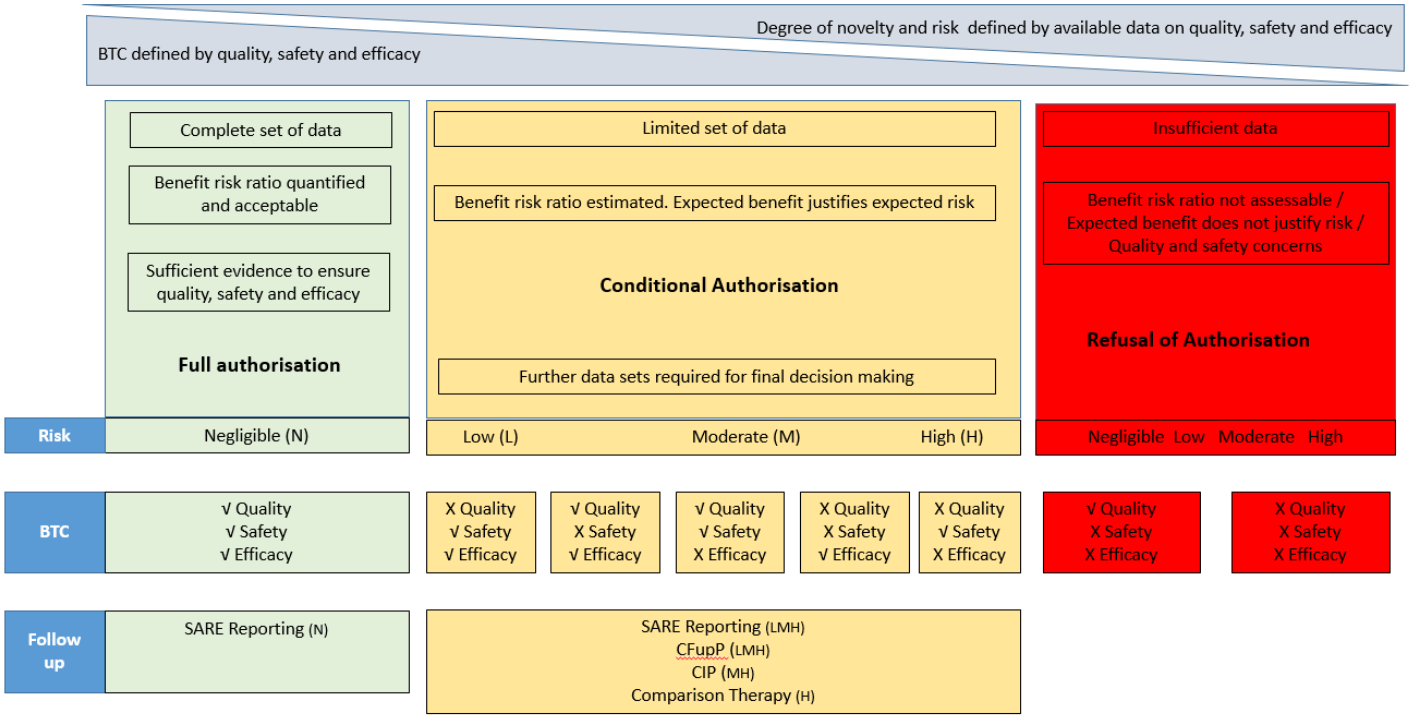
RICORSO AD ISPEZIONI/EXPERT BOARD

VALUTAZIONE DEL PPD

Step 6:

Decisione

AUTORIZZAZIONE PIENA
AUTORIZZAZIONE CONDIZIONATA
AUTORIZZAZIONE RIFIUTATA



AUTORIZZAZIONE CONDIZIONATA

Il **beneficio atteso** giustifica il **possibile rischio**, in assenza di **opzioni alternative**. Sono definiti gli **ulteriori set di dati necessari** per la **decisionale finale (autorizzazione o rifiuto),** entro **un determinato intervallo di tempo, il numero di pazienti, la coorte di pazienti ed i centri che gestiranno il BTC.**

CENTRO NAZIONALE SANGUE

CONSIDERAZIONI AGGIUNTIVE

TEMPISTICHE

- *Negligible risk*: **3 mesi**
- *Low risk*: **3 mesi**
- *Moderate risk*: **6 mesi**
- *High risk*: **6 mesi**

EXPERTISE ED EXTERNAL ADVISORS

- Professionisti CA formati su EuroGTPII e LG GAPP
- Disponibilità di un ***gruppo di esperti*** di supporto nella revisione del PPD

ISPEZIONI

Eseguite secondo procedure nazionali e con riferimento alle LG VISTART, in base alle informazioni presentate nell' application ed alla valutazione del rischio

NUOVI BTC

Possibile necessaria **collaborazione di esperti** che forniscano conoscenze e competenze specifiche nel settore in questione.

Può essere valutata l'aggiunta all'*European Tissue and Cell Compendium* o l'inclusione nelle *guide EDQM*

CENTRO NAZIONALE SANGUE

TECHNICAL ANNEX I

Technical annex 1- *Authorization of changes in donation, procurement and collection, processing, preservation, storage and distribution (including labelling and package inserts)*

Raccomandazioni per la valutazione di qualità e sicurezza dei processi da autorizzare, con **metodi e criteri relativi alle diverse fasi**, (donazione, approvvigionamento/raccolta, lavorazione, conservazione, stoccaggio e distribuzione) per **sangue (B), tessuti e cellule (T&C), terapia con cellule staminali ematopoietiche (HSC) e Riproduzione medicalmente assistita (MAR).**

La **valutazione di un processo di preparazione (PP)** è basata sulla valutazione dei **parametri critici di processo (CPP)** e, ove applicabile, sugli **attributi critici di qualità (CQA). Per MAR** proposti gli **indicatori chiave di processo (KPI).**

Per ciascun ambito, vengono individuati:

- **I tipi esistenti di BTC**
- **I processi di preparazione noti**
- **Gli attributi critici di qualità (CQA)**
- **I parametri critici di processo (CPP)**
- La validazione/approvazione della modifica/innovazione in relazione alla valutazione del rischio

TECHNICAL ANNEX II

Technical annex 2- Assessing the quality and safety of donor testing, pathogen reduction and sterilisation steps as part of Preparation Process Authorisation (PPA)

Requisiti e criteri per la sicurezza microbiologica di sangue, tessuti e cellule in accordo alle DE.

Descrizione degli aspetti che le CA devono considerare ai fini della valutazione.
In particolare:

- Competenze dei **laboratori** che eseguono test sulle malattie infettive del donatore e test microbiologici dei BTC;
- **Affidabilità dei kit di analisi dei marcatori** di malattie infettive dei donatori;
- **Efficacia dei processi di riduzione degli agenti patogeni** durante la lavorazione di BTC;
- **Efficacia dei metodi di sterilizzazione durante la lavorazione** di BTC;
- **Status microbiologico di prodotti finali di BTC.**

TECHNICAL ANNEX III

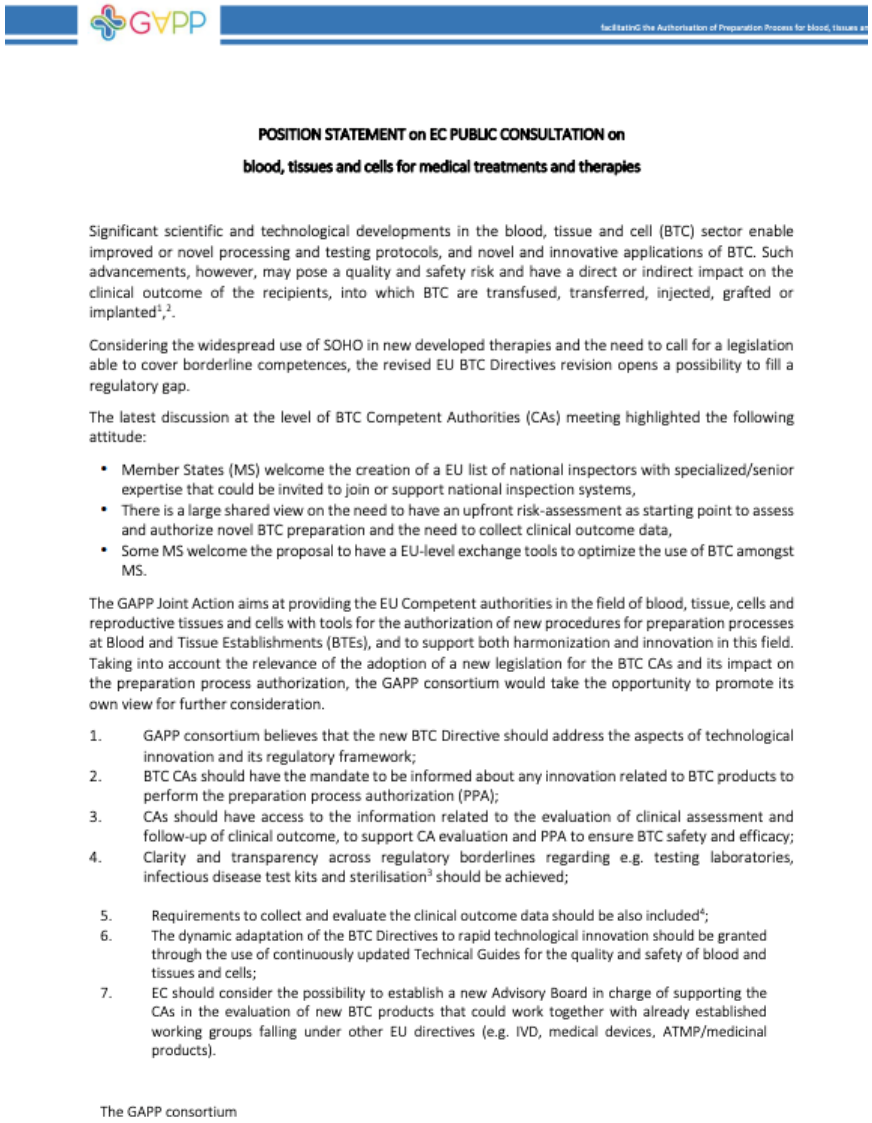
Technical annex 3: Assessing clinical data as part of PPA

Valutazione dei **dati clinici** richiesti **per i processi di autorizzazione** in seguito **all'introduzione di eventuali innovazioni negli attuali protocolli di trattamento e sperimentazione dei prodotti BTC per uso umano.**

In particolare, sono evidenziati:

- Gli elementi da tenere in considerazione al momento della valutazione delle PPD in termini di completezza e idoneità da parte delle CA;
- L'eventuale necessità del **Clinical Investigator Plan (CIP)** o del **Clinical Follow-Up Plan (CFUpP)** per supportare l'autorizzazione di nuovi processi di preparazione di **BTC e/o di nuova applicazione terapeutica**
- I contenuti necessari del CIP e del CFUpP;
- La **tipologia di dati clinici necessari per dimostrare sicurezza ed efficacia dei BTC umani dopo l'applicazione**.

POSITION STATEMENT



GAPP facilitatinG the Authorisation of Preparation Process for blood, tissues a

POSITION STATEMENT on EC PUBLIC CONSULTATION on

blood, tissues and cells for medical treatments and therapies

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].

Considering the widespread use of SOHO in new developed therapies and the need to call for a legislation able to cover borderline competences, the revised EU BTC Directives revision opens a possibility to fill a regulatory gap.

The latest discussion at the level of BTC Competent Authorities (CAs) meeting highlighted the following attitude:

- Member States (MS) welcome the creation of a EU list of national inspectors with specialized/senior expertise that could be invited to join or support national inspection systems,
- There is a large shared view on the need to have an upfront risk-assessment as starting point to assess and authorize novel BTC preparation and the need to collect clinical outcome data,
- Some MS welcome the proposal to have a EU-level exchange tools to optimize the use of BTC amongst MS.

The GAPP Joint Action aims at providing the EU Competent authorities in the field of blood, tissue, cells and reproductive tissues and cells with tools for the authorization of new procedures for preparation processes at Blood and Tissue Establishments (BTEs), and to support both harmonization and innovation in this field. Taking into account the relevance of the adoption of a new legislation for the BTC CAs and its impact on the preparation process authorization, the GAPP consortium would take the opportunity to promote its own view for further consideration.

1. GAPP consortium believes that the new BTC Directive should address the aspects of technological innovation and its regulatory framework;
2. BTC CAs should have the mandate to be informed about any innovation related to BTC products to perform the preparation process authorization (PPA);
3. CAs should have access to the information related to the evaluation of clinical assessment and follow-up of clinical outcome, to support CA evaluation and PPA to ensure BTC safety and efficacy;
4. Clarity and transparency across regulatory borderlines regarding e.g. testing laboratories, infectious disease test kits and sterilisation[3] should be achieved;
5. Requirements to collect and evaluate the clinical outcome data should be also included[4];
6. The dynamic adaptation of the BTC Directives to rapid technological innovation should be granted through the use of continuously updated Technical Guides for the quality and safety of blood and tissues and cells;
7. EC should consider the possibility to establish a new Advisory Board in charge of supporting the CAs in the evaluation of new BTC products that could work together with already established working groups falling under other EU directives (e.g. IVD, medical devices, ATMP/medicinal products).

The GAPP consortium

- Considering the **widespread use of SOHO** in new developed therapies, the revised EU BTC Directives should address the **aspects of technological innovation and its regulatory framework.**
- BTC **CAs should be informed about any innovation related to BTC products** to perform the preparation process authorization (PPA);
- **CAs should have access to the information of clinical assessment and follow-up of clinical outcome, to support CA evaluation and PPA to ensure BTC safety and effic**acy;
- EC should consider the **possibility to establish a new Advisory Board in charge of supporting the CAs in the evaluation of new BTC products**

CENTRO NAZIONALE SANGUE

ONLY ONE

PLASMA ITALIA

CENTRO NAZIONALE SANGUE

Istituto Superiore di Sanità

Grazie per l'attenzione!