EDQM Blood Conference

Innovation in Blood Establishment Processes

14-15 January 2025
Strasbourg, France

Workshop:

Development of innovative blood components and their authorisation / implementation

(13:30 – 15:00)

Moderator: **Richard Forde**, CD-P-TS Secretary, EDQM

Hosts: **Ryan Evans**, Scottish National Blood Transfusion Service (SNBTS), Scotland
Linda Larsson, Karolinska Institute/The National Board of Health and Welfare, Sweden
Simonetta Pupella, Italian National Blood Centre (CNS), Italy

Please note:

- *Food and drink are not permitted in the conference rooms*
- *Photography & filming during the presentations are strictly forbidden*
- *Photos and videos may only be taken by Council of Europe staff members*
- *The workshop will be recorded for internal purposes only*

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Disclosures

- The presenters hereby declare that they have neither financial nor nonfinancial relationships related to any of the products or services described, reviewed, evaluated or compared in this presentation.

- This workshop is interactive using **Slido** to collect answers from the audience: Answers are submitted anonymously, and results will be aggregated. The data may be used by the EDQM GTS group for the purposes of planning for review of the 23rd Edition, by completing the Slido poll you consent to this use.
- We encourage all delegates to participate in the workshop, but specific questions can be skipped if preferred.
- Your responses and feedback will be most valuable to us in the revision of blood guide monographs.

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EDQM Guide:
Blood Component Lifecycle

Novel component > Monograph > Archive

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Learning objectives

Describe the blood component monograph life cycle:

- Maintaining the monographs
- Novel blood components

Describe the current gaps and plans for the EDQM Guide 23rd Edition

- Illustrate the UK process used for the Red Book
- Consider impact of EU SoHO regulation and EuroGTPII tool

Through interactive discussion we aim to:

- Evaluate if the proposed changes would be effective for managing the blood component lifecycle
- Feedback on opportunities, risks or obstacles

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The Blood Guide monographs

The monographs today

Chapter 5 – Component monographs

- Part A. Whole blood components
- Part B. Red cell components
- Part C. Platelet components
- Part D. Plasma components
- Part E. White cell components

Chapter 6 – Component monographs for intrauterine, neonatal and infant use

- Part A. Components for intrauterine transfusion
- Part B. Components for neonatal exchange transfusion
- Part C. Components (small-volume) for neonatal and infant transfusion

Chapter 7 – Blood components for topical use or injection

- Part A. Components for topical use (serum eye drops)

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The monographs today – features

B-2. RED CELLS, LEUCOCYTE-DEPLETED IN ADDITIVE SOLUTION

Definition and properties

Red Cells, Leucocyte-Depleted in Additive Solution (LD-AS) is a red cell component derived from *Whole Blood* by removing the leucocytes, removing the majority of the plasma and adding an additive solution, or from leucocyte filtration of *Red Cells, AS* or *Red Cells, Buffy Coat Removed-AS (BCR-AS).*

Red Cells, LD-AS contains a minimum haemoglobin content of 40 g. The haematocrit is 0.50 to 0.70.

Red Cells, LD-AS contains less than 1×10^6 leucocytes.

Preparation

Generally, a filtration technique is used to produce *Red Cells, LD-AS.* Leucocyte depletion within 48 hours after donation is the standard.

Red Cells, LD-AS can be produced:

- By leucocyte filtration of *Whole Blood*, with subsequent centrifugation and removal of the plasma and immediate addition of the additive solution, followed by careful mixing;
- By leucocyte filtration of *Red Cells, AS* or *Red Cells BCR-AS.*

Requirements and quality control

As indicated for *Whole Blood, LD* except for the parameters specified in Table 5B-2.

Table 5B-2

Parameter to be checked	Requirements	Frequency of control
Volume [a]	To be defined for the system used	as determined by SPC
Haematocrit [a]	0.50–0.70	as determined by SPC
Haemoglobin per final unit [a]	Minimum 40 g	as determined by SPC

[a] A minimum of 90 % of units tested should meet the required value

Storage and transport

As indicated for *Whole Blood, LD.*

Labelling

As indicated for *Whole Blood, LD.*

Warnings

As indicated for *Whole Blood, LD* with the following addition:

- Not for exchange transfusion in newborns, unless used within 5 days of donation and only if the additive solution is replaced by fresh frozen plasma on the day of use.

The monographs today – features

"As indicated for *Whole Blood, LD*"

Requirements and quality control

Table 5A-2 lists the requirements. Additional testing may be required to comply with national requirements (see also Chapter 9 – Screening for markers of transfusion-transmissible infection).

Table 5A-2

Parameter to be checked	Requirements	Frequency of control
ABO, RhD	Grouping	All units
Anti-HIV 1 & 2	Negative by approved screening test	All units
HBsAg	Negative by approved screening test	All units
Anti-HCV	Negative by approved screening test	All units
Volume [a]	450 ± 50 mL volume (excluding anticoagulant) A non-standard donation should be labelled accordingly	as determined by SPC
Haemoglobin per final unit [a]	Minimum 43 g	as determined by SPC
Residual leucocytes per final unit [a]	$< 1 \times 10^6$	as determined by SPC
Haemolysis at the end of storage [a]	< 0.8 % of red cell mass	as determined by SPC

a A minimum of 90 % of units tested should meet the required value.

Storage and transport

Whole Blood, LD for transfusion must be kept at a controlled temperature between + 2 °C and + 6 °C *(Directive 2004/33/EC, Annex IV)*. The storage time depends on the processing system and anticoagulant/preservative solution used and should be validated.

Validated transport systems should ensure that the temperature does not go below + 1 °C or exceed + 10 °C over a maximum transit time of 24 hours. Transport times may exceed 24 hours if temperature conditions are maintained between + 2 °C and + 6 °C.

Whole Blood, LD for preparation of blood components may be kept between + 2 °C and + 6 °C. Alternatively, it may be kept for up to 24 hours between + 20 °C and + 24 °C, which is a prerequisite for the production of platelet preparations from *Whole Blood, LD*.

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The monographs today – features

"As indicated for *Whole Blood, LD*"

Labelling

The labelling should comply with relevant legislation and, where in place, international agreements. The following information on *Whole Blood, LD*for transfusion must be shown on the label or contained in the component information leaflet, as appropriate *(Directive 2002/98/EC, Annex III)*:

- The name of the blood component and the applicable product code;
- The volume or weight of the blood component;
- The unique donation (identity) number;
- The producer's identification;
- The ABO and RhD groups;
- The date of expiry;
- The storage temperature;
- The name of the anticoagulant solution.

The following additional information should be shown on the label or contained in the component information leaflet, as appropriate:

- The date of donation;
- Blood group phenotypes other than ABO and RhD (optional);
- Additional component information: irradiated, etc. (if appropriate);
- That the component should not be used for transfusion if there is abnormal haemolysis or other deterioration;
- That the component should be administered through an approved blood administration set.

Warnings

Compatibility of *Whole Blood, LD* with the intended recipient should be verified by suitable pre-transfusion testing.

RhD-negative female recipients of childbearing age or younger should not be transfused with red cells from RhD-positive donors.

Whole Blood, LD is not recommended in cases of:

- Anaemia without blood volume loss;
- Plasma intolerance.

Adverse reactions include:

- Haemolytic transfusion reaction;
- Non-haemolytic transfusion reaction (mainly chills, fever and urticaria);
- Anaphylaxis;
- Alloimmunisation against red cell antigens;
- Transfusion-related acute lung injury (TRALI);
- Post-transfusion purpura;
- Transfusion-associated graft-versus-host disease (TA-GvHD);
- Sepsis due to inadvertent bacterial contamination;
- Viral transmission (hepatitis, HIV, etc.) is possible, despite careful donor selection and screening procedures;

(...)

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The monographs tomorrow

Future ideas – restructuring

- **Requirements and quality control**: A **general** and a **specific** table

Why?

- Reported difficulty to interpret/find all applicable parametres

Example

- Red cells, cryopreserved

Example: B-9 Red cells, cryopreserved

Requirements and quality control

As indicated for *Whole Blood* or *Whole Blood, LD* (depending on whether the starting component is leucodepleted) except for the parameters specified in Table 5B-8.

Table 5B-9

Parameter to be checked	Requirements	Frequency of control
Volume[a]	> 185 mL	as determined by SPC
Haemoglobin in supernatant of final unit[a, b]	< 0.2 g	as determined by SPC
Haematocrit[a]	0.35–0.70	as determined by SPC
Haemoglobin per final unit[a]	Minimum 36 g	as determined by SPC
Osmolarity[a]	Maximum 20 mOsm/L above osmolarity of resuspending fluid	as determined by SPC
Microbial control	No growth	as determined by SPC

[a] A minimum of 90 % of units tested should meet the required value.
[b] Final suspending solution, as a process control for washing.

"Why should we not measure haemolysis?"

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The monographs tomorrow

Future ideas – restructuring

Requirements and quality control: A **general** and a **specific** table

- **General** table
  - Once per component group (whole blood, red cells, platelets, plasma, white cells)
  - No referens to other components (i.e. red cells will not refer to whole blood)
- **Specific** table
  - For every component
  - All relevant quality control and process control parameters, even if repeated

The monographs tomorrow

Future ideas – restructuring

Requirements and quality control: A **general** and a **specific** table

- **General** (first table per component monograph section):
  - ABO/Rh
  - Virus testing
  - Visual control including leakage
  - Irregular Abs
  - Microbiological control
- **Specific** (for every component, regardless of similar to other monographs):
  - Volume, residual cells, count, haemoglobin, haemolysis, glucose etc. (whatever is applicable for that specific component)

Blood component monographs

Archive

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The monographs tomorrow

Future ideas – monograph archive

- Only include state-of-the-art monographs
- "Archive" monographs that are "outdated"
  - Non-leucodepleted components?
  - Red cells stored without additive solution?
  - Others?
- CD-P-TS Annual Survey
  - ISBT-abstract on use of non-leucodepleted components

Abstract, ISBT 2024

Towards removal of non-leucocyte depleted blood components from European standards

L Larsson*[1,2], TRL Klei[3], K Baróti-Tóth[4], R Evans[5], HV New[6], ÓE Sigurjónsson[7], R Grubovic Rastvorceva[8,9], B Samuelsen Sørensen[10], V De Angelis[11], R Forde[8]

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Table 1. Red cell components (B-1 to B-6)

<20 %	20-40 %	40-70 %	>70 %

Main Component	Monograph	Attributes	% In use	% In use but phasing out	% In use but only as exception	% Not in use
Red cells	B-1	Leucocyte-depleted	38	0	9	53
	B-2	Leucocyte-depleted, in additive solution	97	3	0	0
	B-3	Non-leucodepleted	3	0	6	91
	B-4	Non-leucodepleted, buffy coat removed	12	0	3	85
	B-5	Non-leucodepleted, in additive solution	18	0	3	79
	B-6	Non-leucodepleted, buffy coat removed, in additive solution	24	3	3	71

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Table 2(a) Platelet components, recovered (C-1 to C-6).

Main Component	Monograph	Attributes	% In use	% In use but phasing out	% In use but only as exception	% Not in use
Platelets, recovered	C-1	Non-leucocyte depleted, single unit, in plasma	18	0	3	79
	C-2	Non-leucocyte depleted, pooled, in plasma	9	0	6	85
	C-3	Leucocyte depleted, pooled, in plasma	35	0	6	59
	C-4	Non-leucocyte depleted, pooled, in additive solution	15	0	0	85
	C-5	Leucocyte depleted, pooled, in additive solution	79	0	0	21
	C-6	Leucocyte depleted, pooled, pathogen-reduced	47	0	0	53

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Overall

- 56% of MS had completely removed non-leucodepleted components from their blood supply.
- 35% of MS still used non-leucodepleted red cells and another 35% still used non-leucodepleted platelets.
- Of the MS using either non-leucodepleted red cells or platelets, 75% were overlapping.
- No MS used non-leucodepleted components exclusively.

Conclusions

More than half of the MS already leucodeplete 100% of their blood supply. Additional MS are considering phasing out non-leucodepleted components, and in some cases, only using them as exception. No MS completely lacks leucodepleting measures. Collectively, the data suggest that leucodepletion is becoming state-of-the-art all across Europe. In line with acknowledged best practice to increase patient safety, this survey provides a solid basis for a future proposition to remove non-leucodepleted components from the Blood Guide.

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Novel blood components

What is a novel blood component?

- No existing monograph or specification?
  - Is there a similar monograph or a specification in other parts of the world?
- Made using novel processes?
- Are other Blood Establishments authorised to manufacture and supply?
- Made using novel equipment / consumables / additives?
  - Are they CE-Marked yet?
- Are the indications for use novel?
- What evidence is available to assess its safety and efficacy?

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UK process for assessing novel blood components

- Within the UK there is a well-established process for development of novel components and/or processes:
- New blood components are brought for advice and review through SACBC and JPAC for inclusion in Red Book
- Chapter 8 provides guidance on process, annex 3 lists provisional blood components

UK process for assessing novel blood components

Identify the need

Assess novelty (exclude standard components)

Characterise the new component

(phase 0)- Draft specification

Standing Advisory Committee on Blood Components (SACBC) / JPAC review

Add as a new specification (low novelty)?

Or Provisional blood component?

UK process for assessing “low” novelty blood components

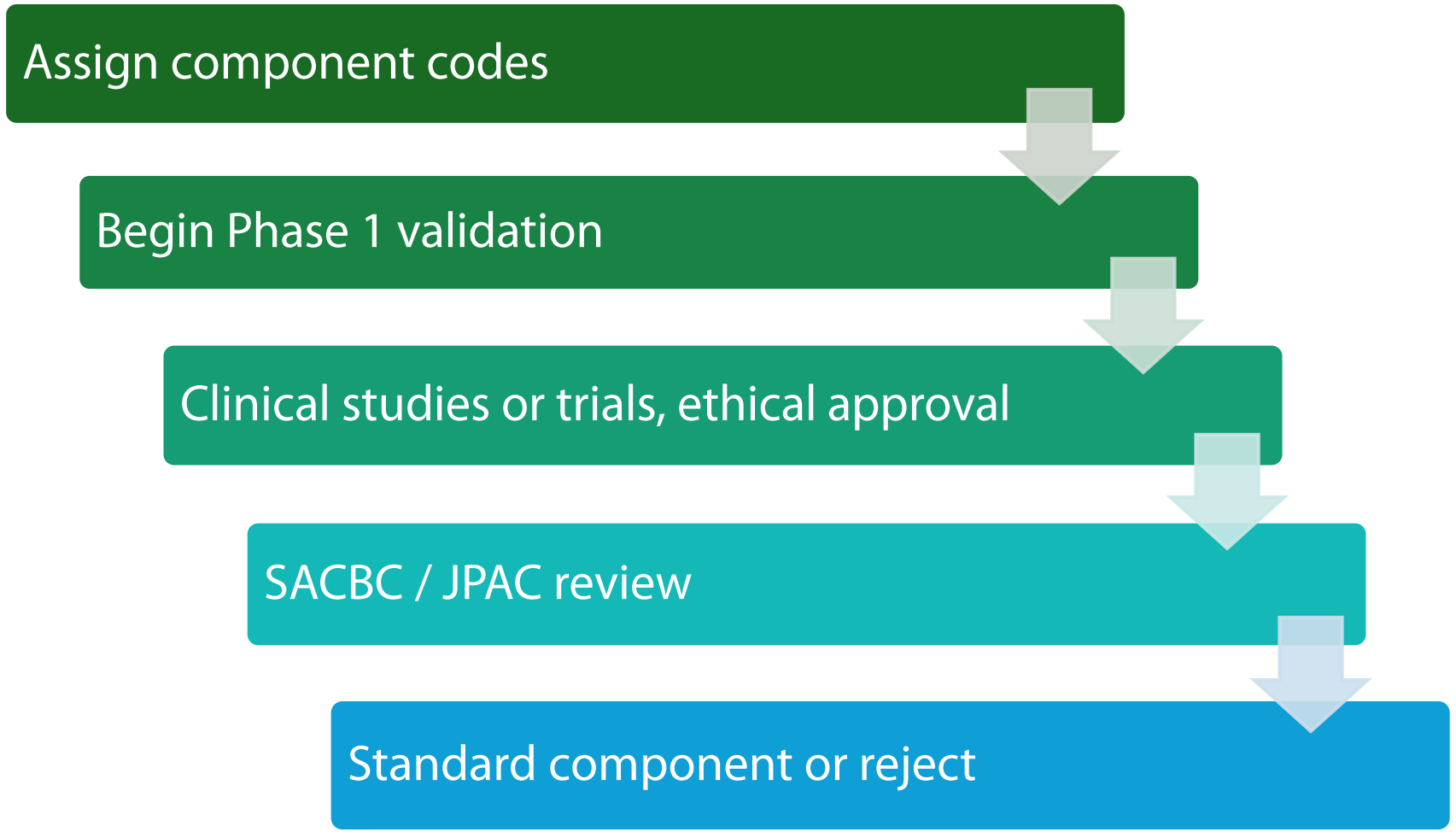
Assign component codes

Begin Phase 1 validation

Standard component

Other UK Blood Establishment can implement with local validation against specification

Provisional components - UK process for assessing "high to medium" novelty blood components



UK process for assessing novel blood components

Degree of novelty	Regulatory	Clinical data/experience	Extent of laboratory validation required	Clinical use
Very High	Produced using medical device/process that is **NOT** CE/UKCA/UKNI marked, or covered by manufacturer's IFU. A notice of no objection from the MHRA would be required for any trial.	No clinical use in humans	Extensive laboratory validation and data in relevant animal models. Likely to have to define all key critical variables that determine product quality.	First in man/phase I studies. HRA approval required and not to be used outside of approved study.
High	Produced using medical device that is **NOT** CE/UKCA/UKNI marked, or covered by manufacturer's IFU. A notice of no objection from the MHRA would be required for any trial.	Clinical data likely to be limited to small scale studies as part of R+D, or historical use or use outside of Europe.	Extensive laboratory validation. Likely to have to further define some critical variables in product quality.	Likely to be a phase II/III research study. HRA approval required and not to be used outside of approved study.

UK process for assessing novel blood components

Degree of novelty	Regulatory	Clinical data/experience	Extent of laboratory validation required	Clinical use
Low	Produced using medical device that is CE/UKCA/UKNI marked **WITHIN** its intended use & manufacturer's IFU. Currently NO specification in Red Book or not for the usage proposed. Likely to be a specification for product elsewhere e.g. Council of Europe or AABB guidelines. Use would not be precluded by content of BSQR or relevant EU directives. Use would require local validation and approval by SACBC/JPAC.	Not used recently in UK, or change in clinical use of an existing component. Might be in routine use elsewhere internationally but not the UK.	Extent of laboratory work guided by nature of change to be made and any uncertainties in published data e.g shelf-life.	Use might either be considered a change in clinical practice or as part of an approved research study, to be determined based on clinical usage/data to date. Use might be restricted in first instance to pilot sites. Safety might be monitored through haemovigilance which might be enhanced above standard based on risk.

UK process for assessing novel blood components

Degree of novelty	Regulatory	Clinical data/experience	Extent of laboratory validation required	Clinical use
Standard component (therefore not a 'provisional component specification')	Produced using medical device that is CE/UKCA/UKNI marked **WITHIN** its intended use & manufacturer's IFU. Has **APPROVED** specification in Red Book. In routine use in the UK and manufactured to approved specification in Red Book.	Widespread clinical experience from routine use in the UK and elsewhere.	Introduction would require local validation.	As per clinical guidelines.

UK process for blood component Life Cycle

Within the UK there is a well-established process for development of novel components and/or processes:

Process	Testing	Phase 0	Phase1	Phase 2 (see 8.7)	Local process validation
Whole blood collections	Component evaluation	10-16 See Tables 8.2 to 8.5	None	None	None
	Quality monitoring	10-16 100% tested	125 100% tested	2000 from each of two batches Minimum 1% tested or as determined by statistical process control	125 100% tested
Apheresis collection	Component evaluation	10–16 See Tables 8.2 to 8.5	None	None	None
	Quality nonitoring	10–16 100% tested	125 100% tested	300 100% tested	10 (each machine) 100% tested

Validation guidance:

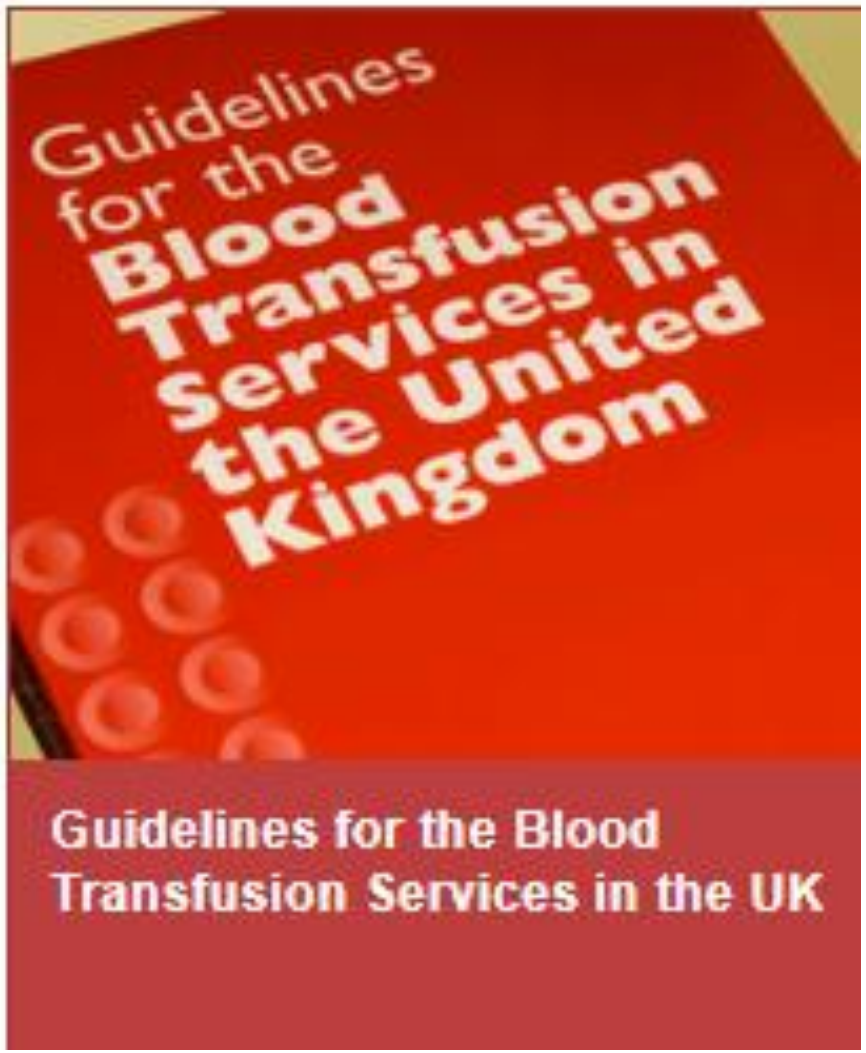
Phase 0 Provisional component specification

Phase 1 Operational validation

Phase 2 Post implementation review, haemovigilance

Recommended tests

UK process advantages



There are only Scotland, England, Wales and Northern Ireland Blood Establishments

All are National Services

All are represented on SACBC/JPAC

MHRA are also represented on JPAC as the competent authority for the whole of the UK

Red Book is online- quick to response to necessary updates

Provisional Components listed in Annex 3

Considerations for the EDQM Guide 23rd edition

- Currently the EDQM CoE guide 22nd edition does not contain "provisional" or trial components
- This has been discussed and may be considered by the EDQM GTS group for inclusion in the 23rd edition

Considerations for the EDQM Guide 23rd edition

- How do components become included as a monograph?
- Benefits:
  - share best practices
  - work towards a single specification

In summary

GAPP – EuroGTP II – Blood

EuroGTP II Process to assess the novelty of a new process or the revision of an existing process

Simonetta Pupella

Italian National Blood Centre - CNS

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Basic concepts

- An early access for patients to new blood components (BC) addressing unmet clinical needs, and/or providing potentially improved safety and efficacy, requires **adapted regulatory tools** and concepts using **risk-based approaches** to evaluate quality, safety, and effectiveness/efficacy of BC.

- **Clinical data** are required to evaluate novel BC or BC products prepared with newly developed methodologies.

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Application for SoHO preparation authorisation

"The SoHO establishments shall **submit applications** for SoHO preparation authorisation to the competent authority in their territory."

"Applications for SoHO preparation authorisation shall include the **results of a benefit-risk assessment** conducted in respect of the combination of the activities performed for the SoHO preparation, together with the intended clinical indication."

Article 39. Regulation 2024/1938 on standards of quality and safety for SoHO origin intended for human application

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Application for SoHO preparation authorisation

"In cases where the indicated risk is greater than negligible, or the expected clinical effectiveness is unknown, a proposed plan for clinical-outcome monitoring is proposed for providing further evidence, where necessary, for the SoHO preparation authorisation, in line with the results of the benefit-risk assessment."

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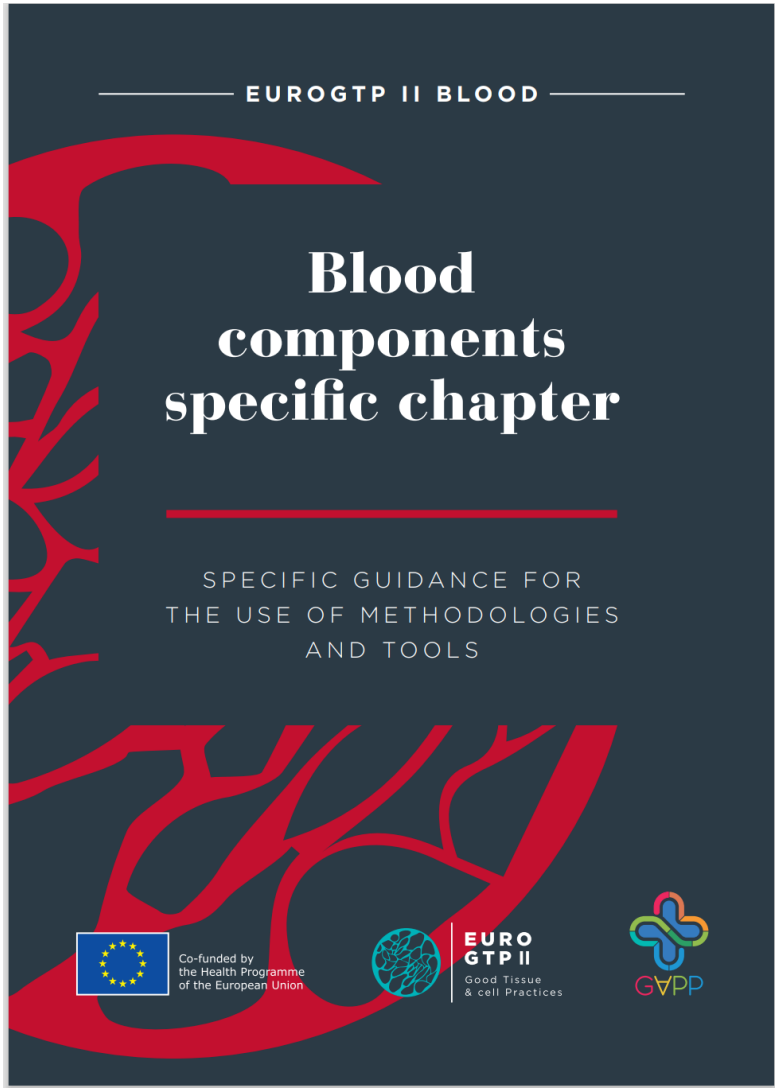
EuroGTP II Guide



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EuroGTP II Tool – methodology

1 **Identify**

- Novelty questions

2 **Evaluate**

- Justify the answers to the novelty questions

3 **Detect**

- Detect risk factors for each activities including the risk consequences

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EuroGTP II Tool – methodology

4 **Assessment of the risk reduction**. This step has the objective to adjust the risk score by taking into account other external sources of information (published data in peer reviewed literature, unpublished data from external sources, advice and information from external experts, clinical outcome data form external sources, etc.)

5 **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.

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2. LEVEL RISK ANALYSIS – steps 2a and 2b

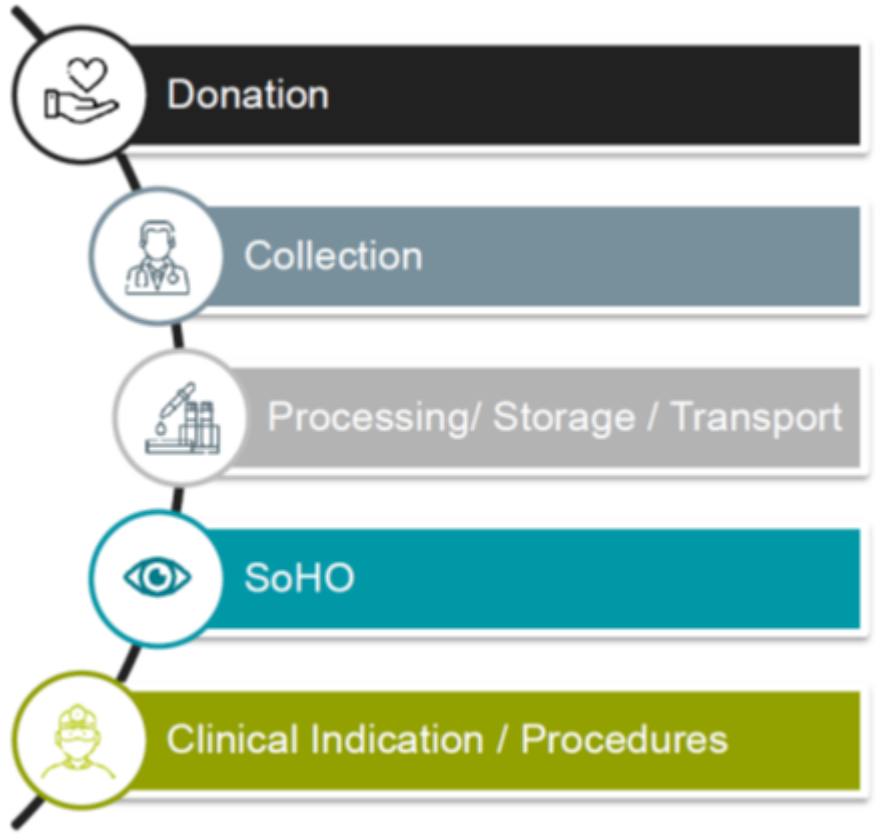
Identification of risk factors and risk consequences

Risk factors

i) Donor Characteristics
ii) Collection process and environment
iii) Processing and environment
iv) Reagents/Added components*
v) Reliability of Testing
vi) Storage Conditions
vii) Transport Conditions
viii) Presence of unwanted residues
ix) Clinical indications

Risk consequences

i) Unexpected immunogenicity
ii) Failure to perform clinically*
iii) Disease transmission
iv) Toxicity/Carcinogenicity
v) Other



***Clinical performance:** The ability of a BC to yield results that are correlated with a particular clinical condition or a physiological or pathological process or state in accordance with the target population and intended user.

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2. LEVEL RISK ANALYSIS – step 2c

Quantification of the risk

i) The probability of the risk occurring.

LEVEL OF PROBABILITY

ii) The severity of the consequences should the risk occur.

LEVEL OF SEVERITY

iii) The probability that the source of the harm for the risk consequences will be detected before the BC is transfused/applied.

LEVEL OF DETECTABILITY

iv) Any existing evidence that can be used to mitigate the risk.

PERCENTAGE OF RISK REDUCTION

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RISK SCORING

EuroGTP II Algorithm for the calculation of Final Risk Score

1. Estimate the Preliminary Score associated with the BC:

$$\text{Preliminary Score} = \Sigma \text{ risks} = \Sigma ((S \times P \times D) - ((S \times P \times D) \times (\% \text{ risk reduction}))$$

P = Probability
S = Severity
D = Detectability

The combined risk is determined following the described steps:

$$\text{Combined Risk Value} = \frac{\text{Preliminary Score} \times \text{Highest Possible Score}}{(\text{Max S} \times \text{Max P} \times \text{Max D} \times \text{Number of Applicable Risks Consequences})}$$

Max P = 5
Max S = 4
Max D = 5

Applicable Number of Risks Consequences = Range from: 1 to 45

Highest Possible Risk Score = (Max S × Max P × Max D × Number of Risks) × Risk Factors = 4500

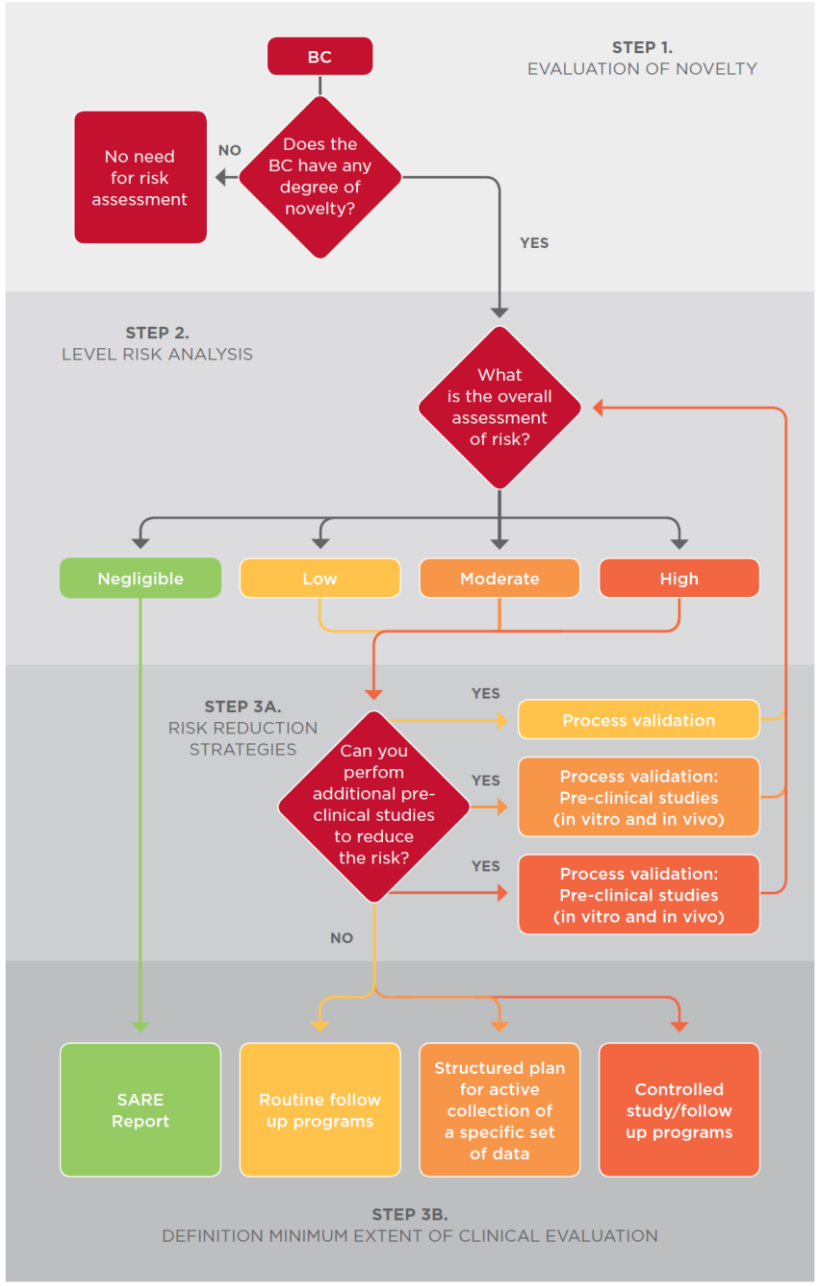
$$\text{Final Risk Score} = \frac{\text{Combined Risk Value} \times 100}{\text{Highest Possible Score}}$$

Two ancillary rules have been implemented in the algorithm to ensure that individual highly scored risks are not masked by adding various low risk scores. Thus, independently of the determined Final Risk Score, individual risks with scores higher than 30, result in “moderate risks” and, individual risks with scores higher than 50, result in “high risks”.

0 - 2
>2 - 6
>6 - 22
>22

Risk levels	Type of clinical follow-up plan
Negligible risk	Standard vigilance procedures should be in place and verified to be in compliance with the EUTCDs/EUBDs SARE reporting requirements.
Low risk	Negligible risk criteria apply. Appropriate recipient’s clinical progress should be documented by the physician as foreseen in normal clinical practice. In addition, a clinical follow-up plan has to be established that monitors the patients regularly. Results to be reported by the clinician to BE/TE and/or CA should be specified. A periodic review of pertinent literature has to be undertaken with results to be summarized and to be submitted to the BE/TE and/or CA.
Moderate risk	Low risk criteria apply. The clinical follow-up plan should be designed to specifically consider potentially critical clinical side effects. These should be monitored through a defined typology/frequency of controls. They should where possible fit into the standard medical practice. The clinical follow-up study should be supplemented where possible by registry data, if possible at a European level.
High risk	Moderate risk criteria apply. Systematic collection of safety/effectiveness results through observational or clinical trials, according to GCP principles. Protocol designed to detect unidentified risks and reduce level of uncertainty /lack of knowledge, if applicable compared to standard therapy.

OVERALL FLOW



GAPP

EURO GTP II
Good Tissue & cell Practices

Co-funded by the Health Programme of the European Union

Methodologies for Assessing the Risks
associated to novel Blood Components (BC)

The IAT is accessible on-line (**https://bloodtool.goodtissuepractices.site/**).

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Learning objectives

- You will be shown an example of a processing change proposed by a Blood Establishment (BE)
- Based on the information provided, you will:
  - Evaluate if the proposed change has significant novelty
  - Identify the risk factors that are impacted by the proposed change
  - For each **risk factor**, you will identify the relevant **risk consequences** that require assessment
- We will not carry out the individual risk assessments, as these require specific expertise, detailed information and significant time commitment. However, you may wish to attempt these in your own time, using the EuroGTPII interactive assessment tool

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Case study: Cold Stored Platelets (CSP)

- With the recognition of the hemostatic efficacy of cold-stored platelets (CSP) contained in whole blood, platelets stored at 4°C are emerging as a potentially beneficial product.

- Although CSP have documented lower recovery and survival, lower yields, and morphological changes, they have an activated profile, which may result in greater hemostatic efficacy as compared to room temperature platelets, especially in acutely bleeding patients*.

*Reddoch-Cardenas KM, Bynum JA, Meledeo MA, Nair PM, Wu X, Darlington DN et al. Cold-stored platelets: a product with function optimized for hemorrhage control. Transfus Apher Sci 2019;58(1):16–22.

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Case study: Cold Stored Platelets (CSP)

- Your BE provides blood components for Hospital Blood Banks (HBB) in different hospitals.
- Some supplied hospitals asked for availability of cold storage platelets (CSP) for assisting cardio surgery patients.
- Your BE decides to introduce the preparation process of CSP from WB to accomodate to the request.
- Your BE routinely prepares platelets, stored at room temperature (RT) for 5 days
- The preparation process of CSP includes also an extension of the storage time from 5 to 7 days.

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EuroGTP II novelty questions

		YES	NO	NA
1.	Has this type of BC* previously been collected, processed/prepared and issued for clinical use by your establishment?			
2.	Will the starting material used to prepare this BC be obtained from the same donor population previously used by your establishment for this type of BC*?			
3.	Will the starting material for this BC be procured/collected using a procedure used previously by your establishment for this type of BC*?			
4.	Will this BC be prepared by a procedure (processing/preparation, decontamination/pathogen reduction and preservation) used previously in your establishment for this type of BC*?			
5.	Will this BC be packaged, stored and distributed using a protocol and materials used previously in your establishment for this type of BC*?			
6.	Will this type of BC* provided by your establishment be applied/infused clinically using an application/transfusion/infusion method used previously?			
7.	Has your establishment provided this type of BC* for the same clinical indication or for application/transfusion/infusion into a same anatomical site?			

* Should be interpreted as the type of BC (examples: platelets, red cells, plasma).
It aims to ask if despite the novelty your Blood Establishment (BE) has experience handling this BC.

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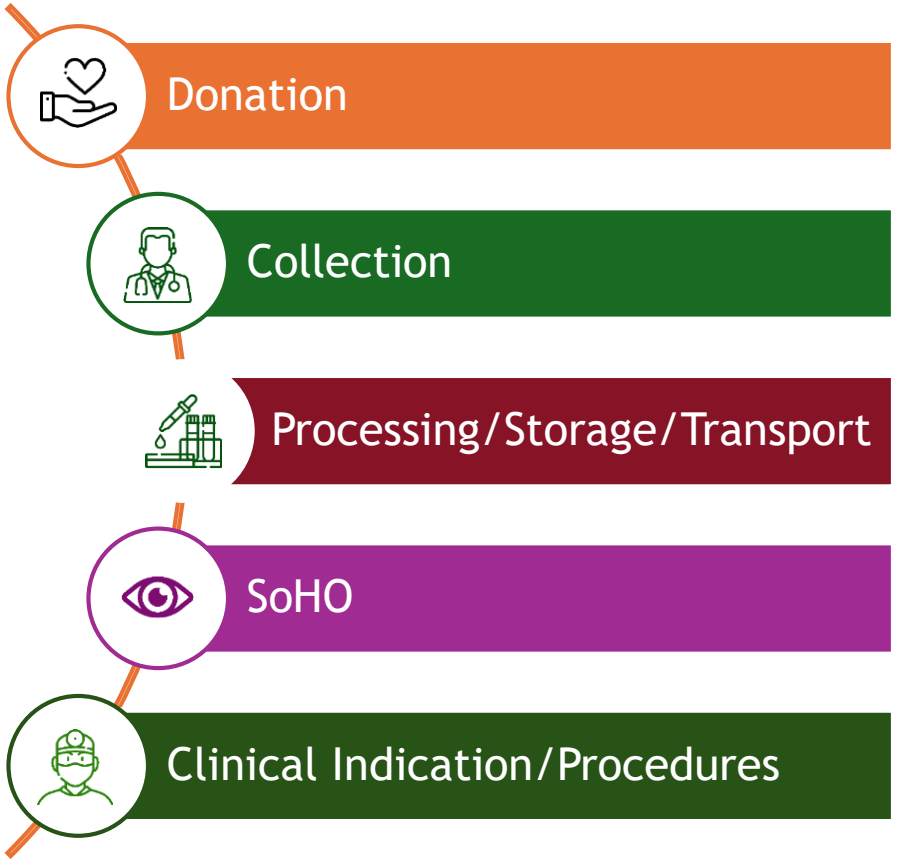
Risk consequences

1. Unexpected immunogenicity
2. Failure to perform clinically ✓
3. Disease transmission
4. Toxicity / carcinogenicity
5. Other



	Risks factors	Explanation	Risks	Examples/Explanations
Processing/storing/transport	**Storage Conditions**	Consider any potential risk arising from how the BC are stored, between collection and processing, during processing, and between processing and transfusion.	Unexpected immunogenicity	Can a change in the plastics (e.g. DEHP) of primary packaging cause enhanced immunogenic material in the BC
			Failure to perform clinically	Could the storage temperature affect the functionality of the BC (cells, factor VIII, etc.)?
			Disease transmission	Could the storage temperature increase the risk of an extant contamination? (e.g. Room temperature vs Cooling)
			Toxicity/ Carcinogenicity	Can the material of the primary container cause toxic reactions in the recipient of the BC?
			Other	No example provided: Consider other risks if applicable
	Transport Conditions	Consider any potential risk arising from how the BC are transported. For example, between the sites of collection and processing, and between the sites of storage and transfusion.	Unexpected immunogenicity	Can the transport conditions damage the cells and produce an unexpected immunogenic reaction in the recipient?
			Failure to perform clinically	Can the duration of the transport/shipment influence the quality/number of relevant cells present in the component?
			Disease transmission	Could the duration of the transport induce the risk of an extant contamination?
			Toxicity/ Carcinogenicity	Could transport conditions (e.g. heavy shaking) lead to damage of the packaging and chemical contamination of the BC.
			Other	No example provided: Consider other risks if applicable

Blood Component	**Presence of unwanted residues**	Consider the risk of the presence of unwanted/ excess cells/cellular residues originating from the donated component.	Unexpected immunogenicity	Do centrifugation forces during apheresis cause the presence of cell debris?
			Failure to perform clinically	Could the presence of inactivated cells lead to failure to perform clinically?
			Disease transmission	It is unlikely this combination of risk and risk factor could occur associated with BC
			Toxicity/ Carcinogenicity	It is unlikely this combination of risk and risk factor could occur associated with BC.
			Other	No example provided: Consider other risks if applicable

Quantification of risk: Scoring the risk consequences

Which is the scoring for "failure to perform clinically"?

LEVEL OF PROBABILITY
1 - Rare
2 - Unlikely
3 - Possible
4 - Likely
5 - Almost certain

LEVEL OF SEVERITY
1- Non-serious
2- Serious
3- Life-threatening
4 - Fatal

LEVEL OF DETECTABILITY
1 - Very high
2 - Moderately high
3- Low
4 – Very low
5 - Cannot be detected

PERCENTAGE RISK REDUCTION	
0	None
25	Limited
50	Moderate
75	Substantial
95	Extensive

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Risk Score

>2 - 6	Low Risk

Low

Step 3A. Risk reduction strategies

Implementing a standard procedure or treatment in a BE that might be in routine use elsewhere internationally, but has never been performed in the BE. This procedure requires an **intensive validation**. Training of staff is necessary in order to reach the outcomes published in scientific literature.

A learning curve might be expected and should be part of the validation report. When implementing the procedure, additional quality controls must be performed to **monitor Critical Process Parameters (CPPs) and Critical Quality Attributes (CQAs)**.

Step 3B. Extent of clinical investigation

The clinical use of the novel BC or therapy should be done as defined in clinical guidelines.

A **safety Clinical Follow-up Plan (CFUpP)**, proportionate to the level of risk, should be implemented. The use of the novel BC/therapy might be restricted in the first instance to pilot sites. Safety might be monitored through haemovigilance which might be enhanced above standard based on risk.

Follow up procedures should also focus on assessing efficacy, comparing the clinical follow up with the results obtained before the implementation of the change in the process and in relation to the results published in scientific literature.

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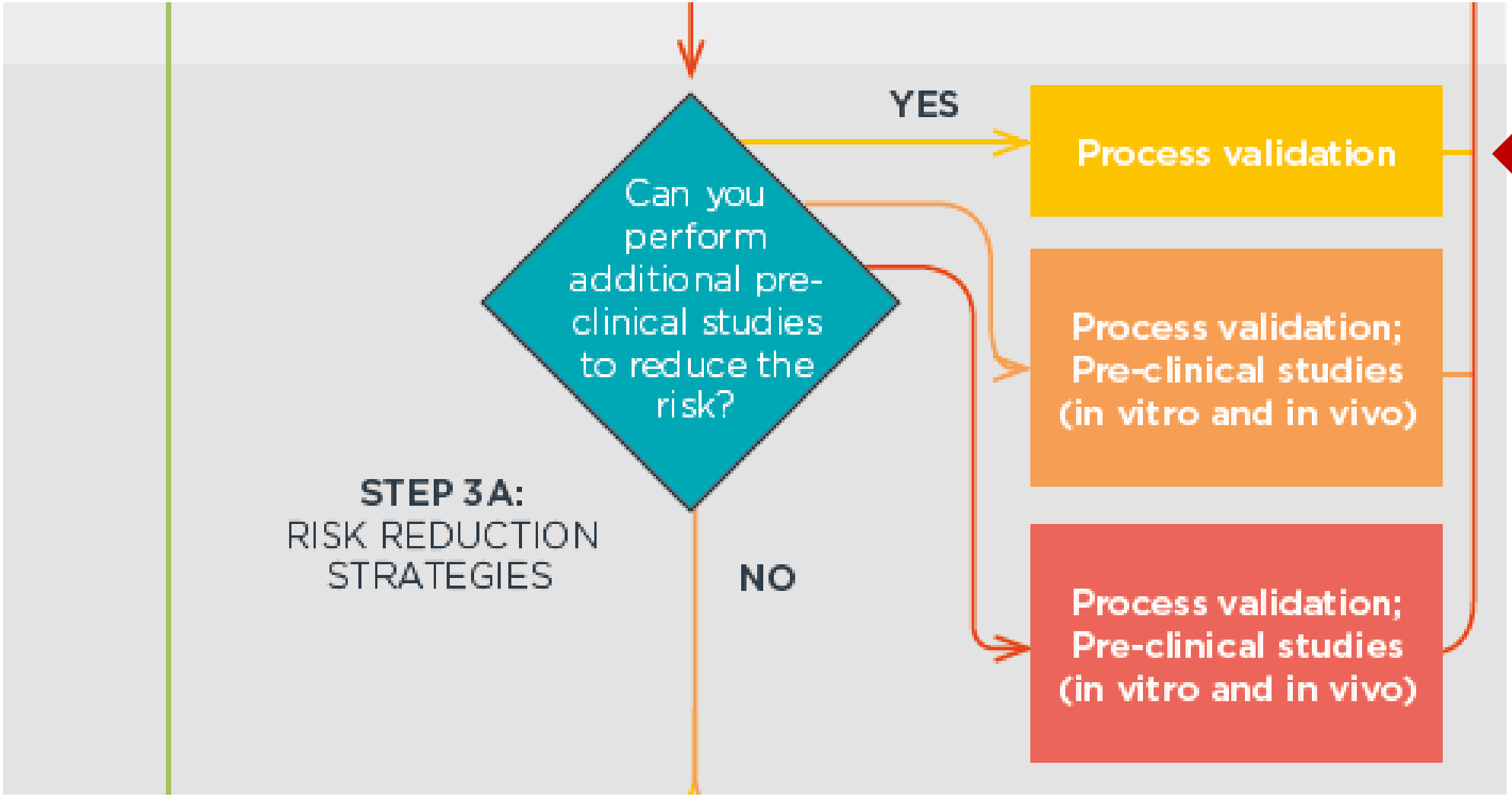

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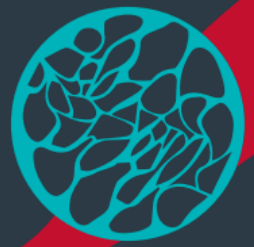

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Closing remarks

Closing remarks

Blood component monograph life cycle:

- Maintaining the monographs
- Monograph Structure
- Archiving of Monographs

Novel blood components

- Provisional Monographs
- Authorisation – Euro GTPII Tool

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