PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

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PIC/S GUIDANCE DOCUMENT FOR INSPECTORS

PIC/S AIDE MEMOIRE TO INSPECTIONS OF BLOOD ESTABLISHMENTS (incl. hospital blood banks) AND PLASMA WAREHOUSES

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1. DOCUMENT HISTORY

Adoption by the PIC/S Committee	3 June 2003
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2. INTRODUCTION

2.1 The quality and safety of products derived from human plasma rely both on the source plasma material and the further fractionation processes. Therefore, the collection, testing, storage and transport of human plasma to the fractionation company are major factors in the quality assurance of the manufacture of biological medicinal products.

2.2 Plasma for further fractionation can be collected by apheresis (source plasma) or be obtained from whole blood collections (recovered plasma). Donation testing is often performed in separate laboratories. The storage of plasma and/or whole blood is performed in the collection centre/at the processing site itself for an intermediate time period and in bigger (central) warehouses - often associated with the fractionation site – for longer periods of time.

Collection of human plasma for further fractionation as well as testing must follow Good Practice Guidelines (GPG) while all subsequent steps (processing/freezing, storage and transport) should be in line with Good Manufacturing Principles (GMP) in order to ensure the expected product quality.

2.3 Criteria for companies collecting and testing human plasma for further fractionation are defined in different documents, especially the “PIC/S Good Practice Guidelines” (PE 005). Basic GMP requirements for the subsequent steps (processing/freezing, storage and transport) are laid down particularly in the “PIC/S Guide to Good Manufacturing Practice for Medicinal Products” (PE 009) or its Annex 14 “Manufacture of Products derived from Human Blood and Human Plasma”. Additional requirements may be defined at the national or regional level[1].

3. PURPOSE

3.1 It is recognised that due to their background and experience the majority of GMP inspectors are more familiar with the inspection of finished products. Therefore, to assist inspectors not specialised in the inspection of blood establishments (incl. hospital blood banks) collecting, processing and storing human plasma for fractionation this document has been developed to provide training and guidance for the preparation and performance of such inspections.

3.2 This Aide-Memoire should also contribute to a harmonised approach for inspections of such blood establishments between the different PIC/S Members.

[1] For example the European Pharmacopeia monograph on “Human Plasma for Fractionation” in the EU.

4. SCOPE

4.1 This Aide Memoire focuses on the preparation of inspections of blood establishments (incl. hospital blood banks) for the collection of source and/or recovered plasma and of source plasma warehouses (hereafter referred to as organisations) taking into account chapters and/or sections of GPG (PE 005).

4.2 The Aide Memoire also provides information on GMP requirements for storage of plasma. Generally, the same GMP criteria are applicable for the storage of plasma in collection facilities (e.g. reach-in or walk-in freezers) and in bigger facilities (e.g. a central plasma warehouse), the information applies to both kind of facilities if not otherwise indicated.

4.3 The Aide Memoire is supplemented by two additional PIC/S documents [Site Master File for Source Plasma Establishments (SMF-SPE in PI 019)) and Site Master File for Plasma Warehouses" (SMF-PW in PI 020)]. Both have been adapted to the special requirements of source plasma establishments and source plasma warehouses and will be regularly adapted to current facts, if necessary.

4.4 At the time of issue, this document reflected the current state of the art. It is not intended to be a barrier to technical innovations or the pursuit of excellence.

5. AIDE MEMOIRE

1. General Considerations

Inspection Element	Workflow	Supporting documents
Preparation of a plasma inspection	Review of inspection history.	- Inspection reports, follow-up and outcome of any previous inspections carried out
	Review the most recent information on collection centers and activities, storage and transport companies, look back notification requirements, freezing requirements, etc.	- Manufacturing authorisation, license and/or Plasma Master File
	Prepare and distribute inspection announcement / notification letter: incl. inspection date and team, scope, legal framework and a request for documents required for the preparation.	
	Request documents to prepare for the inspection, e.g. Site Master File, organisational chart, floor plans, list of critical equipment (e.g. freezers) incl. qualification/validation status, qualification /	

	validation reports of critical equipment / processes, quality manual (incl. list of SOPs), SOPs (e.g. donor eligibility and deferral criteria, processing, release), lists of changes, deviations, look backs/recalls, and sub-contracts.	
	Prepare and distribute the inspection agenda: including scope (initial inspection, regular inspection, re-inspection, triggered inspection, etc.), inspection team, dates and timelines, routine/general inspection or focus on specific areas.	- Documents requested in preparation of the inspection such as previous inspection reports and information from additional sources (e.g. other agencies)
	Prepare inspection plan based on the agenda: checklist covering general and / or specific aspects based on inspection focus (e.g. donor selection, processing), follow-up from previous inspections.	- Documents requested in preparation of the inspection such as previous inspection reports and information from additional sources (e.g. other agencies)
Opening meeting	Welcome and short overview by the lead inspector: scope and legal framework, brief discussion of the agenda and preliminary timelines to limit interference with routine operations.	- Inspection notification and agenda
	Tour de table: introduction of inspection team and organisation representatives (management and key personnel including the QA person).	- List of participants
	Getting an overview of the company's organisation and activities.	- Presentation by the company, e.g. short overview of the overall organisation, the facility, the quality management system - Review of the SMF incl. registrations/ licenses, organisational charts, floor plans, specific products/ programmes (e.g. immunisation programmes) - information on significant changes (since the last inspection and planned)

Tour of the facility	In general, follow the donor/product flow covering areas critical to the quality/safety of the product (e.g. donor selection, collection, processing, storage, distribution/transport).	- floor plan incl. flow of donors and donations
	The inspection should cover thorough observation of staff conducting duties and comparison with defined written procedures as well as a check of rooms and equipment. Special attention should be given to relevant deficiencies of the previous inspections (if applicable) and their rectification.	- Inspection reports, follow-up and outcome of any previous inspections carried out
	The donor's consent should be obtained prior to the observation of donor screenings and physical exams. In general, observation of physical exams should by conducted in a confidential manner and the donor should be presented with an opportunity to disclose any personal information without the inspector's presence.	
	Premises: • Size, layout, lighting, etc. • Donor, product flow and waste flow • Maintenance & cleaning • Access control • Temperature/humidity control & monitoring • Eating, drinking and chewing should not be allowed in production areas incl. the donor floor (except for reactions)	- PE 005-4 - Good Practice Guidelines For Blood Establishments and hospital blood banks, chapter 3
	Equipment: • Maintenance • Log books • Handling of defective/out of service equipment and repair • Temperature control & monitoring (e.g. freezers)	- PE 005-4 - Good Practice Guidelines For Blood Establishments and hospital blood banks, chapter 4
	Personnel: • Available in sufficient number? • Appears well trained and knowledgeable?	- PE 005-4 - Good Practice Guidelines For Blood Establishments and hospital blood banks, chapter 2
	Observations should be discussed with key personnel as they arise but preferably not in the presence of donors.	

Final meeting	Findings should be summarised and the outcome of the inspection should be discussed with management and key personnel of the company including the QA person of the organisation.	- List of findings and pending issues
	Critical observations should be highlighted. The final classification of remaining deficiencies should be done in the office of the Competent Authority.	
	Corrective actions should be initiated at the earliest date.	
	Explanation of further steps, e.g. inspection report and distribution thereof, timeline for company responses, issuance of license.	
Inspection report	Should contain, e.g. reason for the inspection (routine, regular, follow-up, re-inspection, etc.), participants, any major changes, brief report of inspection activities undertaken, observations, relevant attachments, timelines for company responses.	- PIC/S Inspection Report Format (PI 013-3)
Classification of observations	Deficiencies will normally be specified and divided into categories (e.g. critical, major or other deficiencies as well as recommendations, if applicable).	- PIC/S Inspection Report Format (PI 013-3) and PICS/S Guidance on Classification of GMP Deficiencies (PI 040-1)
Company response	Timeline and format for the submission of responses should be defined and communicated.	
	Corrective actions that cannot be completed by the due date for the company response: target completion dates for those issues should be defined. The inspection team will then confirm if the proposed corrective actions and timescales are considered to be acceptable and finalise the report.	
Information between inspections	Define which information should be communicated by the company between inspections (e.g. any significant changes to critical equipment & processes, key personnel, SOPs, testing laboratories used, etc.) and expected timelines.	

2. Blood collection and processing

Area of operations / items	Crucial questions/Show me	References to PE 005 (GPG)
Donor identification	Verify procedure is defined and acceptable documents are used (e.g. picture IDs initially and donor ID, full name, date of birth etc. during the process).	6.1.1., 6.1.2., 6.1.3.
	Is identification repeated at critical points (e.g. registration, venipuncture, after change in personnel).	6.2.1., 6.2.2.
Donor registration	Only permanent addresses should be acceptable.	6.1.2.
	Is a current list of unsuitable addresses available (e.g. missions, homeless shelters)?	6.1.2., 6.1.3.
	Is a deferral list for previously rejected donors (e.g. company based or national/industry-wide) in place and checked?	6.1.3.
	Is the donor advised of risks associated with donating, testing of donations, possibility of self-deferral, etc.?	6.1.5.2., 6.1.5.3.
Health assessment (e.g. electronic or paper questionnaire, physical exam)	Verify confidentiality during the health assessment is given, and separate from all processing areas.	3.2.1., 6.1.11.
	Is donor suitability checked in line with national regulations (e.g. appearance, temperature, blood pressure, pulse, total protein, haemoglobin/hematocrit, suitability of venipuncture site, physical exam) and by qualified personnel?	6.1.5., 6.1.5.1., 6.1.7., 6.1.12.
	Is the process defined (e.g. responsibilities, acceptance and exclusion criteria, handling of out of range results)?	6.1.3., 6.1.5., 6.1.7.
	Is the health assessment/questionnaire and the informed consent form signed by the donor?	6.1.5.3., 6.1.6.
	Are the records of suitability and final health assessment of the donor signed by the person who performed it? Are these records kept?	6.1.13., 6.1.14.
	Are abnormal findings reviewed by a qualified health professional and adequate action taken?	6.1.16.
	Are systems for handling of deferred and/or rejected donors in place?	6.1.14.
Collection area	Is there adequate space allowing for safe collection procedure and appropriate treatment of donors in case of reactions?	3.3.1., 3.3.2., 3.3.4., 6.2.8.
	Do procedures for collection minimise the risk for errors and microbial contamination.	6.2.8.

	Are procedures for hand disinfection and personal hygiene in place?	6.2.8.3.
	Apheresis process should preferably be automated to avoid mix-ups.	6.2.8.
	Closed sterile systems should be used for collections.	6.2.5., 6.2.8.1., 6.6.3.
	If machines are pre-set, verify timelines are according to the manufacturer's manual.	
	Verify aseptic technique is applied if connections are necessary (e.g. spiking of solutions, connecting the harness set to the bowl).	6.6.3.
	Randomly check records to verify lot numbers of the disposables (e.g. bags/ bottles) and solutions (e.g. anticoagulant) are recorded.	6.2.16.
	Disposables should be checked for contamination and defects. Check defects are documented and reported.	6.2.8.2.
	Verify labelling of collections, samples, collection systems, and records allows full traceability and complies with national requirements (e.g. unique donation numbers, name and address of collection establishment, storage temperature, date of collection, etc.). Process should avoid the risk of mix-up.	6.2.1., 6.2.3., 6.2.5., 6.2.10., 6.2.16
	Controlled procedure in place for handling of unused donation numbers?	6.2.4.
	Verify the venipuncture is performed in line with defined procedures (e.g. venipuncture site free from lesions, antiseptic solution to be used, contact time during disinfection) and disinfectant has not expired.	6.2.8.4., 6.2.8.5., 6.2.8.6.
	For whole blood collection, verify bag is mixed at regular intervals when anticoagulant is used.	6.2.8.7.
	Are samples taken at time of donation, labelled correctly, and stored appropriately? Are they representative of the unit from which they are drawn (e.g. inversion of source plasma collection bottles, stripping of lines)?	6.2.9., 6.2.10.
	Verify that maximum collection time to accept a donation for component preparation is defined and adhered to.	6.2.8.8.
	Are blood containers checked for defects after collection and is tubing sealed adequately?	6.2.8.9.
	Are processes in place for handling unsuccessful donations or re-sticks?	6.2.8.10.

	Are donations handled, stored, and transported to maintain their quality? Is the maximum time period between end of collection and start of processing/sampling defined?	6.2.11., 6.2.13.
	Handling of biohazardous waste should avoid contamination.	
Processing area	The area should be segregated with controlled access.	3.4.1.
	Equipment and technical devices used in line with SOPs?	6.6.1.
	Processes (incl. freezing) should be validated and avoid the risk of contamination/microbial growth.	6.6.2.
	Are closed systems in use?	6.6.3.
	Are sterile connecting devices in use? Is the process validated? Are seals checked for integrity?	6.6.5.
	Are measures in place to avoid mix-ups (e.g. of donations, samples, records, etc.) and cross-contamination? For example, 2-person check or electronic measures (e.g. double blind entry).	3.4.2.
	Are sensitive instruments protected from vibration, electrical interference (connect to Uninterruptible Power Supply if necessary), humidity, and extremes of temperature?	3.4.3.
	Is there traceability of equipment and programmes (e.g. identification number of the centrifuges and documentation of the programme number or centrifugation parameters used for separation, the identification number of the freezers used for freezing of plasma, etc.).	
	Randomly check documentation for correctness, traceability and completeness.	
Irradiated Components	Is there evidence of compliance with other legislative requirements (e.g. radioprotection) for the facility and storage of the radioactive source? Is dose-mapping of irradiation equipment performed regularly? Does the setting for the exposure time ensure that all blood and blood components receive the specified recommended minimum dose, with no part receiving more than the maximum recommended dose? Has the expiry date on the blood unit label been modified to reflect the date of irradiation in accordance	6.7.1.

	with applicable criteria? The use of a Cobalt source requires additional considerations.	
	Are radiation indicators used to differentiate irradiated from non-irradiated blood and blood components?	6.7.2.

3. Testing and quality control

Area of operations / items	Crucial questions/Show me	References to PE005 (GPG)
Laboratory Testing	Is testing performed at each donation and are respective specifications defined? Is the list of tests in agreement with legal requirements? And regularly reassessed?	6.3.1, 6.4.1.-6.4.3, 11.1.1
	Is the time between donation and receipt of test results monitored and trended?	6.4.10.
	Have all test methods been validated or verified by on-site testing before use to prove that the performance specifications of manufacturer are met?	6.3.2., 6.3.3., 11.2.1., 11.2.3.
	Are donation testing activities separate from diagnostic testing of patients?	6.3.4.
	Is the performance of the test procedure and the QC-lab regularly assessed by participation in an external formal system of e.g. proficiency testing?	6.3.12., 11.2.6.
Samples for testing infectious markers	Is a sampling plan designed and in agreement to provide the intended info?	11.2.4.
	Is a reconciliation process implemented upon receipt of samples (received vs. expected samples)?	6.3.6.
	Is the testing performed on the original sample tube?	6.4.4.
	Are secondary samples only allowed for NAT testing (mini-pools)? Is the system of labelling/identification of samples, the process and the algorithm to reassign pool results to individual donors validated?	6.4.4., 6.4.5.
	Are retention samples for retesting available in a frozen state and in accordance with national requirements?	6.4.9.
Handling of test results	Is the handling of test results defined (e.g. transcription, collation and interpretation of test results)?	6.3.10.
	Are non-conforming test results managed according to SOP (e.g. retesting performed in duplicate, different test method used)?	6.4.6., 6.4.7., 6.4.8.

	Are non-conforming test results clearly identified to ensure that blood or blood components of that donation remain segregated and quarantined?	6.3.11.
	Is appropriate donor management taking place, including the provision of information to the donor and follow-up procedures in case of non-conforming test results?	6.4.7
Blood group serological testing of donors and donations[2]	Is there a SOP in place describing testing for specific groups of donors (e.g. first-time donor)?	6.5.1.
	Are ABO and RhD tested at each donation? Are the results compared with historical data? Are first-time donors tested for irregular red-cell antibodies?	6.5.2., 6.5.3., 6.5.4.
Reagents	Are data available to confirm suitability of reagents for blood component samples and donor samples?	6.3.7., 6.3.9.
	Are all test reagents licensed or evaluated and considered to be suitable by the responsible CA?	6.5.6.
	Is the manufacturer of ABO, Rh anti-Kell reagents certified by an authorised body?	6.5.7.
	Are instructions from the manufacturer regarding the use of reagents/test kits followed?	11.2.5.
Documentation	Are SOP's implemented for equipment, handling and processing of samples (including pre-analytical treatment, quality control runs, storage and transport, reagents and the different techniques like ABO determination, RhD blood grouping, etc.)	6.3.5., 6.5.8., 11.2.3.
	Are records available and is good documentation practice applied?	11.2.7., 6.3.10.

4. Quality Management System

Area of operations / items	Crucial questions/Show me	References to PE005 (GPG)
Quality system (QS)	Is a QS in place based on the principles of Quality Risk Management (QRM) by incorporating the Good Practice Guidance?	1.1.1.-1.1.2, 1.1.5.-1.1.6., 1.2.1.-1.2.3. 1.3., 1.4.
	Verify that the Quality Manual (or equivalent document) clearly states quality policies, objectives, and management responsibilities.	1.2.4., 1.2.7.

[2] Not necessarily required for source plasma collections

	Is the QS supported by the senior management and personnel on all levels within the organisation?	1.1.3.-1.1.4.
	Are responsibilities of senior management defined? For example: • Appropriate resources are available? • The roles and responsibilities are defined, communicated and implemented? • Regular checks of suitability and effectiveness of the system (via management review) with evidence of action taken?	1.2.5.-1.2.6., 1.2.14.-1.2.15.
Quality assurance (QA)	Verify function is independent and includes: • review and approval of all quality related documents, and • assurance that all procedures, premises, and equipment (having an influence on the quality and safety of blood/blood components) are qualified, validated and revalidated at regular intervals.	1.2.8.-1.2.11.
Change Control	Ask for SOPs & lists of change controls in certain timeframes or areas, and select examples to verify the records that: • such change is planned, evaluated, documented, and implemented according to the QRM with written procedures; • the procedure is applied whenever a change is planned or necessary; • such changes are authorised and approved by responsible persons with sufficient supporting data; • the evaluation of changes is well documented, and an assessment according to QRM of the potential impact on the blood component/product is included as well as the potential requirements for validation, additional testing, qualification, training or updating lists, documents etc.; • the effectiveness of change is evaluated; • the change control system is applicable for changes in raw materials, specifications, process, methods, equipment, environment and changes that may affect donor safety, blood component quality or reproducibility of the process; and • the SOPs covering the notification to regulatory authority have been followed.	1.2.12., 4.6.1.-4.6.6., 5.3.7
Handling of deviations, non-	Ask for SOPs & lists of deviations and non-conformances in a certain timeframe, and select examples to verify records that:	1.2.13., 9.1.2.-9.1.10., 9.4.6.-9.4.7.

conformance and CAPAs	• those deviations and non-conformances are investigated with appropriate level of root-cause analysis, • any impact is being assessed, • the release decision of non-standard blood or blood components by a designated person is clearly documented, • appropriate CAPAs are identified and taken, and effectiveness of CAPAs are monitored and assessed, and • responsible (and/or senior) management is notified in timely manner.	
	Trend analysis and identification of recurrences?	9.4.2., 9.4.5.
Product quality reviews (PQR)	Ask for the latest PQR reports to verify that: • PQR is conducted at least annually; • the review covered starting materials, critical in-process controls, results of quality control and quality monitoring, all changes, the qualification status of equipment, technical agreements and contracts, all significant deviations, non-conformances, and the CAPAs implemented, findings of internal and external audits and inspections, and the corrective actions implemented, complaints and recalls, donor acceptance criteria, donor deferrals and look-back cases; and • trends and improvement in both component and process are identified.	1.2.16.-1.2.17. 9.4.8.
Quality risk management (QRM)	Has a QRM been implemented as the part of the Quality System to ensure the control of outsourced activities and quality of purchased materials?	1.4.1.-1.4.2.

5. Personnel and Organisation

Area of operations / items	Crucial questions/Show me	References to PE 005 (GPG)
Organisation	Is there an adequate number of personnel with the necessary qualifications and experience available?	2.1.-2.3.
	Does personnel (e.g. Responsible Person, processing manager, quality control manager, quality assurance manager, physician) have adequate qualification and authority to carry out their responsibilities?	2.3., 2.5.

	Are the relationships between key personnel clearly shown in the managerial hierarchy in the organisation chart?	2.3.1.-2.3.5.
	Are the processing manager and QA manger independent from each other?	2.4.
	Review examples of job descriptions to verify that: • the job descriptions are up-to-date and responsibilities clearly defined, and • the individual understanding of responsibilities are assessed and recorded (e.g. personnel signature lists should be available).	2.4.-2.6., 2.11.
Training	Is there a written training programme for all personnel that includes: • initial and ongoing training appropriate to their specific task, • maintained written records, and • technical, maintenance and cleaning personnel?	2.1., 2.7.-2.8.
	Are there written policies and procedures to describe the approach to training, including a record of training that has taken place, its contents, and its effectiveness?	2.9.
	Are the contents of training programmes and the competence of personnel assessed/evaluated periodically?	2.10.
Safety and hygiene	Verify the safety and hygiene requirements during the site tour, including: • written instructions are available, understood and followed (e.g. Gowning requirements in the different areas, reporting on health condition, medical examinations if necessary) • visitors or untrained personnel are given information about personal hygiene and the prescribed protective clothing and closely supervised; and • no person affected by an infectious disease or having open lesions on the exposed surface of the body is engaged in the preparation of blood components.	2.12.-2.17.

6. Premises (incl. mobile sites)

Area of operations / items	Crucial questions/Show me	References to PE005 (GPG)
General requirements	Does construction allow for effective cleaning and maintenance and enable work to proceed in a logical sequence?	3.1.1.
	Is lighting, temperature, humidity and ventilation appropriate? (Check monitoring records)	3.1.2.
	Is premises in an adequately clean and tidy condition? Check cleaning records.	3.1.5., 3.5.3.
	Is premises free from insects or other animals? Check pest control records.	3.1.3.
	Does the design of security measures prevent unauthorised entry?	3.1.4.
	Are areas/rooms used for the processing of blood components in an “open process”: operation should preferably be under Grade A environment with a Grade B background, with environmental monitoring available.	3.1.9.
	Check that toilets are not directly open to processing, laboratory or storage areas.	3.6.2.
	Check that maintenance workshops are separated from preparation areas.	
	Check that a waste disposal area is available.	3.7.1.
Donor sessions (including mobile sessions)	Is the site of sufficient size to allow an orderly flow of work and an adequate privacy for donor interviews?	3.3.2.1.
	Is there suitable ventilation, electrical supply, lighting, toilet and hand-washing facilities?	3.3.2.3.
	Is there reliable communication?	3.3.2.4.
	Is there guarantee of adequate interim storage of and transport of material and collected units?	3.3.2.5.
Storage area	Are there separated rooms or segregated area with clear indication for materials and different blood components/products (in quarantined, released, rejected and returned/recalled, irradiated vs non-irradiated)?	3.5.1., 3.5.4. 3.5.7., 3.5.8., 6.7.2.
	Do the storage conditions (e.g. temperature, humidity) reflect the manufacturer’s requirements? Check the monitoring & alarm records, deviations and actions taken to verify storage facilities was maintained within	3.5.5.

	predefined temperature limits and equipped with alarm system.	
	If any computerised or other system is used to replace physical quarantine, does the arrangement provide appropriate security?	3.5.7.
	Are printed packaging materials (including sets of donation identifier labels) stored in safe and secure condition?	3.5.9.
	Is there a SOP available to handle equipment or power failure events?	3.5.2.
	Is the area for receiving/dispatch materials/products, separated, designed to protect materials/products from the weather, and allow for cleaning containers of incoming materials?	3.5.6.

7. Equipment

Area of operations / items	Crucial questions/Show me	References to PE 005 (GPG)
Cleaning	Verify design allows for easy and effective cleaning. Check that suitable cleaning equipment is used and stored, and is not a source of contamination.	4.1.17.
	Verify that parts of equipment coming into contact with blood are effectively cleaned.	4.1.19., 4.1.20.
Maintenance, calibrations, qualifications, operating instructions	Review inventory record, log books, calibration records, monitoring plans, qualification documents and/or summary reports, etc.	4.1.1., 4.1.3., 4.1.4., 4.1.14., 4.7.2.1., 4.7.2.3.
	Verify procedures are in place defining responsibilities, frequency, accuracy, acceptance criteria, etc. for maintenance, calibrations, and qualifications.	4,1.7.
	Review training records of in-house technicians, e.g. for apheresis machines.	4.7.2.1.
	Review trending of calibration and monitoring results as well as equipment failures.	4.7.2.2.
Validation of critical processes	Review risk assessments, validation records and/or summary reports.	4.3.1.1.

Changes (modifications, enhancements, etc.)	Check whether changes are handled per change control procedure. The suitability of the implemented change should be tested. Criteria requiring re-qualification/re-validation should be defined.	4.1.6., 4.3.1.2., 4.3.1.3., 4.7.2.4.
	Verify potential new training needs have been identified and training has been performed.	4.7.2.5.
New, repaired and defective equipment	Verify it is qualified and authorised before use.	4.1.5.
	Verify that procedures for handling of malfunction are in place, e.g. labelling/segregation of equipment, root cause investigation, impact assessment (potential effect on product quality), and approval process before returning equipment to use.	4.1.8., 4.1.22., 4.7.1.3.3., 4.7.1.4.
	Is equipment performance assessed before use after relocations, where appropriate?	7.7.1.3.
Balances and measuring equipment	Is the range, accuracy and precision appropriate for intended use? Check calibration records for adherence to defined frequency, appropriate reference standards used, values obtained prior to any adjustment, etc. Are failed calibrations handled as non-conformances and investigated appropriately (e.g. potential impact on the product)?	4.1.21.
Monitoring of temperatures (e.g. freezers)	Randomly check documentation of previous months as well as investigations associated with alarms/temperature fluctuations.	

8. Materials

Area of operations / items	Crucial questions/Show me	References to PE 005 (GPG)
Purchase of materials	Materials used are from approved suppliers? Audit of suppliers?	4.1.9., 4.7.1.2.6.
	Is there evidence that materials that come into contact with blood or blood components are suitable for its intended use and do not affect their quality?	4.1.20.
Release of critical supplies/ materials	Verify that procedures are in place, acceptance criteria are defined and verified as part of the release process.	4.1.10.

	Are sterile materials provided with a release certificate for each batch? Is there a certificate of analysis provided for critical materials?	4.1.10., 4.7.1.2.3.
	Are appropriate checks on received goods? Critical materials released by a person qualified for this task?	4.7.1.2.2., 4.1.9.
Storage of materials	Is status clearly indicated?	4.1.11.
	Are materials stored under appropriate conditions and in an orderly manner?	4.1.12.
	Is the FEFO (first expired first out) principle followed?	4.1.13.
	Are inventory records retained?	4.1.14.

9. Data processing systems

Area of operations / items	Crucial questions/Show me	References to PE 005 (GPG)
Computerised systems (hardware and software)	Are systems validated before use and maintained in a validated state (e.g. after a change)? Is user-testing included to demonstrate system performance?	4.2.1., 4.2.3.
Maintenance	Is there a documented maintenance plan?	4.2.2., 4.2.1.
Data protection/ integrity	Is the system protected against unauthorised use and unauthorised changes? Verify if preventive measures to ensure data protection, unauthorised entry, are taken.	4.2.5., 4.2.4.
	Is a back-up procedure in place? Is there a disaster plan for restore of data?	4.2.1.
	Is prevention of release of non-conforming blood or blood components included in the design of the computer system? Are measures preventing release of blood from future donations of a deferred donor included?	4.2.5.

10. Qualification and validation

Area of operations / items	Crucial questions/Show me	References to PE 005 (GPG)
General principles	Is there policy or procedure for Qualification/Validation? Is appropriate qualification (DQ, IQ, OQ, PQ) conducted for critical equipment and ancillary systems and including process validations? How can you demonstrate that the processes are robust ensuring that consistent blood and blood components are manufactured, stored and released? What type of validations are used?	4.3., 4.3.1., 4.3.1.1., 4.3.1.2., 4.3.1.4., 4.3.2.4.-4.3.2.6., 4.4.1., 4.4.1.6. -4.4.1.9., 4.4.2.1.-4.4.4.6.
Risk management	What is the risk management and life cycle concept of blood and blood component collection, processing storage testing and release for supply?	4.3.2.1., 4.3.2.2., 4.3.1.3., 4.3.2.7.
Organising and planning for validation	Is the company's overall validation policy documented in a validation master plan (VMP)?	4.3.2.3.
Documentation including VMP	Are the qualification / validation procedures integrated in the quality system including management of changes to the programme? How are documents in complex validations and/or from third party validation services handled assure a clear documentation of the qualification and validation activities?	4.3.3.1.-4.3.3.6.
	How are results that fail to meet the pre-defined acceptance criteria managed and are they fully investigated? How are they managed?	4.3.3.7.-4.3.3.9.
Re-qualification	Are there procedures and processes that define re-qualification and over what specific period should it be done to show that the system remains in a state of control?	4.3.5.1., 4.3.5.2.
Process validation	Is the validation process justified using extensive process knowledge from the development stage using an appropriate statistical control? Does the process validation established consider all quality attributes and process parameters? What is a critical quality attribute (CQA) and a critical process parameter (CPP) and are they clearly documented?	4.4.1.3.-4.4.1.5., 4.4.4.7., 4.4.4.8.

	Are product quality reviews used to confirm that the process under review remains validated? What areas of QMS and production are covered in a review of PQR?	
Validation of test methods	Are the test or measuring methods that are used in qualification or validation adequately qualified, verified or validated before used? Show me the validation of the testing method of product, residues or surfaces to detect microbial contaminations.	4.5.1., 4.5.2., 4.5.3.

11. Documentation / Document Control

Area of operations / items	Crucial questions/Show me	References to PE 005 (GPG)
Generation and control of documents	Is an adequate documentation systems in place?	5.3.1.
	Is there an SOP for review, revision and archiving of documents? Are appropriate controls implemented?	5.3.2.
	Is a distribution list included in the documentation control procedure?	5.3.3.
	Are documents approved, signed and dated? Are they uniquely identifiable with an effective date defined?	5.3.4.
	Are documents reviewed regularly and kept up to date?	5.3.6.
Good documentation practices	Are records legible?	5.3.8., 5.4.1.
	Are operations traceable?	5.4.2., 5.4.3.
	Are alterations signed and dated?	5.4.4.
Retention of documents	Is record integrity maintained throughout the retention period?	5.3.2., 5.5.1.
	Is the retention period according to requirements?	5.5.2.
Instructions	Are instructions laid out in an orderly fashion and written in an imperative mandatory style?	5.3.5.
	Check the content of instructions and compare with observed practice and or records, e.g. for processing of products.	5.7.1.
Specifications	Are authorised and dated specifications available for starting and packaging materials, finished blood and blood components?	5.6.1.

Procedures and records	Are procedure and records available for materials receipt? Check some records of the receipts.	5.9.1.1.
	Are records of the distribution of blood components available and ensure full traceability of each blood component?	5.11.2.
	Are records on all relevant activities available? Are they complete and allow full traceability?	5.11.4.
Labelling	Is a standard labelling methodology implemented?	6.8.1- 6.8.3.
	Check the labels for collected blood, intermediate and finished components.	5.8.1., 6.8.4., 6.8.5.

12. Release of blood components and plasma for further manufacture

Area of operations / items	Crucial questions/Show me	References to PE 005 (GPG)
Release of blood and blood components	Do procedures, records, and environmental monitoring indicate that controls are in place to avoid mix-up, contamination and cross contamination? Who is responsible for the release for supply and how can it be demonstrated? What records are reviewed to ensure that all blood components have met all acceptance criteria?	6.9.1.
	What are the release criteria for blood and blood components? Are they clearly documented, validated and approved?	6.9.2.
	Define the exceptional release of non-standard blood and blood components?	6.9.3.
	Is there a segregation process for quarantined, released and rejected blood and blood components and how are they labelled?	6.9.4., 6.9.5.
	Does the Information Management system encompass all activities from blood donors to distribution of blood and blood components to end users? Is the information management system validated?	6.9.6. (a-d)
	Are historical records reviewed prior to release of blood and blood component?	6.9.7., 6.9.8.
	How are other components managed if there is positive test result?	6.9.9.

	Are records updated to ensure that donors do not make further donation?	6.9.10.

13. Storage and transport/distribution

Area of operations / items	Crucial questions/Show me	References to PE 005 (GPG)
Storage and distribution	Are facilities for the storage and distribution of blood and blood components comply with the requirements of GPG?	7.1.-7.3.
	Is there a system to ensure that stock rotation is operating according to procedures? Are there appropriate records of inventory and distribution including the management of special components?	7.4.-7.7.
	Are records kept of the distribution of blood components between blood establishments and hospital blood banks? What information is available on records?	7.8.
	Is there a requirement that the integrity of the packaging is maintained during distribution and transportation?	7.9.
	How is it demonstrated that transport conditions are clearly defined, validated and or verified? Is there a risk assessment performed to consider the impact of variables e.g., delays during transportation, failure of monitoring devices or any other relevant information?	7.10.1.-7.10.3.
	Is there continuous temperature monitoring during transportation, if not, is it justified?	7.10.4.
	Are written procedures available for return of blood and blood components and how can blood establishment ensure the integrity of blood components is fulfilled? Do the records identify that the blood component has been inspected before re-issue?	7.11., 7.12.

14. Outsourced activities

Area of operations / items	Crucial questions/Show me	References to PE 005 (GPG)
Outsourced activities -	Is there a written contract defining the tasks that are performed externally?	8.1.1.

General Principles	What specific areas are considered and are the responsibilities of each party documented to include the contract giver and the contract acceptor?	8.1.2.-8.1.4., 8.15., 8.16., 8.4.1.
The contract giver & acceptor	What are the responsibilities of the contract giver and contract acceptor?	8.2.1., 8.2.3., 8.3.1., 8.3.2.
	What information should be included by the contract and should a copy of the specifications of blood components be included?	8.2.2.
	Is subcontracting entrusted to a third party without prior approval by the contract giver and evaluated by contract acceptor?	8.3.3.
	Are there processes in place to refrain from any activity that may adversely affect quality of blood and blood components prepared by contract giver?	8.3.4.
The contract	Does the contract specify the procedure by which the Responsible Person or Authorised Person releasing the blood and blood components for supply can ensure that each component had been prepared and / or distributed in compliance with the requirements of GDP and regulatory requirements?	8.4.2., 8.4.3.
	Are there systems in place to easily permit a recall? Has its effectiveness been demonstrated and who will be in control of the recall?	8.4.4.
	Is there a system in place to permit the contract giver to audit the facilities and processes of the contract acceptor?	8.4.5.

15. Non-conformance, Recalls & Look backs

Area of operations / items	Crucial questions/Show me	References to PE 005 (GPG)
Randomly selected cases	Review for timely completion, accuracy and appropriate actions taken.	
Complaints (incl. serious adverse reactions and serious adverse events)	Are complaints documented, investigated and statistically evaluated according to written procedures? Responsibilities and notification requirements (e.g. Competent Authorities) need to be defined. The potential effect on related blood and blood components should be evaluated and recalls initiated when necessary.	9.2.1.-9.2.5., 9.3.1.

	Corrective and preventive actions should be triggered.	
Recall/Look Back	Are triggers defined based on national requirements (e.g. viral marker repeat or confirmed reactive test results or other post donation information)? Are timelines for actions and notifications (e.g. look back department, customer, etc.) defined? Are confirmatory test results also communicated to the customer? Is the Look Back period defined based on the trigger and/or window periods (e.g. 6 months prior to the last negative donation)? Is the time window defined for the search of the last negative unit prior to the collection that tested reactive or caused the look back? Are Look Back numbers statistically evaluated with thresholds established and corrective actions taken as required? Is the personnel responsible for initiating/ coordinating recalls independent of the company's commercial management? Are re-called blood components/products identified and segregated adequately (e.g. physical quarantine and/or electronic measures)?	9.3.

16. Self-inspection and audits

Area of operations / items	Crucial questions/Show me	References to PE 005 (GPG)
Self-inspection programme	Verify that self-inspections are carried out regularly by trained persons and according to approved procedures	10.1.
	Are results documented and CAPA implemented?	10.2.

6. REVISION HISTORY

Date	Version Number	Reasons for revision
1 July 2004	PI 008-2	Change in the Editor's co-ordinates
25 September 2007	PI 008-3	Change in the Editor's co-ordinates
1 June 2021	PI 008-4	Complete revision