Guidelines for the Blood Transfusion Services

8.1: Aims and introduction

http://www.transfusionguidelines.org/red-book/chapter-8-evaluation-of-novel-blood-components-production-processes-and-blood-packs-generic-protocols/8-1-aims-and-introduction

8.1: Aims and introduction

This chapter aims to describe how a proposed novel blood component, production process or blood pack is to be evaluated to:

- gain sufficient data to validate the component and production method
- gain sufficient data to support the clinical use of the component
- allow the Standing Advisory Committee on Blood Components (SACBC) to recommend to the Joint UK Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC) that the component should be included in the Red Book, either within the 'Specifications for blood components' section or as a Provisional Component specification in the 'Provisional Components' section
- provide sufficient information to prevent all Blood Establishments (other than those performing a full evaluation) from having to complete a full validation of the novel component before it enters routine production. They will only need to undertake installation and process validation.

The chapter starts by identifying the steps that a group of investigators will need to undertake to submit a novel blood component for inclusion in the Red Book (see Table 8.1a), thereby allowing it to be produced on a routine basis throughout the UK. Guidance on assessing the degree of novelty of components prior to embarking on the process is given in Table 8.1b.

It is recognised that some novel components may be developed by a group of investigators in conjunction with a commercial company undertaking speculative research. As a result, the group of investigators may wish to enter the process at Step 8. In this case the SACBC will expect any requirements for data collection in the preceding steps to be complied with when the protocols and reports are submitted to the SACBC Chair for consideration. If sufficient data are not included then a request for extra data will be made (Step 9).

It is also recognised that there may be a need for Blood Establishments to produce blood components for clinical use on a temporary basis. This may be to undertake a clinical study or operational assessment of a new component in order to inform the decision as to whether there is a need to manufacture the component on an ongoing basis. In such circumstances the most appropriate course of action is to seek approval for a Provisional Component specification (see section 8.1.1 and Table 8.1c).

Guidance on how specific novel components should be tested is included in sections 8.2–8.5, and is followed by information on generic protocols for the evaluation of apheresis equipment (section 8.6) and blood packs (section 8.7). For guidance on phases of validation and sample size, please refer to Table 8.1d

Table 8.1a Steps for evaluation of novel components

Step	Details	Information
1. Investigators identify requirement for a novel blood component.	The requirement must be derived from R&D work or as the result of clinical discussions. The blood component needs: • to fulfil an unmet clinical need OR • provide production benefit and have a Blood Service proposer. Investigators will need preliminary data to support their application.	The new component may be derived from a commercially available product. In this case data to support the submission may be derived from the manufacturer. Investigators must critically appraise data already available. All data must be maintained on file. Data will be used to demonstrate validation has been completed in support of Blood Establishment licensing activities. Data required may include clinical outcome.
2. Investigators may obtain initial advice from the SACBC Chair as to whether the component should be treated as novel. Table 8.1b describes likely degrees of novelty and clinical use of components.	Yes: Go to Step 3. No: Undertake local validation and produce the component locally under the general principles of good manufacturing practice and the Red Book (Phase 1, Table 8.1d).	The proposed new component may require evaluation even if it complies with existing Red Book guidelines if: • a new production technique is involved (e. g. leucocyte-depleted red cells produced by apheresis). • there are different steps in the production process (e.g. white-cell filtration immediately following collection). • definitive advice about the need for full-scale evaluation will be provided from the SACBC following a written submission.
Characterise the new blood component		

3. Investigators define the intended specification for the blood component.	Written specification to include: • expected characteristics (e.g. leucocyte count) • testing characteristics (blood grouping, microbiology etc.) • sampling time, sampling method and sample handling conditions to confirm that the component meets specification. Reference should also be made to the research papers from which the specification is derived.	Specify all key points which will allow subsequent production of the component to be well controlled.
4. Write the protocol for component evaluation (Phase 0).	Investigators' group writes procedures for: • component production • monitoring of performance • clinical use • outcome measurement • adverse incidents in production/use of the blood component or uses manufacturer's documentation to produce 'in-house' protocols.	Principles of good clinical and good manufacturing practice should apply. Comply with generic protocols (Table 8.1d and sections 8.2–8.7). Laboratory studies should comply with local standards. Must include in the procedure the sampling regimes, data analysis and expected ranges, which will be used to confirm that production of the component is under control. Must include detail of the data analysis methods.
5. Investigators should ensure their protocol complies with Chapter 8 and may seek advice from the SACBC.		
6. Obtain ethics committee approval, if required.		Must comply with local consenting and ethics policies for the use of donated material.

7. Investigators apply protocol.	Document evidence of protocol being implemented. Investigation should be subject to independent quality audit.	Audit may be carried out on behalf of collaborating manufacturers even though this may be confidential regarding the data collected. A summary outlining non-compliances against good clinical and manufacturing practice must be made available to the Blood Transfusion Service involved, for submission as part of the supporting documentation to the SACBC.
Obtain SACBC listing of the component		
8. Investigators submit report and supporting data and a draft Component specification to the SACBC for consideration.	Investigators review outcomes and produce a report, which summarises findings and supports the case for a new blood component to be listed. The SACBC decides if: • the blood component is novel • the data support the ability to produce the blood component on a regular basis • the blood component is efficacious and safe.	Investigators who have been conducting speculative research with a manufacturer may enter the process at this point. This may also include data supplied by manufacturers, other Blood Services, and published studies. Investigators should submit a draft specification for the component.
9. The SACBC decides whether the component may be recommended for inclusion in Chapter 7, the 'Specifications for blood components' section of the Red Book guidelines.	If the SACBC decides that the blood component will be listed, it submits this recommendation to the JPAC, providing copies of the data and report used to accept the new blood component. If the SACBC decides that the blood component will not be listed, it informs the submitting group and provides an explanation.	The SACBC may request further data in support of the submission prior to listing the blood component.
Joint Professional Advisory Committee		

10. Consider the recommendation that a new component should be listed.	Notify the SACBC of the decision. If not accepted, provide the SACBC with detailed reasons for the decision. If accepted, notify Medical Directors and Quality Managers of the four UK Blood Transfusion Services. Include the Component specification in Chapter 7 of the Red Book guidelines.	
SACBC		
11. Communicates the JPAC decision to appropriate parties.	If accepted inform investigators who must complete a Component Code Request form and submit to Chair of the SACBC. The form is assessed by the SACBC and if approved this request is passed to the SACIT to proceed with the provision of appropriate labels. If not accepted inform investigators, with supporting reasons.	Component Code Request form is available in the Document Library on the JPAC website (which also includes guidance on requesting codes for non-novel components).
SACIT		
12. Provides codes for the new blood component.	Code will be unique. ISBT 128/ABC Codabar will be supported.	
13. Provides a component label and updates the UKBTS Component Portfolio.	Label will be unique. Completed Component Code Request form returned to the SACBC and requestor.	Label text will describe the key attributes of the component.
Blood Establishment		
14. Begin production of the new blood component.	Base procedures on those used during validation studies. Complete installation and process validation (Phase 1, Table 8.1d).	Demonstrates without redoing the above validation that the blood component produced is equivalent to that defined in the UK guidelines.

15. Produce the blood component routinely.	Confirm procedures.	Continue to monitor production to the Red Book specification (Phase 2, Table 8.1d or routine quality monitoring).

Table 8.1b Degrees of novelty of 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.
Medium	Produced using medical device that is CE/UKCA/UKNI marked, but **OUTSIDE** of its intended use or manufacturer's instructions for use (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/small scale clinical use or use.	Laboratory validation required guided by data to date and intended use. Likely to have to validate changes to key variables such as temperature or duration of storage.	Likely to be a phase II /III research study. HRA approval required and not to be used outside of approved study.

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.
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.

8.1.1: Provisional Component specification

This process should be used where it is uncertain whether there will be a requirement to produce the novel component on an ongoing basis, yet there is a need for clinical use of the component. Provisional Component specifications once approved will be posted in the 'Provisional Components' section of the Red

Book.

The purpose of approval of a provisional component specification is to:

- ensure that there is sufficient data to support progression from phase 0 to phase 1 & 2 studies and the clinical use of the component.
- document a draft specification for the component including suitable quality monitoring parameters and testing regime for phase 1 and 2 studies.

Table 8.1c Steps for approval of a provisional component specification

Step	Details	Information
Investigators undertake steps 1-7 in Table 8.1a.	Gather Phase 0 and other data necessary to proceed to step 8.	Seek advice from SACBC in advance with respect to validation requirements if needed.
Obtain SACBC listing of the provisonal component		
8. Investigators submit report and supporting data and a draft Provisional Component specification to the SACBC for consideration.	Investigators review outcomes and produce a report, which summarises findings and supports the case for a provisional component to be listed. The SACBC decides if: • the blood component is novel • the data support the ability to produce the blood component for its intended use • the blood component is efficacious and safe. • the specification and associated quality monitoring for subsequent phases of study are adequate • data support progression to phase 1 & 2 studies and clinical issue of the component.	Investigators who have been conducting speculative research with a manufacturer may enter the process at this point. This may also include data supplied by manufacturers, other Blood Services and published studies. Investigators should submit a draft specification for the component.
9. The SACBC decides whether the component may be recommended for inclusion in the 'Provisional Component' section of the Red Book guidelines.	If the SACBC decides that the blood component will be listed, it submits this recommendation to the JPAC, providing copies of the data and report used to accept the new blood component. If the SACBC decides that the blood component will not be listed, it informs the submitting group and provides an explanation.	The SACBC may request further data in support of the submission prior to listing the blood component.
Joint Professional Advisory Committee		

10. Consider the recommendation that a new component should be listed.	Notify the SACBC of the decision. If not accepted, provide the SACBC with detailed reasons for the decision. If accepted, notify Medical Directors and Quality Managers of the four UK Blood Transfusion Services. Include the Component Specification in the 'Provisional Components' section of the Red Book guidelines.	
SACBC		
11. Communicates the JPAC decision to appropriate parties.	If accepted inform investigators who must complete a Component Code Request form and submit to Chair of the SACBC. The form is assessed by the SACBC and if approved this request is passed to the SACIT to proceed with the provision of appropriate labels and component code. If not accepted inform investigators, with supporting reasons.	Component Code Request form is available in the Document Library on the JPAC website (which also includes guidance on requesting codes for non-novel components).
SACIT		
12. Provides codes for the new blood component.	Code will be unique. ISBT 128/ABC Codabar will be supported.	
13. Provides a component label and updates the UKBTS Component Portfolio.	Label will be unique. Completed Component Code Request form returned to SACBC and requestor.	Label text will describe the key attributes of the component.
Blood Establishment		
14. Proceed to phase 1 & 2 studies.	Base procedures on those used during validation studies. Complete installation and process validation.	Monitor component against trial specification.
15. Decide if there is a need to produce the component on an on-going basis.		Submit report on phase 1 and 2 studies and clinical data if relevant to SACBC and the final specification for the component to be included in the Red Book.

Table 8.1d Summary of testing numbers required for evaluations and validations

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