Annex-VI (A)

REQUIREMENTS FOR GRANT OF DRUG MANUFACTURING LICENSE BY THE WAY OF BASIC & SEMI-BASIC MANUFACTURING FOR BLOOD/ PLASMA ESTABLISHMENTS

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1. INTRODUCTION

The Drug Regulatory Authority of Pakistan has developed these requirements to establish robust standards for all activities related to human plasma intended for fractionation and subsequent manufacture of Plasma-Derived Medicinal Products.

The above activities require application of Good Manufacturing Practice (GMP) principles throughout the entire plasma supply chain. The principles of GMP, when properly implemented, create a comprehensive framework that ensures plasma is consistently collected, tested, processed, stored, and distributed according to quality standards appropriate for its intended use as a starting material for manufacturing of life-saving medicines.

2. PURPOSE

These requirements serve a reference document for the applicants intended to apply for grant of Drug Manufacturing Licenses for Blood/Plasma Establishments by way of basic/semi-basic manufacturing. The requirements aim to facilitate harmonization with international regulatory requirements, enabling Pakistani plasma establishments to meet the stringent standards required by international fractionators and foreign regulatory authorities.

However, for grant of Drug Manufacturing Licenses by way of formulation for Blood/Plasma Establishments, the requirements shall be as per PIC/S requirements for blood/ plasma products.

3. SCOPE

3.1 Applicability

These requirements are applicable to a broad range of entities and activities within the plasma supply chain. All Plasma Establishments that hold Drug Manufacturing Licenses and engage in the collection, testing, processing, storage, or distribution of human plasma intended for fractionation only must comply with these requirements. This also includes blood establishments licensed with Provincial Blood Transfusion Authorities that collect whole blood from which plasma is recovered.

3.2 Types of Plasma Covered

These requirements apply to various types of plasma collected and processed for use as starting material in the manufacture of plasma-derived medicinal products.

- Recovered plasma, which is separated from whole blood donations collected primarily for the preparation of blood components for transfusion, falls within the scope of these requirements when it is designated for fractionation.
- Source plasma, which is collected by automated plasmapheresis from donors who have been specifically qualified for plasma donation through a rigorous two-donation testing process, is comprehensively addressed.

All plasma types covered by these requirements are intended exclusively for fractionation into plasma-derived medicinal products and are not intended for direct transfusion, which is governed by separate regulations. However, pooled plasma is not acceptable for fractionation.

3.3 Activities Covered

The scope of these requirements encompasses the complete range of activities involved in plasma collection and distribution which involves:

- Plasma processing activities, including separation from whole blood, pooling where applicable, and the preparation of plasma for freezing.
- Freezing, storage, and cold chain management requirements ensure that plasma quality is maintained from collection through delivery.
- Packaging and labeling requirements necessary for plasma distribution.
- Distribution of plasma to fractionators, whether located within Pakistan or internationally, including all associated quality assurance and documentation requirements.
- Quality assurance and quality control systems
- Documentation and record-keeping requirements to enable traceability and regulatory oversight.

However, the standards for donor recruitment/registration, ethical sourcing, education, and management activities, donor eligibility assessment, selection procedures and donation volume which are critical to ensuring both donor safety and plasma quality shall be addressed as per procedure or as decided by the National Technical & Advisory Committee (NTAC). There shall be National Donor Registration and Management System (DRMS) which shall be maintained as per decision of NTAC.

4. LEGAL BASIS

These requirements are issued under the authority of the Drug Regulatory Authority of Pakistan Act of 2012 (Act No. XXI of 2012) hereinafter referred as the DRAP Act. Schedule I of the DRAP Act includes plasma and plasma derived medicinal products under definition of biologicals including others. Section 7 (c) of DRAP Act has empowered the Authority for issuance requirements for licensing/ registration of therapeutic goods, including biologicals and implementation of internationally recognized standards las aid down by stringent regulatory authorities and World Health Organization.

Rule 15 of the Drug (Licensing, Registering & Advertising) Rules, 1976 provides provision & conditions for issuance of Drug Manufacturing License by the way of basic and semi-basic manufacturing and these are applicable to the blood/plasma establishments involved in the collection, testing, processing, storage, or distribution of plasma intended for fractionation for manufacturing of PDMP's.

The National Blood Policy of 2025 provides that Blood & Plasma Establishment shall obtain license from DRAP for plasma collection and further processing.

5. DEFINITIONS AND ABBREVIATIONS

5.1 Definitions

Throughout these requirements, specific terms are used with defined meanings to ensure clarity and consistency.

Adverse Event

An adverse event refers to any untoward medical occurrence in a donor or recipient that may or may not have a causal relationship with the plasma donation or transfusion, encompassing a broad range of occurrences from minor reactions to serious medical emergencies.

Apheresis

Apheresis describes a sophisticated procedure in which blood is withdrawn from a donor, specific components are separated and retained using automated equipment, and the remaining blood components are returned to the donor, enabling the collection of larger volumes of plasma than would be possible through whole blood donation.

Blood Establishment

A blood establishment encompasses any facility engaged in the collection, testing, processing, storage, or distribution of blood or blood components, as defined in provincial blood transfusion legislation.

Blood Establishment Computer Software

Blood Establishment Computer Software, commonly referred to as BECS, consists of validated computer systems used for comprehensive donor management, plasma inventory control, and traceability functions.

Cold chain management

Cold chain management describes the sophisticated temperature-controlled storage and transportation systems that maintain plasma integrity throughout its journey from collection through processing and delivery to fractionation facilities, incorporating continuous monitoring and comprehensive documentation requirements to ensure that the frozen state is never compromised.

Critical Quality Attributes

Critical Quality Attributes represent physical, chemical, biological, or microbiological properties or characteristics that should be maintained within appropriate limits, ranges, or distributions to ensure the desired product quality, in accordance with principles established by the International Council for Harmonisation.

Good Manufacturing Practice

Good Manufacturing Practice, often abbreviated as GMP, constitutes that essential part of quality assurance which ensures that plasma is consistently collected, tested, processed, stored, and distributed according to quality standards appropriate for its intended use as a pharmaceutical starting material.

Fractionation

Fractionation describes the sophisticated industrial manufacturing process that separates plasma into its constituent proteins, which are then further purified, formulated, and processed into medicinal products.

Lookback

Lookback refers to the critical process of identifying and quarantining plasma from donors who are subsequently found to have a transfusion-transmissible infection, requiring immediate investigation and notification to prevent the use of potentially infectious material.

Nucleic Acid Testing

Nucleic Acid Testing, universally known as NAT, represents an advanced molecular testing technique capable of detecting viral genetic material in blood and plasma donations during the window period before antibodies develop.

Plasma for fractionation

Plasma for fractionation specifically denotes plasma that has been collected and processed as starting material for the manufacture of plasma-derived medicinal products and is not intended for direct transfusion.

Plasma Master File

Plasma Master File constitutes a comprehensive documentation package describing all aspects of the collection, testing, and processing of plasma used as starting material for plasma-derived medicinal products.

Qualified Donor

A qualified donor represents a source plasma donor who has successfully completed the qualification process, including two negative viral marker tests separated by at least sixty days, and who maintains qualification through regular donation.

Qualified Person

The Qualified Person, often designated as QP, is an individual with appropriate education, training, and experience who is authorized to certify and release plasma batches for fractionation, bearing ultimate responsibility for ensuring that each batch meets all specifications and requirements.

Quality Agreement

A quality agreement is a written contract established between a plasma establishment and fractionator that clearly defines the responsibilities, specifications, and procedures governing their relationship.

Recovered Plasma

Recovered plasma specifically refers to plasma that has been separated from whole blood donations that were collected primarily for transfusion purposes.

Responsible Person

The Responsible Person bears individual responsibility for ensuring that plasma collection, testing, processing, storage, and distribution comply with all applicable laws and regulations.

Source Plasma

Source plasma denotes plasma collected by automated plasmapheresis from qualified donors specifically for use in fractionation, representing the highest quality plasma for pharmaceutical manufacture.

Stringent Regulatory Authority

A Stringent Regulatory Authority, abbreviated as SRA, refers to a regulatory authority that is a member of the International Council for Harmonisation (ICH) or an ICH Observer and which performs audits and inspections for GMP compliance.

Traceability

Traceability encompasses the ability to trace each plasma unit from the original donor through to final disposition, including all intermediate steps, in both forward and backward directions.

Transfusion-Transmissible Infection

A transfusion-transmissible infection describes any infectious disease that can be transmitted through blood or blood components, representing the primary safety concern in plasma collection.

5.2 Abbreviations

Abbreviation	Full Form
ACD	Acid Citrate Dextrose
ALT	Alanine Aminotransferase
Anti-HBc	Antibody to Hepatitis B Core Antigen
Anti-HCV	Antibody to Hepatitis C Virus
BPD	Biological Product Deviation
CAPA	Corrective and Preventive Action
CPD	Citrate Phosphate Dextrose
DRAP	Drug Regulatory Authority of Pakistan
EDQM	European Directorate for the Quality of Medicines
EIS	Electronic Information System
EMA	European Medicines Agency
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HTLV	Human T-Lymphotropic Virus
ICH	International Council for Harmonisation
IQ	Installation Qualification
IQPP	International Quality Plasma Program
ISBT	International Society of Blood Transfusion
NAT	Nucleic Acid Testing
NDDR	National Donor Deferral Registry
NOC	No Objection Certificate
OQ	Operational Qualification

Abbreviation	Full Form
PDMP	Plasma-Derived Medicinal Product
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PMF	Plasma Master File
PQ	Performance Qualification
PPTA	Plasma Protein Therapeutics Association
QA	Quality Assurance
QC	Quality Control
QMS	Quality Management System
QP	Qualified Person
RP	Responsible Person
SOP	Standard Operating Procedure
SRA	Stringent Regulatory Authority
TTI	Transfusion-Transmissible Infection
vCJD	Variant Creutzfeldt-Jakob Disease
WHO	World Health Organization
WNV	West Nile Virus

6. GENERAL PRINCIPLES

6.1 Foundation of Quality

Every plasma establishment operating in Pakistan must develop and maintain a comprehensive Quality Management System that is firmly grounded in Good Manufacturing Practice principles as outlined in PIC/S requirements and carefully adapted for the Pakistani regulatory and operational context. Quality cannot be viewed as the responsibility of a single department or individual; rather, it must be recognized as the shared responsibility of all persons involved in plasma collection, testing, processing, storage, and distribution activities, from the most junior staff member to senior management.

6.2 Risk-Based Approach

Modern quality management recognizes that not all activities and processes carry equal risk, and resources should be focused where they can provide the greatest benefit to quality and safety. All activities affecting plasma quality should incorporate risk assessment principles that enable informed decision-making and appropriate resource allocation.

Risk assessment begins with the systematic identification of potential hazards to plasma quality and safety, considering both the probability of occurrence and the potential severity of consequences. Once hazards are identified, risks must be evaluated to determine their significance and priority.

Implementation of appropriate control measures based on the risk assessment ensures that critical risks are adequately controlled while avoiding unnecessary burden on lower-risk activities. The effectiveness of control measures must be monitored on an ongoing basis to ensure they remain adequate as circumstances change. Regular review and improvement of risk management activities ensures that the risk-based approach remains current and effective.

7. QUALITY MANAGEMENT SYSTEM

7.1 Quality Policy and Objectives

Top management must establish and document a comprehensive quality policy that articulates the organization's commitment to quality and provides the foundation for all quality activities. The quality policy must be appropriate to the specific purpose and context of the organization, recognizing the unique responsibilities involved in collecting plasma for pharmaceutical use.

The policy must include an explicit commitment to comply with all applicable requirements, both regulatory and contractual, leaving no ambiguity about the organization's obligations. An equally important commitment to continual improvement signals that the organization will not be satisfied with merely meeting minimum standards but will actively seek opportunities to enhance performance.

7.2 Quality Assurance

The establishment of an independent Quality Unit represents one of the most important structural elements of the Quality Management System. This unit must be truly independent from production operations, reporting separately to senior management to ensure it can exercise its authority without conflict of interest or undue pressure. The Quality Unit possesses the authority to approve or reject plasma for release, a power that must be exercised based solely on whether specifications and requirements are met. All quality-related records are subject to review by the Quality Unit, ensuring comprehensive oversight of operations. The Quality Unit approves all procedures, specifications, and changes that affect product quality, ensuring that appropriate controls are in place before implementation.

Investigation of all deviations, complaints, and adverse events falls within the Quality Unit's purview, ensuring that problems are thoroughly understood and appropriately addressed. The Quality Unit oversees all validation activities, including qualification of facilities and equipment, validation of processes, and validation of computer systems. Internal audits are conducted or overseen by the Quality Unit to provide independent assessment of GMP compliance. The Quality Unit must be headed by a person with appropriate qualifications, training, and experience, recognizing that the role requires both technical knowledge and the judgment to make difficult decisions.

Key responsibilities of the Quality Unit include:

- Ensuring overall GMP compliance throughout the organization,

- Making batch release decisions based on comprehensive review of all relevant data and records,
- Providing oversight of the change control system to ensure changes are properly managed,
- Managing the deviation system to ensure problems are investigated and resolved,
- Overseeing the CAPA system to ensure effective problem-solving, conducting trend analysis,
- Identify emerging issues before they become serious problems,
- Managing supplier qualification and oversight to ensure that external parties meet quality requirements.

7.3 Quality Control

Quality control is responsible for performing the testing and verification activities that provides objective evidence of quality. Quality control laboratory facilities must be established with appropriate equipment and instrumentation that is suitable for the tests to be performed and properly maintained. The laboratory must be staffed with qualified personnel who have the education, training, and experience necessary to perform testing competently. All test methods must be validated before use to demonstrate they are fit for purpose, and detailed documented procedures must be followed to ensure consistent performance. Participation in proficiency testing programs provides external verification of laboratory competence and helps identify areas for improvement.

All testing must be performed according to approved validated methods that have been shown to provide reliable results. Current standards and specifications, whether pharmacopeial or established through quality agreements, define the acceptance criteria for test results.

Good laboratory practices must be observed at all times to ensure the integrity and reliability of test results. Test results must be reviewed by qualified personnel before being approved, ensuring that unusual results are identified and investigated before release decisions are made. Documentation of all testing activities provides the permanent record necessary to demonstrate compliance and support investigations when problems occur.

7.4 Document Control

Document management system is essential to ensure that all personnel have access to current, approved procedures and that obsolete documents are removed from use. Distribution and access control mechanisms ensure that documents reach the people who need them while preventing unauthorized access to confidential information. Documents must be readily retrievable when needed, whether for routine use or for investigations and audits. The revision and update process enables documents to remain current as procedures evolve and requirements change. Archiving and retention of superseded documents provides a historical record that may be needed for investigations or regulatory inquiries.

All documents must be clear and legible, avoiding ambiguity that could lead to misinterpretation. Unique identifiers enable precise reference to specific documents and versions. Effective dates and version numbers clearly communicate when a document becomes effective and how it relates to previous versions. Approval by authorized personnel provides assurance that documents have been properly reviewed before implementation.

7.5 Change Control

Changes made without proper control can inadvertently affect product quality or introduce compliance issues. A formal change control system provides the structure necessary to manage changes effectively while maintaining quality and compliance. The change control system must document all proposed changes, creating a permanent record of what was changed, why, and how. Obtaining appropriate approvals ensures that changes are reviewed by qualified individuals with the authority to authorize them.

Implementation of changes must be managed in a controlled manner, with appropriate training, updating of documentation, and validation where necessary. Changes should be categorized based on their risk and impact level, with more extensive review and approval requirements for higher-risk changes. No changes that could affect plasma quality may be implemented without proper authorization by the Quality Unit or designated authorities.

7.6 Deviation Management

All deviations from established procedures must be promptly identified and documented, ensuring that they do not go unrecognized and unaddressed. Thorough investigation for root cause is essential to understand why the deviation occurred and what can be done to prevent recurrence.

Assessment of impact on plasma quality and safety determines whether product has been affected and what actions are necessary to protect quality. CAPA systems are implemented as appropriate based on investigation findings, addressing both immediate corrections and long-term preventive measures.

Critical deviations, those that could significantly impact product quality or safety, must be reported to DRAP, fractionation partners, and other affected parties as required by regulations and agreements. This transparency ensures that all stakeholders are aware of significant issues and can take appropriate actions.

7.7 Corrective and Preventive Actions

The CAPA system represents the organization's systematic approach to identifying and eliminating the causes of quality problems. This system must be established to investigate quality problems thoroughly, going beyond superficial explanations to identify true root causes. Once root causes are determined, corrective actions address the immediate problem and prevent its recurrence. Preventive actions go further, identifying opportunities to prevent problems that have not yet occurred but could, based on knowledge of the system.

Implementation of CAPA must be followed by verification of effectiveness, ensuring that actions taken actually solved the problem and did not create new issues. Prevention of recurrence is the ultimate goal of CAPA, demonstrating that the organization learns from its mistakes. All CAPA activities must be documented in detail and tracked to completion, ensuring accountability and providing evidence of effective quality management.

7.8 Internal Audits

Internal audits provide independent, objective assessment of whether the quality system is working as intended and whether operations comply with GMP requirements. A program of regular internal audits must be established to verify GMP compliance across all areas of operation, assess the effectiveness of the quality management system, identify opportunities for improvement, and ensure adherence to established procedures. Audits must be conducted by trained auditors who are independent of the areas being audited, ensuring objectivity.

Audit frequency and scope should be based on risk assessment and previous audit findings, with higher-risk areas or areas with historical problems audited more frequently. All audits must be thoroughly documented, including observations, findings, and recommendations. Action plans developed in response to audit findings must be tracked to completion. Follow-up activities verify that corrective actions have been effective. The frequency of internal audits should be at least annually for all critical areas, with more frequent audits for areas where problems have been identified.

8. PERSONNEL REQUIREMENTS

8.1 Organizational Structure

A clear organizational structure must be established and documented, showing the relationships between different positions and departments within the plasma establishment. This structure should clearly illustrate reporting relationships so that each person understands to whom they report and who reports to them. Roles and responsibilities must be explicitly defined for each position, eliminating ambiguity about who is responsible for what activities. Lines of authority must be clear, ensuring that decisions are made by appropriately authorized individuals. Segregation of duties is essential to prevent conflicts of interest, particularly ensuring that quality control functions are independent of production operations.

Key positions that must be established include the Responsible Person or Authorized Person who bears ultimate responsibility for ensuring regulatory compliance, the Quality Manager or Quality Assurance Head who leads the quality function, the Production Manager who oversees collection and processing operations, the Laboratory Manager who directs testing activities, and where applicable, a Medical Director who provides medical oversight of donor selection and management.

8.2 Qualified Person / Responsible Person

At least one Qualified Person or Responsible Person must be designated with clearly defined responsibilities for critical quality and compliance functions.

The Qualified Person or Responsible Person must possess appropriate qualifications including

- a master’s degree in blood transfusion/blood banking, hematology, pharmaceutical sciences, medicine, pharmacy, biological sciences including biotechnologist, or a related field as defined by CLB that provides a foundation for understanding the scientific and technical aspects of plasma collection and quality.
- A minimum of three years of practical experience in blood banking, plasma collection, or pharmaceutical quality assurance is required to ensure the individual has sufficient exposure to the field.

The Qualified Person or Responsible Person must be permanently and continuously available to the establishment, not serving in this capacity on a part-time or occasional basis, as the responsibilities require ongoing attention and availability for decision-making.

8.3 Personnel Hygiene and Health

Personnel health programs must be established to protect both personnel and plasma quality. These programs should include:

- Pre-employment health assessments to establish baseline health status and identify any conditions that might preclude certain duties, periodic health surveillance to monitor ongoing health and detect problems early, management of illnesses and injuries that occur during employment, and measures to prevent disease transmission from personnel to plasma or donors.
- Personnel must be clearly instructed to report any illnesses that may affect plasma quality or safety, infections that could be transmitted, open wounds or skin conditions that could contaminate product or collection areas, and any circumstances that may compromise their ability to maintain appropriate hygiene.
- Personnel who are suffering from conditions that may adversely affect plasma quality must be excluded from direct contact activities until the condition is resolved, even if this creates staffing challenges, as product quality cannot be compromised.

Personal hygiene requirements must be established and enforced, including proper hand washing procedures that are performed at appropriate times, appropriate protective clothing that is clean and suitable for the work area, restrictions on jewelry that could harbor microorganisms or interfere with work, restrictions on cosmetics in production areas where they could contaminate product, and absolute prohibitions on eating, drinking, and smoking in production areas where such activities could introduce contaminants.

9. PREMISES AND EQUIPMENT

9.1 General Requirements for Premises

- Premises where plasma collection and processing occur must be carefully designed, constructed, and maintained to support high-quality operations.
- Location should be selected considering factors such as accessibility for donors and staff, freedom from environmental hazards, and adequacy of utilities.
- Design and construction must facilitate proper operations, with appropriate space allocation, suitable finishes, and infrastructure to support equipment and activities.
- The size and layout must be sufficient for the activities to be performed, avoiding cramped conditions that could lead to errors or cross-contamination.
- Facilities must be protected from adverse external conditions such as extreme temperatures, flooding, or pest infiltration that could compromise operations.
- Design should minimize contamination risk through appropriate materials, surfaces, and airflow patterns.
- Premises must be easy to clean and maintain, with smooth, non-porous surfaces and accessible areas.
- Adequate space must be provided for equipment and materials, avoiding overcrowding that could lead to mix-ups or damage.
- Different operations should be performed in defined areas with appropriate separation to prevent cross-contamination and confusion.
- Access must be controlled to prevent unauthorized entry to sensitive areas and to maintain security.
- Appropriate environmental controls, including heating, ventilation, and air conditioning where necessary, maintain suitable conditions for operations.
- Adequate lighting enables personnel to perform tasks accurately and safely. Proper ventilation provides fresh air and removes heat and contaminants.

9.2 Donor Areas

Donor areas must be designed with donor comfort, safety, and privacy in mind while also supporting efficient operations which includes:

- Reception and waiting areas should be comfortable and welcoming, creating a positive impression that encourages repeat donation.
- Registration areas must provide sufficient space and privacy for collecting donor information.
- Medical screening rooms must afford complete privacy for confidential discussions about medical history and examination.
- Collection areas must provide adequate space between beds or chairs to allow visual observation of all donors while maintaining reasonable privacy, with a recommended minimum of two square meters per collection station.
- Emergency equipment must be readily accessible in collection areas to enable rapid response to adverse reactions.

- Hand washing facilities must be conveniently located for staff use.
- Appropriate temperature and ventilation must be maintained to ensure donor comfort.
- Rest and refreshment areas allow donors to recover from donation before leaving.
- Emergency treatment facilities must be available to manage serious adverse reactions.
- Throughout donor areas, confidentiality must be maintained through private interview rooms, visual barriers that prevent donors from seeing others' medical information, sound barriers where necessary to prevent conversations from being overheard, and controlled access to documents and computer screens displaying donor information.

9.3 Processing Areas

Plasma processing areas must be segregated from donor areas to prevent confusion and cross-contamination, with clear physical separation and controlled access. These areas must provide:

- dedicated space for different activities to prevent mix-ups, prevent cross-contamination between different batches or types of plasma, maintain controlled environmental conditions appropriate for the processes performed, and have appropriate surfaces that are smooth, impervious to liquids, and easy to clean and sanitize.
- Critical processing areas that must be established include a blood or plasma component separation area where whole blood is centrifuged and plasma is separated,
- sampling area where samples are collected for testing under controlled conditions, a quarantine storage area where plasma awaits test results and release decision,
- released plasma storage area where plasma approved for fractionation is held until shipment,
- rejected plasma storage area that is clearly segregated where plasma that cannot be used is held pending disposal, and cleaning and sanitation areas where equipment and materials are cleaned.

9.4 Storage Areas

- Appropriate storage areas must be provided for plasma awaiting testing which is held in quarantine status, released plasma that has been approved for fractionation, rejected or discarded plasma which must be clearly segregated to prevent accidental use, materials and supplies used in operations, equipment and spare parts to support maintenance, and documents and records which may be stored electronically or in paper form.
- Plasma storage facilities are particularly critical and must maintain required temperatures, with frozen plasma stored at minus twenty-five degrees Celsius or colder to preserve plasma proteins.
- Temperature monitoring and alarm systems must provide continuous surveillance and alert personnel to any deviations.
- Backup power systems and potentially backup freezers to protect against power outages that could result in loss of valuable plasma.
- Storage capacity must be adequate for the volume of plasma being collected and the holding period before shipment.
- Organized inventory systems enable efficient tracking and retrieval of specific units. Access must be controlled to prevent unauthorized removal or tampering.
- The availability of multiple freezers or freezing rooms is desirable to enable segregation of different plasma types or statuses, facilitate maintenance and cleaning activities without disrupting all storage, and provide emergency backup capacity if one unit fails.

9.5 Laboratory Areas

- Laboratory facilities must be separated from production areas to prevent cross-contamination and maintain the integrity of testing.
- Adequate space and appropriate layout enable efficient workflow and prevent crowding that could lead to errors.
- Environmental controls maintain suitable conditions for testing, particularly temperature control for reagent storage and equipment operation.
- Proper ventilation and safety features protect personnel from chemical or biological hazards.
- Laboratory areas should include a sample receiving and processing area where samples are logged in and prepared for testing,
- Testing areas dedicated to specific types of testing such as serology, nucleic acid testing, and blood grouping, equipment rooms housing large instruments, sample storage areas where samples are held before and after testing at appropriate temperatures, and waste disposal areas where biological and chemical wastes are safely held pending disposal.

9.6 Supporting Areas

Additional facilities necessary to support operations include office and administrative areas where management and support functions are performed, staff facilities including changing rooms where personnel can change protective clothing, lockers for personal belongings, and rest rooms, cleaning equipment storage where cleaning supplies and equipment are kept separate from product areas, waste management facilities where waste is held pending collection and disposal, maintenance workshops where equipment repairs can be performed, and archives for long-term storage of records in controlled conditions.

9.7 Environmental Monitoring

- Environmental conditions throughout the facility must be appropriate for the activities performed and must be monitored to ensure they remain within acceptable ranges.
- Temperature is particularly critical in storage areas but also important in collection and processing areas for donor comfort and product stability.
- Humidity may be relevant in certain areas, particularly where hygroscopic materials are handled.
- Particulate levels in critical processing areas should be monitored to ensure cleanliness.
- Microbial contamination monitoring may be appropriate in areas where product is exposed to the environment or where required.
- Monitoring may be continuous, as with temperature monitoring in freezers using data loggers, or periodic, as with environmental sampling for microorganisms.
- All monitoring results must be documented and reviewed regularly.
- Deviations from acceptable ranges must be investigated to determine cause and impact, with appropriate corrective actions implemented.

9.8 Equipment General Requirements

- All equipment used in plasma collection, processing, testing, and storage must be suitable for its intended use, designed and constructed to facilitate cleaning and maintenance, constructed of materials that are

compatible with plasma and will not leach harmful substances, located appropriately to support efficient workflow, and maintained in proper working order through regular maintenance and repair.

- Every piece of equipment must be uniquely identified with a clear identification number or name.
- Equipment must be included in preventive maintenance programs with scheduled maintenance performed according to manufacturer recommendations.
- Calibration of measuring and monitoring equipment must be performed at appropriate intervals using traceable standards to ensure accuracy.
- Qualification of equipment through Installation Qualification, Operational Qualification, and Performance Qualification must be completed before equipment is placed into use.
- All equipment must be operated according to written procedures that have been validated to ensure consistent results.
- Only DRAP approved equipment/ medical devices shall be allowed.

9.9 Critical Equipment

Certain equipment is particularly critical to plasma quality and safety. Blood collection equipment, both automated and manual, must be properly maintained and operated to ensure safe donation and product quality.

- Apheresis devices used for source plasma collection are complex instruments requiring specialized training and maintenance.
- Centrifuges used to separate plasma from whole blood must operate at correct speeds and times to ensure proper separation.
- Plasma expressers must apply appropriate pressure to extract plasma without contamination.
- Heat sealers must create secure seals on collection bags to prevent leakage and contamination.
- Freezers and refrigerators must maintain appropriate temperatures reliably over extended periods.
- Temperature monitoring devices must be accurate and reliable as they provide critical data about product storage conditions.
- Laboratory analyzers used for testing must provide accurate and reproducible results. Blood Establishment Computer Systems control critical functions including donor management, inventory control, and release decisions.
- Scales and other measurement devices must be accurate as they determine important parameters such as donation volumes.

9.10 Equipment Qualification and Validation

All critical equipment must undergo a systematic qualification process before being placed into routine use to ensure it is properly installed, operates correctly, and performs reliably under actual use conditions.

- Installation Qualification,
- Operational Qualification
- Performance Qualification

Re-qualification must be performed after major repairs or modifications that could affect equipment performance, after equipment is relocated to a different area, and at defined intervals based on risk assessment and equipment history.

9.11 Calibration

Instruments and equipment used to measure or monitor critical parameters must be calibrated to ensure they provide accurate readings.

- Calibration must be performed before equipment is first placed into use, establishing its initial accuracy.
- Re-calibration must be performed at defined intervals determined by the type of equipment, manufacturer recommendations, and historical performance.

9.12 Maintenance

A comprehensive preventive maintenance program must be established to ensure equipment remains in good working order and to minimize unexpected failures.

9.13 Cleaning and Sanitation

Written procedures must be established for cleaning and sanitizing all premises, equipment, and collection devices where reusable equipment is employed. These procedures must specify the cleaning agents to be used, dilutions or concentrations, cleaning methods, frequency of cleaning, and persons responsible.

9.14 Computerized Systems

Blood Establishment Computer Systems play a critical role in modern plasma establishments, controlling many functions that directly affect product quality and safety. These systems must be:

- validated before implementation to demonstrate they function correctly and reliably.
- capable of preventing release of non-conforming plasma through programmed controls that check all release criteria.
- generate complete and accurate reports providing the information needed for decision-making and regulatory compliance.
- Protection against unauthorized access must be provided through user authentication, role-based access controls, and audit trails that record who accessed the system, what they did, and when.
- Regular backups of all data must be performed to prevent loss of critical information.
- All changes to the system must be managed through a formal change control process. Systems must comply with DRAP guidance on computerized systems and international standards for data integrity.

Blood Establishment Computer Systems must support essential functions including:

- comprehensive donor management and traceability from registration through all donations,
- collection scheduling to optimize donor flow and prevent over-donation,
- test result entry with verification to prevent errors in critical data,
- plasma inventory management tracking every unit from collection through disposition,
- release decisions based on programmed business rules that enforce all release criteria,
- lookback capabilities enabling rapid identification of affected units when a donor tests positive,
- and reporting and trending functions that provide management with visibility into operations and quality performance.

Electronic records and signatures must comply with regulatory requirements, ensuring that computerized systems provide the same level of control and assurance as paper-based systems.

System validation must demonstrate that the system works correctly and reliably. Audit trails must capture all significant events and changes, recording who performed each action, what action was performed, when it occurred, and in some cases why it was performed. Data integrity must be maintained through controls that ensure data is:

- Attributable to the person who created it
- Legible and permanent
- Contemporaneous with the event
- Original or a certified true copy
- Accurate and complete
- Complete with all relevant data
- Consistent without contradictions
- Enduring through the entire retention period
- Available when needed.
- Security and access controls prevent unauthorized access while enabling authorized users to perform their duties.
- Record retention systems ensure that electronic records remain readable and usable throughout the required retention period, which may span decades for plasma records.

10. BLOOD AND PLASMA COLLECTION

10.1 Collection Procedures

All blood and plasma collection procedures must be performed according to detailed written standard operating procedures that have been developed, reviewed, approved, and implemented. Collection may only be performed by personnel who have been trained in the relevant procedures, have demonstrated competency, and are authorized to perform collections. Collection procedures must be designed and executed to ensure aseptic technique throughout the process to prevent microbial contamination, appropriate vein selection and preparation to ensure safe venipuncture, proper use of all equipment according to manufacturer instructions and validated procedures, maintenance of donor comfort and safety throughout the procedure, and accurate labeling and documentation of all activities.

10.2 Pre-Collection Preparation

Before beginning any collection procedure, all equipment and supplies must be carefully prepared and verified. Every item must be verified for correct identity to ensure the right product is being used for the intended purpose. Each item must be inspected for integrity, checking that packages are intact, bags are not leaking, and equipment shows no signs of damage. Expiry dates must be confirmed to ensure all materials are within their period of validity. Appropriate storage temperature must be verified for temperature-sensitive materials.

The donor's identity must be positively verified using multiple methods to ensure the correct donor is being prepared for collection and to prevent donor substitution. Collection bag labels or equipment labels must be carefully checked for correct donor identification matched to the donor present, unique donation number that will enable tracking throughout the process, ABO and RhD blood group if this is known from previous donations, and collection date. Any discrepancies noted during these checks must be resolved before proceeding with collection.

10.3 Venipuncture and Collection

Preparation of the donor's arm must follow established aseptic procedures designed to minimize the risk of introducing microorganisms during venipuncture. In some protocols, the initial flow of blood may be diverted into a sample pouch or discarded to remove any skin plugs or contaminants that might have been introduced despite careful preparation. The actual collection must be performed strictly according to equipment manufacturer's instructions, as deviations could affect product quality or donor safety; established institutional procedures that have been validated; and requirements for collection volume and timing that ensure proper anticoagulant ratio and product quality.

Throughout the collection procedure, multiple parameters must be continuously monitored. The donor's status and comfort must be observed to detect any adverse reactions quickly, with particular attention to signs of vasovagal reactions such as pallor, sweating, or dizziness. Collection progress must be monitored to ensure appropriate flow rate and volume. Equipment function must be observed to detect any malfunctions promptly. Any adverse events that occur must be managed immediately according to protocols, documented thoroughly, and reported as required.

The volume collected must be appropriate to the donor's weight, ensuring that the donation does not exceed safe limits for the individual donor; the capacity of the collection system, as overfilling can cause problems with processing; and anticoagulant ratio requirements, as incorrect blood-to-anticoagulant ratios can compromise product quality and sterility.

10.4 Automated Plasmapheresis

Automated apheresis equipment used for source plasma collection involves sophisticated technology that must be properly controlled. All equipment must have been qualified and validated before being placed into routine use, demonstrating that it operates correctly and consistently. Maintenance must be performed according to manufacturer recommendations to ensure continued reliable performance. Only personnel who have been specifically trained in the operation of the particular model of equipment being used may operate automated apheresis devices.

Plasmapheresis procedures must be designed and executed to ensure correct setup and priming of the disposable set with all connections secure and air removed from lines, appropriate anticoagulant ratios throughout the procedure to prevent clotting in the disposable set and ensure product quality, proper separation efficiency that effectively separates plasma from cellular components, safe return of blood components to the donor without air embolism or other complications, and accurate volume control that ensures the correct volume of plasma is collected and returned blood volume is appropriate.

Only single-use disposable sets specifically designed for the equipment may be used, as reuse could introduce contamination, cause equipment malfunction, or compromise product quality. These disposable sets must be used only once and then appropriately discarded. Machine alarms and alerts must be responded to appropriately and promptly, as they indicate potential problems that could affect product quality or donor safety. All alarm events must be documented, including what alarm occurred, how it was resolved, and any impact on the procedure or product.

10.5 Sample Collection

Samples for laboratory testing must be collected at the time of donation to enable testing for transfusion-transmissible infections, blood grouping, and other required tests. Samples must be collected aseptically using proper technique to prevent contamination that could cause false-positive microbiology results, labeled immediately with unique identifiers that link the samples to the specific donation, collected in appropriate containers specified

for each type of test, and transported to the laboratory under specified conditions including appropriate temperature and timing to ensure sample integrity.

The integrity of samples must be ensured through proper collection technique that prevents hemolysis and contamination, appropriate handling that avoids rough treatment or exposure to extreme temperatures, and timely transport that gets samples to the laboratory within the required timeframe for testing.

10.6 Post-Collection Procedures

After the collection procedure is completed, appropriate care must be provided to the donor. Appropriate pressure must be applied to the venipuncture site for sufficient time to ensure hemostasis and prevent hematoma formation. Post-donation care instructions must be provided verbally and in writing, covering topics such as keeping the bandage in place, avoiding strenuous activity, maintaining adequate hydration, and recognizing delayed adverse reactions. The donor must remain under observation during a defined recovery period, typically fifteen to thirty minutes, during which time staff can detect and manage any delayed reactions. Refreshments, particularly fluids and light snacks, should be offered to help the donor recover. The donor must be assessed as fit to leave before departure is permitted, ensuring they are stable, alert, and not experiencing any concerning symptoms.

10.7 Anticoagulation and Plasma Collection Bags

Only approved anticoagulant solutions may be used for plasma collection, specifically citrate-based anticoagulants such as ACD (acid citrate dextrose), CPD (citrate phosphate dextrose), and similar formulations that have demonstrated safety and efficacy. All anticoagulants must comply with pharmacopeial standards. Anticoagulants must be used within their expiry dates to ensure potency, and appropriate storage conditions specified by the manufacturer must be maintained.

Blood collection bags must be from reputable manufacturers and should ideally be CE marked or possess equivalent certification demonstrating conformity with applicable standards. Bags must comply with relevant international standards such as those established by ISO or included in pharmacopeial monographs. All bags must be used within their expiry dates, stored according to manufacturer instructions to prevent degradation, and carefully inspected before use for any signs of damage or contamination.

The ratio of anticoagulant to blood or plasma must be carefully controlled to ensure adequate anticoagulation that prevents clotting during and after collection, suitable plasma quality that meets specifications for protein content and other parameters, and conformity with specifications established by fractionators and regulatory authorities.

10.8 Labeling

Every plasma unit must be properly labeled to ensure correct identification and prevent mix-ups that could have serious consequences. Labels must include the unique donation identification number that enables tracking through the entire system, the donor identification number that links the unit to the donor, ABO and RhD blood group once determined, collection date and time, volume collected or present after processing, type of anticoagulant used, expiration date or time by which the unit must be processed or discarded, storage temperature requirements such as "Keep Frozen," establishment identification showing where the plasma was collected, and a clear indication that the plasma is "For Fractionation Only" and not for transfusion.

All labels must be securely attached to the plasma container in a manner that prevents them from falling off or becoming illegible. Labels must remain legible and durable throughout storage and transport despite exposure to freezing temperatures and handling. Labels should comply with relevant international standards such as ISBT 128

that facilitate universal identification and tracking. The use of barcodes is strongly encouraged as they enable rapid, accurate scanning and tracking throughout the plasma supply chain, reducing the risk of transcription errors.

The establishments having exclusive license of DRAP shall label the plasm “For Fractionation Only”.

10.9 Adverse Events During Collection

Procedures must be established for managing a range of adverse events that may occur during or shortly after collection. Vasovagal reactions, including fainting and dizziness, are the most common adverse events and must be managed through appropriate positioning, monitoring, and supportive care. Hematomas can occur at the venipuncture site and require prompt application of pressure and cold compresses. Citrate reactions may occur during plasmapheresis when citrate anticoagulant causes hypocalcemia, presenting with tingling, numbness, or muscle spasms. Allergic reactions to materials used during collection require assessment and treatment. Equipment malfunctions during automated apheresis must be managed according to device-specific protocols to ensure donor safety.

Emergency equipment including oxygen, airway devices, medications for treating severe reactions, and equipment for managing cardiovascular emergencies must be readily accessible in all collection areas. Staff must be trained in cardiopulmonary resuscitation and emergency response, with at least one staff member with advanced training present during all collection activities.

All adverse events, regardless of severity, must be documented in detail including description of the event, timing and circumstances, symptoms experienced by the donor, interventions provided, outcome of the event, and any follow-up care provided. Events must be investigated to determine contributing factors and identify opportunities to prevent similar events in the future. Adverse events must be reported as required to DRAP , to fractionation partners as specified in quality agreements, and internally through the quality system for trending and analysis. Analysis of adverse event data reveals patterns and trends that may indicate systemic problems requiring management attention and corrective action. Serious adverse events including death, life-threatening events, events requiring hospitalization, or events causing permanent disability must be reported to DRAP and thoroughly investigated.

11. TESTING REQUIREMENTS

Every plasma donation intended for fractionation must undergo comprehensive testing for transfusion-transmissible infections before release for fractionation to prevent the transmission of infectious diseases through plasma-derived medicinal products. All testing must be performed in licensed laboratory facilities that meet applicable standards for medical laboratories, using validated test methods that have been shown to be reliable and fit for purpose, by qualified personnel who have been trained and assessed as competent, according to approved procedures documented in standard operating procedures, and with appropriate quality controls to ensure result validity. Test results must be reviewed and approved by authorized qualified personnel before any plasma release decision is made, ensuring that questionable results are identified and appropriately investigated.

11.1 Mandatory Testing for Transfusion-Transmissible Infections

Each individual donation must be comprehensively tested for transfusion-transmissible infections using methods that detect current or past infection. Serological tests represent the minimum testing requirements and must include testing for following:

- Hepatitis B surface antigen (HBsAg) which indicates current HBV infection,

- Antibodies to HIV-1 and HIV-2 which indicate HIV infection,
- Antibodies to Hepatitis C virus (anti-HCV) indicating HCV exposure,
- Antibodies to Hepatitis B core antigen (anti-HBc) which is strongly recommended as it detects additional HBV-infected donors who may be HBsAg-negative,
- Antibodies to Human T-Lymphotropic Virus I and II (anti-HTLV-I/II) which may be required based on regional epidemiology or fractionator requirements,
- Testing for Treponema pallidum (syphilis) antibody.
- Testing for Parvo B19.
- Testing for HAV.

Nucleic acid testing provides an additional layer of safety by detecting viral genetic material during the window period before antibodies develop and must include testing for HIV-1 RNA, HCV RNA, and HBV DNA. NAT testing may be performed on individual donations in what is termed ID-NAT or individual donation nucleic acid testing, or alternatively on mini-pools of samples, typically containing six to twenty-four samples, provided that full traceability is maintained and positive pools can be resolved to identify the specific reactive donation.

Additional testing beyond these mandatory requirements may be needed based on the epidemiological situation in the region, such as West Nile Virus in areas where this is endemic, Zika virus in areas with active transmission, Dengue virus in endemic regions, or Malaria testing for donors with relevant travel history; fractionator requirements which may exceed minimum regulatory requirements; destination country requirements when plasma is being exported to countries with specific testing mandates; and risk assessment considering local infectious disease patterns and emerging threats.

The mandatory requirement of NAT/serological testing shall be as per recommendation of NTAC. Moreover, the reporting of epidemiological data for the viral markers to foreign authorities shall also be placed before the NTAC.

11.2 Quality Control of Testing

Robust quality control procedures must be implemented to ensure testing reliability. These procedures must include daily controls for each test method, running both positive and negative controls with every batch of testing, internal quality control assessment in which control results are reviewed and must be within acceptable ranges before patient results are released, and participation in external quality assessment schemes conducted by independent bodies that send proficiency testing samples to laboratories for blind testing. Control results must be documented in detail, trended over time to detect shifts or trends indicating potential problems, and investigated thoroughly if results fall outside specifications. Equipment calibration and maintenance must be performed according to established schedules to ensure continued reliable performance.

The matter wherein the fully automated random access CMIA analyzers are used, the above requirements shall be determined by the NTAC.

11.3 Sample Management

Samples must be positively identified with the unique donation number using labels or other identification methods that will remain secure and legible, transported to the laboratory under appropriate conditions considering time and temperature requirements, logged upon receipt with verification that expected samples have been received and are in acceptable condition, tested within specified timeframes to ensure sample integrity, and stored appropriately after testing in case retesting is needed. Retention samples must be kept for a defined period, typically six to twelve

months at appropriate temperature, enabling retesting if required for investigations or quality issues, and supporting troubleshooting of discrepant results or equipment problems.

11.4 Testing Algorithms

Initial testing of all samples involves testing each sample once with each required assay to screen for potential infections. When reactive results are obtained, initially reactive samples must be retested in duplicate using the same assay, and if either or both repeat tests are reactive, the donation is classified as repeatedly reactive. Repeatedly reactive results mean the plasma must be permanently quarantined and may not be used for fractionation due to the unacceptable risk of containing infectious material, samples may be sent for confirmatory testing to definitively determine infection status, donors must be deferred and appropriately counseled about the finding and its implications, and lookback procedures must be initiated to identify other donations from the same donor.

Confirmatory testing involving supplemental tests such as Western blot for HIV, RIBA for HCV, or other specific assays are performed to confirm or refute initial screening results and guide donor counseling and permanent deferral decisions. Indeterminate results require established procedures for management, which may include donor deferral and scheduled repeat testing, consultation with the medical director to determine appropriate action, and clear communication with the donor about the uncertainty and follow-up plans.

11.5 Blood Grouping

ABO and RhD typing must be performed on the first donation from each donor to establish the donor's blood type, confirmed on subsequent donations per a defined schedule which may require confirmation on every donation or periodic confirmation such as annually, using validated methods that provide reliable results, and with appropriate controls run to verify test system functionality. Any discrepancies between current and previous results must be thoroughly investigated to determine the cause, which could include technical error, sample mix-up, rare blood group variants, or recent transfusion; resolved before plasma can be released; and documented with conclusions and corrective actions.

To accurately determine a donor’s blood group, the industry standard is to perform full blood grouping on the vacutainer sample taken from the blood bag at the time of draw. This includes Forward and Reverse grouping, along with Weak D testing for Rh-negative donations. The forward group can also be reconfirmed from the sample collected from the blood bag tubing, a process we refer to as blood group reconfirmation. The donor’s blood group is recorded and labeled only after confirming concordance between these results. The aforesaid requirement shall be determined by the NTAC.

11.6 NAT Testing Procedures

Nucleic acid testing requires specialized laboratory infrastructure, equipment, and practices. A specialized laboratory environment with physically separate areas for pre-amplification activities where samples and master mix are prepared, amplification area where PCR or other amplification occurs, and post-amplification area where amplified products are detected is essential to prevent contamination. Sophisticated equipment including validated NAT platforms from reputable manufacturers must be properly maintained. Personnel must receive specialized training in molecular methods, contamination prevention, and troubleshooting. Stringent contamination control procedures are absolutely essential as amplified DNA or RNA from previous tests can easily contaminate subsequent tests causing false-positive results.

When mini-pool NAT is performed, samples are pooled according to a validated algorithm that specifies pool size, pooling procedure, and documentation requirements. Positive pools must be resolved to identify which individual donation is reactive through a systematic process that may involve re-testing individual samples from the pool or testing smaller sub-pools. Full traceability must be maintained throughout the pooling and resolution process to ensure every sample can be tracked. Detailed standard operating procedures must clearly define all aspects of pooling, testing, and resolution to ensure consistency and reliability.

Individual donation NAT, in which each donation is tested separately without pooling, offers higher sensitivity for detecting early infections, eliminates the complexity of pool resolution, and is preferred where resources permit, though it is more expensive than mini-pool testing.

However, for closed automation systems, the above requirement can be exempted if approved by NTAC.

11.7 Test Result Management

Test results must be carefully managed to prevent errors that could result in release of infected plasma. Results must be entered into the computer system with verification for manual entry to prevent transcription errors, reviewed by authorized personnel who are qualified to interpret results and identify anomalies, and approved before release decision to ensure no infected plasma is released or be electronically transmitted from the analyzer to the Blood Banking Management Information System.

Results must be communicated to production and release areas in a timely manner to avoid unnecessary delays. Electronic information systems must be designed and validated to prevent release of plasma with reactive or missing test results through programmed business rules, provide alerts for pending results that could delay release, block release of future donations from reactive donors permanently, and maintain comprehensive audit trails of all data entry and changes.

Comprehensive test result records must document donation identification, test name and kit or method information including manufacturer and lot number, test date and time, operator identification, raw data from instruments, interpreted results showing reactive, non-reactive, or indeterminate, quality control results demonstrating test system was functioning properly, and approval signatures from authorized personnel.

11.8 Laboratory Documentation

Laboratory operations must be thoroughly documented to demonstrate compliance and enable investigations. Laboratory records must include detailed test procedures in standard operating procedures, equipment maintenance and calibration records demonstrating equipment reliability, reagent receipt, storage, and use records ensuring proper reagent management, quality control results with trending, all test results with interpretations, investigations of atypical results and corrective actions taken, and comprehensive training records demonstrating personnel competency. All records must be retained per regulatory requirements, typically a minimum of ten years after plasma expiry or longer for certain critical records.

11.9 Laboratory Personnel

Laboratory personnel must be appropriately educated with a minimum of a bachelor's degree in medical laboratory technology, clinical laboratory science, microbiology, or a related scientific field providing the necessary foundation. Personnel must be specifically trained for the tasks they will perform, with documented competency

assessment. Personnel must be supervised by a qualified laboratory manager or supervisor who has advanced education and experience. Testing personnel should not be involved in donor screening or collection activities to maintain independence and avoid conflicts of interest that could compromise objectivity.

12. PROCESSING AND STORAGE

12.1 Plasma Processing

Plasma processing must be performed according to well-established procedures that ensure maintenance of plasma protein quality and prevent microbial contamination. Processing must occur within appropriate timeframes to prevent protein degradation, under controlled environmental conditions including appropriate temperature, and with procedures to prevent mix-ups or contamination. When recovered plasma is obtained from whole blood, the process includes centrifugation using a hard spin method to effectively separate plasma from cellular components, expression or extraction of the plasma from the bag, and completion within a defined timeframe from collection, typically eight to twenty-four hours depending on the type of plasma and storage conditions. Source plasma collection by automated apheresis is largely completed during the collection procedure itself, with minimal additional processing required.

12.2 Freezing Requirements

Plasma must be frozen rapidly to a core temperature of minus twenty-five degrees Celsius or colder to preserve protein quality and prevent degradation. Freezing must occur within defined timeframes from collection, typically twenty-four hours for recovered plasma, eight hours for source plasma, or as specified by fractionator requirements. Validated freezing equipment that has been shown to achieve required temperatures consistently must be used. The freezing rate must be rapid enough to preserve plasma proteins and prevent crystal formation that could damage proteins, and must be documented and monitored to verify compliance. The size of plasma containers and stacking configuration must be controlled to ensure all units in a freezer load reach the required temperature within the specified timeframe.

12.3 Storage Conditions

Frozen plasma must be stored at minus twenty-five degrees Celsius or colder, with many facilities maintaining temperatures of minus thirty to minus forty degrees Celsius to provide additional safety margin. Continuous temperature monitoring using validated data loggers or chart recorders provides assurance that temperature is maintained.

All plasma must be protected from temperature excursions through alarm systems, backup power, and emergency procedures. Storage must be in validated freezers or freezing rooms that have been qualified to maintain the required temperature uniformly throughout the storage space. Storage facilities must incorporate alarm systems for temperature deviations that alert responsible personnel immediately when temperature rises above acceptable limits, backup power systems including emergency generators and in some cases backup freezers to protect against power outages, temperature mapping studies to identify any hot or cold spots where temperature may not be uniform, controlled access to prevent unauthorized removal or tampering, and organized storage systems that facilitate inventory management and retrieval.

Plasma must be stored in a manner that prevents physical damage from crushing or dropping, contamination from leaking units or environmental sources, and loss of identification from damaged or detached labels.

12.4 Cold Chain Management

The integrity of the cold chain must be maintained continuously from initial collection through processing, freezing, storage, and transport to the fractionation facility, recognizing that any break in the cold chain could compromise plasma quality. Comprehensive cold chain management encompasses validated freezing procedures that have been shown to achieve required temperatures reliably, validated storage conditions with documented temperature uniformity and stability, validated transport conditions that maintain frozen state during shipping, temperature monitoring throughout all stages with continuous or periodic data collection, documented temperature records that provide permanent evidence of compliance, investigation of any excursions to determine cause and impact, and risk assessment for any deviations to determine whether plasma quality has been compromised.

Temperature excursions, meaning any time when temperature rises above the specified maximum, must be detected immediately by monitoring systems, investigated without delay to determine the cause and extent of the excursion, assessed for impact on plasma quality considering the duration and magnitude of the temperature rise and the susceptibility of plasma proteins to degradation, documented thoroughly including all circumstances and actions taken, reported to the fractionator who must assess whether the affected plasma remains acceptable, and may result in plasma rejection if specifications are not met or if risk is determined to be unacceptable.

12.5 Quarantine Storage

All plasma must be held in quarantine status pending completion of all release requirements. Plasma remains in quarantine until all test results are available and confirmed to be acceptable, donor eligibility has been thoroughly verified, for source plasma from applicant donors the qualifying donation has been completed with negative results confirming the donor's status, and a formal release decision has been made by an authorized Qualified Person. Quarantined plasma must be physically segregated from released plasma through storage in different freezers or freezing rooms, or alternatively electronically quarantined through computer system controls that prevent physical access or release until approved. Quarantine plasma must be clearly labeled with its status as "quarantine" or "not released" to prevent accidental distribution.

For source plasma collected from applicant donors, the minimum quarantine period extends until the qualifying donation is tested and found negative, typically sixty to one hundred eighty days after the first donation, though alternative approaches may be acceptable if approved by the fractionator and supported by appropriate risk assessment.

12.6 Storage Segregation

Storage areas must provide clear segregation for quarantined plasma that is awaiting completion of release requirements, released plasma that has been approved for fractionation and is awaiting shipment, rejected plasma that has failed testing or other release criteria and must be prevented from accidental use, different plasma types including distinctions between source and recovered plasma and separation by blood groups, and different fractionators or customers if the establishment supplies multiple recipients. Segregation may be achieved through physical separation using different freezers, rooms, or designated areas within larger spaces, electronic segregation using computer system controls that limit access based on plasma status, or combination approaches that use both physical and electronic methods.

The risk of mix-ups between different categories of plasma must be minimized through clear and prominent labeling, color coding systems that provide visual distinction, controlled access that prevents unauthorized handling, and verification procedures that confirm identity before any transfer or shipment.

12.7 Plasma Handling Procedures

All procedures for handling frozen plasma must be designed to minimize temperature exposure by limiting time outside freezers and using cold storage during transfers, physical damage by preventing dropping, crushing, or rough handling, and contamination risk through aseptic technique and prevention of cross-contamination. Plasma transfers between storage areas must be performed under cold chain conditions using insulated containers with adequate cooling, documented with transaction records showing what was moved, when, from where to where, and by whom, and verified for accuracy through counts and identity checks. Plasma inventory management should utilize first-in-first-out systems that ensure older plasma is used before newer plasma, regular inventory reconciliation comparing physical inventory to computer records, and investigation of any discrepancies to identify and correct causes of inventory errors.

12.8 Shelf Life and Stability

The shelf life of frozen plasma must be established based on stability studies demonstrating protein stability over time, fractionator requirements which may specify maximum ages for plasma they will accept, and regulatory requirements. Typical shelf life for plasma stored at minus twenty-five degrees Celsius or colder ranges from five to ten years, though specific limits should be established based on data. Expired plasma, meaning plasma that has exceeded its established shelf life, must be segregated from usable plasma, not used for fractionation, and disposed of according to approved procedures.

12.9 Sampling

Samples collected from plasma units for testing must be collected aseptically using proper technique to avoid introducing contamination, in appropriate containers specified for the type of testing to be performed, with clear identification linking the sample to the specific plasma unit, and in a manner that is representative of the plasma in the unit. Sample integrity must be carefully maintained during storage at appropriate temperatures and during transport to the testing laboratory in a timely manner under specified conditions.

13. RELEASE OF PLASMA FOR FRACTIONATION

13.1 Release Requirements

Plasma may only be released for fractionation after all mandatory requirements have been satisfied. All mandatory testing must be completed with acceptable results showing all transfusion-transmissible infection tests are non-reactive. Donor eligibility must be thoroughly verified based on medical history, physical examination, and laboratory parameters. Any quarantine period must be satisfied, particularly for source plasma from applicant donors. All documentation must be complete and accurate with no missing information or unresolved discrepancies. A comprehensive quality review must be performed examining all aspects of the plasma unit's history. Finally, a formal release decision must be made by an authorized Qualified Person who certifies compliance with all requirements.

13.2 Release Criteria

- Plasma must meet all established specifications covering following:
- Donor eligibility according to criteria,

- Test results with all TTI tests negative,
- Blood group confirmation verified,
- Volume and quality parameters meeting specifications,
- Processing requirements completed correctly,
- Labeling requirements with all necessary information present and documentation completeness.

Specifications must be clearly defined in quality agreements with fractionators, documented in standard operating procedures to ensure consistent application, based on regulatory requirements and pharmacopoeial standards, and understood by all personnel involved in release decisions.

13.3 Qualified Person Review and Release

A designated Qualified Person bears ultimate responsibility for plasma release and must review comprehensive batch records, verify all criteria are met through examination of documented evidence, make the release decision based on professional judgment, certify the batch for release through formal signature, and sign release documentation including batch certificates. Only QP-approved plasma may be distributed to fractionators. The Qualified Person must have complete authority to reject non-conforming plasma regardless of business pressures, access to all relevant information including test results, manufacturing records, and investigation reports, and independence from production operations and pressures to enable objective decision-making.

13.4 Electronic Release Systems

Electronic information systems may facilitate and streamline release decisions provided the system is fully validated to demonstrate it functions correctly and reliably, cannot release plasma that fails any criterion through programmed business rules and system controls, requires independent verification for manual entry of critical data to prevent transcription errors, maintains hierarchical access controls that limit who can perform which functions, provides comprehensive audit trails recording all activities and changes, and blocks release of future donations from reactive donors automatically. Despite electronic system capabilities, Qualified Person oversight and authorization remains required, as the QP cannot delegate the ultimate responsibility for release decisions.

13.5 Batch Certification

For each batch or shipment released for fractionation, comprehensive documentation must be prepared and maintained. Documentation includes:

- Batch certificate signed by the Qualified Person,
- Summary of testing results for all units in the batch,
- Confirmation of specification compliance stating that all requirements have been met,
- Detailed list of units included with their individual identification numbers,
- Reference to the quality agreement under which the plasma is supplied, Identification of the fractionator receiving the plasma.

Batch records must be retained for the required period, typically a minimum of ten years after plasma expiry.

13.6 Rejected Plasma

Plasma that fails to meet release criteria for any reason must be clearly labeled as "rejected" or "not for use" to prevent accidental release, physically segregated from released plasma in a designated area, subject to appropriate

disposition through destruction or alternative use if permitted by regulations, and fully documented with detailed explanation of the rejection reason and disposition actions taken. Rejected plasma must never be released for fractionation regardless of business pressures or supply shortages.

14. DISTRIBUTION AND EXPORT

14.1 Distribution Procedures

Distribution of plasma must be performed according to written procedures that ensure maintenance of cold chain throughout distribution, correct product identity with no mix-ups or substitutions, proper packaging to protect plasma during transport, complete documentation providing traceability and regulatory compliance, and full traceability enabling tracking from source to destination. Only plasma that has been formally released by a Qualified Person may be distributed to fractionators.

14.2 Quality Agreements with Fractionators

A written quality agreement must be established with each fractionator receiving plasma, creating a clear understanding of expectations and requirements. The quality agreement must comprehensively cover donor selection criteria specifying the standards donors must meet, testing requirements and specifications defining what tests are required and acceptance criteria, processing requirements describing how plasma must be collected and processed, storage and transport conditions establishing temperature and other requirements, labeling and identification requirements specifying the information that must be present, documentation requirements defining what records must be provided, notification procedures for deviations, adverse events, and quality issues, audit and inspection arrangements allowing verification of compliance, clearly defined roles and responsibilities of each party, requirements for samples and retained samples, Plasma Master File maintenance and updating procedures, and regulatory compliance obligations of both parties.

Quality agreements must be signed by authorized representatives from both organizations, reviewed periodically at least annually to ensure they remain current and appropriate, updated as necessary when requirements change, and available for review by DRAP and other regulatory authorities. Both the plasma establishment and fractionator must comply with all agreement terms, as these agreements create binding obligations that protect plasma quality and safety.

14.3 Packaging for Distribution

Packaging must be designed and validated to maintain the frozen state throughout transport even under adverse conditions, protect against physical damage from dropping, crushing, vibration, or other handling, comply with all applicable transport regulations for dangerous goods, and meet fractionator specifications.

Packaging materials typically include insulated containers with thick walls to minimize heat transfer, sufficient dry ice or other coolant to maintain temperature for the expected transport duration plus a safety margin, shock-absorbing materials such as bubble wrap or foam to protect plasma containers, and appropriate sealing to prevent coolant escape and maintain container integrity.

All packaging procedures must be validated to demonstrate temperature maintenance for the expected transport time plus a margin for delays or adverse conditions, protection against physical damage under simulated transport conditions, and compliance with all transport requirements. Packaging procedures must be documented in standard

operating procedures and performed by trained personnel who understand the critical importance of proper packaging.

14.4 Labeling for Distribution

Each individual plasma container must be labeled with complete identification including unique identification number, blood group, collection date, volume, "For Fractionation Only" designation, storage temperature requirement, and any special handling requirements.

Cartons or boxes containing multiple plasma units must be labeled with shipment identification number, count of units enclosed, description of contents including plasma type, blood groups of units enclosed, recipient information identifying the fractionator, sender information identifying the plasma establishment, storage requirements prominently displayed, handling instructions such as "Keep Frozen" and orientation requirements, and regulatory markings including biohazard symbols as appropriate.

The use of barcode labeling is strongly encouraged as it facilitates automated tracking throughout the supply chain, reduces transcription errors, and enables rapid verification of contents.

14.5 Shipping Documentation

Each shipment must be accompanied by comprehensive documentation including a detailed packing list or manifest listing every unit being shipped, batch certificate certified by Qualified Person, certificate of analysis summarizing test results, test result summaries providing detailed testing information, transport documentation such as air waybill or bill of lading, temperature monitoring records from the shipment, and export documentation for international shipments. All documentation must be complete and accurate to avoid delays or rejection of shipments. Copies of all documentation must be retained by the plasma establishment for traceability and regulatory compliance.

14.6 Transportation

Transport arrangements must ensure reliable maintenance of the frozen state at minus twenty-five degrees Celsius or colder throughout the journey, protection from temperature excursions through validated packaging and procedures, prompt delivery to minimize time in transport, security preventing theft or tampering, and compliance with all applicable transport regulations. Transport may utilize dedicated vehicles operated by the plasma establishment or fractionator, contract carriers specializing in frozen biological materials, air freight for long distances or international shipments, or sea freight for large volumes and longer distances where appropriate.

Transport providers must be carefully qualified based on demonstrated capability to maintain cold chain, reliability and positive track record, robust quality system, and adequate insurance and liability coverage. Transport validation must demonstrate adequate temperature control for the maximum expected duration including delays, worst-case scenarios such as adverse weather conditions or mechanical failures, and all transport modes that will be used.

14.7 Temperature Monitoring During Transport

Temperature monitoring devices must be included in shipments to provide verification of temperature maintenance. These devices may include data loggers that continuously record temperature at set intervals and store the data for later retrieval, temperature indicators that show whether temperature has exceeded specified thresholds, or active monitoring systems that provide real-time temperature reporting for high-value shipments. Monitoring devices must be properly calibrated and validated, placed in representative locations within the shipment rather than directly on

coolant where readings would not reflect product temperature, set to record at appropriate intervals typically every fifteen to thirty minutes, and equipped with alarms for active systems that alert responsible parties when excursions occur.

Temperature records must be retrieved upon arrival and examined for acceptability before plasma is accepted, thoroughly documented in shipment records, and retained for the required period. Any temperature excursions during transport must trigger immediate investigation to determine cause and extent, assessment for impact on plasma quality consulting with quality and technical personnel, reporting to the fractionator to enable their assessment, and may result in plasma rejection if specifications are not met or if risk is deemed unacceptable.

14.8 Export Procedures

Export of plasma from Pakistan to international destinations requires compliance with multiple regulatory frameworks. Establishments must maintain a valid license for plasma collection issued by DRAP, comply with all DRAP export regulations including notification and documentation requirements, obtaining Lot Release Certificate for all batches in shipment from the National Control Laboratory for Biological (NCLB) and No Objection Certificate from QA&LT Division of DRAP for each shipment, comply with all import country requirements of the destination country, and provide required export documentation.

Export applications to DRAP should include detailed information about the fractionator and destination country, quantity and type of plasma being exported, batch certificates and test summaries demonstrating quality, reference to the quality agreement or copy thereof, import permit from destination country if required by that country, and transportation details including carrier, route, and estimated delivery time.

Comprehensive export documentation to obtain NOC from DRAP typically includes:

- Commercial invoice,
- Detailed packing list,
- Certificate of origin,
- Certificate of Analysis,
- Lot Release Certificate issued by NCLB DRAP,
- Transport documents such as air waybill or bill of lading,
- Any other documents as required DRAP or by the destination country's import regulations.

15. TRACEABILITY AND DOCUMENTATION

15.1 Traceability Requirements

A robust and comprehensive traceability system must be established enabling complete tracking of each plasma unit from the original donor through to final disposition, whether that disposition is fractionation, expiry, destruction, or other outcome. The system must track all intermediate processing steps including collection, testing, processing, freezing, and storage. Traceability must function in both forward and backward directions, enabling queries that start with a donor and find all plasma produced, or start with a plasma unit and identify the source donor. This extensive traceability capability must be maintained for a minimum of thirty years, recognizing that lookback investigations may be initiated many years after plasma collection. The traceability system must be capable of supporting lookback investigations when donors are found to have infections, product recalls if quality problems are identified, adverse event investigations to determine whether plasma may have been involved, and regulatory audits that require demonstration of complete traceability.

15.2 Unique Identification Numbers

Unique identification systems must be implemented to enable precise tracking of all entities within the plasma supply chain. Each donor must be assigned a unique donor identification number that remains consistent throughout their relationship with the establishment. Each donation must receive a unique donation number that will follow that specific donation through all subsequent processing. Individual plasma units must have unique identifiers enabling tracking even if units are split or pooled. Test samples must be uniquely identified and linked to the corresponding donation. Each batch or shipment must have a unique identifier enabling tracking of groups of plasma units.

Identification systems should ideally comply with international standards such as ISBT 128, which is the preferred global standard for blood and plasma identification, or equivalent coding systems that enable universal identification and data exchange. The implementation of barcode technology is strongly encouraged throughout the system as barcodes facilitate rapid and accurate scanning, reduce manual transcription errors, enable automated tracking throughout the supply chain, and improve efficiency while reducing the risk of mix-ups.

15.3 Computer Systems for Traceability

Computer Software must provide comprehensive traceability functionality including the ability to link each donor to all donations they have made over time, link each donation to the specific plasma units produced, link plasma units to all corresponding test results, link plasma units to shipments and fractionators, enable rapid lookback queries to identify all plasma from a specific donor, generate traceability reports for audits and investigations, and maintain permanent audit trails of all transactions.

System validation must demonstrate that traceability functions work accurately and reliably under all conditions. Comprehensive data backup and disaster recovery procedures must ensure that traceability data remains available even in the event of system failures, with regular backups stored securely, tested recovery procedures to verify backups can be restored, and off-site backup storage to protect against localized disasters.

15.4 Documentation Requirements

All activities that affect plasma quality and safety must be thoroughly documented, creating a permanent record of what was done, how it was done, when it was done, and who did it. Documentation must be contemporaneous, meaning it is recorded at the time the activity is performed rather than reconstructed later. Documentation must be accurate and complete, containing all necessary information without omissions or errors. All documentation must be legible and permanent, using ink or electronic media that will not fade or degrade. Documentation must be attributable, clearly identifying the person who performed each action. All documents must be dated to establish timing of activities. Critical actions or decisions should be reviewed and approved by appropriate personnel through signatures or electronic approval records.

Key documentation types include Standard Operating Procedures providing detailed instructions, batch records documenting actual production activities, donor records capturing complete donor history, test records documenting all laboratory testing, equipment records covering maintenance, calibration, and qualification, training records demonstrating personnel qualifications, deviation and investigation records documenting problems and resolutions, CAPA records showing systematic problem-solving, audit reports providing independent assessment, quality agreements establishing commitments with fractionators, and shipment records documenting distribution.

15.5 Batch Records

A comprehensive batch record must be generated for each collection session, processing batch, and shipment. Batch records must include batch identification with unique number, date and time of all activities performed, identification of all personnel involved, materials and equipment used with identification numbers, detailed processing steps performed with parameters achieved, environmental conditions during critical steps, all test results with interpretations, any deviations that occurred with explanations, and review and approval signatures from authorized personnel. Batch records must be retained for at least ten years after the plasma expiry date or as specified by DRAP, whichever is longer.

15.6 Record Retention

Records must be retained for specified minimum periods reflecting the long-term nature of plasma traceability requirements and potential investigation needs.

- Donor records must be maintained for a minimum of thirty years after the donor's last donation to enable decades-long lookback. Plasma batch records must be kept for a minimum of ten years after plasma expiry.
- Test records must similarly be maintained for a minimum of ten years after plasma expiry.
- Quality system records should be retained for a minimum of ten years or longer as appropriate for the specific record type.
- Equipment records must be kept throughout the equipment's operational life plus ten years thereafter. Training records should be maintained throughout the individual's employment plus ten years after departure.
- Lookback period for discarded donations to be maintained for six months.

Records may be retained in paper format stored in secure, climate-controlled archives with controlled access and protection from damage, in electronic format using validated electronic record systems with regular backups and long-term readability plans, or in combination approaches using both paper and electronic storage with appropriate controls for each format.

Archived records must be protected from damage, loss, or deterioration through appropriate storage conditions and handling procedures, readily retrievable when needed for investigations, audits, or regulatory inspections, and subject to access controls that prevent unauthorized viewing or modification while enabling legitimate use.

15.7 Electronic Records and Signatures

Electronic records and signatures are increasingly used in plasma establishments and must be properly controlled to ensure they provide equivalent assurance to paper-based systems. These systems must comply with guidance of SRA’s on computerized systems, data integrity principles known as ALCOA+ requiring that data be Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring, and Available, and principles similar to 21 CFR Part 11 used internationally for electronic records and signatures.

Electronic systems must incorporate robust user authentication through passwords, biometrics, or other secure methods, comprehensive audit trails that capture all significant events including who performed each action, what action was performed, when it occurred, and why it was performed if the system requires reason codes, record security and backup to prevent loss or corruption, validated operation demonstrated through testing before implementation, and migration plans for long-term retention addressing how records will remain readable as technology evolves.

Electronic signatures must be unique to each individual user, verified at each use through secure authentication, permanently linked to the records they sign in a manner that prevents separation, and non-repudiable meaning the individual cannot later deny having signed.

15.8 Document Control

All controlled documents within the quality system must be managed through formal document control procedures covering their entire lifecycle. Version control enables management of multiple revisions without confusion, with each version clearly marked. The review and approval process ensures documents are examined by appropriate personnel before implementation. Distribution management ensures those who need documents receive them and that copies can be retrieved when revisions are issued. Training on new or revised documents ensures personnel understand changes before implementation. Retrieval of obsolete versions prevents their continued use, which could lead to errors or non-conformances. Archive management maintains superseded versions for historical reference.

Document changes must always be made through the formal change control process, never through informal or undocumented revisions.

16. ADVERSE EVENT REPORTING AND LOOKBACK PROCEDURES

16.1 Adverse Events in Donors

All adverse events occurring in donors during or after donation must be thoroughly documented including detailed description of the event and symptoms, severity classification using established criteria, immediate management and interventions provided, outcome and resolution, investigation findings identifying contributing factors, and preventive actions to reduce recurrence risk.

Serious adverse events must be promptly reported to DRAP within defined timeframes, typically twenty-four to forty-eight hours, thoroughly investigated to determine root causes, subject to CAPA to address identified problems, and reviewed for causality to determine relationship to the donation procedure. Serious adverse events include death of a donor, life-threatening events requiring emergency intervention, events requiring hospitalization or prolonged medical care, events causing permanent disability or impairment, and any events requiring significant medical intervention to prevent serious outcomes.

16.2 Adverse Events Related to Plasma

Although plasma undergoes viral inactivation and pathogen reduction during fractionation, any adverse events related to plasma-derived medicinal products must be carefully managed. Information must flow from fractionator to plasma establishment when product problems occur, from plasma establishment to DRAP for regulatory awareness, and from DRAP to international pharmacovigilance/ hemovigilance platforms. Even with pathogen inactivation, any potential transmission events must be thoroughly investigated to understand how they occurred and prevent recurrence. The Adverse Events Related to Plasma shall be reported in accordance with DRAP Pharmacovigilance Rules 2022.

16.3 Lookback Procedures

Formal lookback procedures must be established to identify all plasma from donors who subsequently test positive for transfusion-transmissible infections, quarantine affected units to prevent their use, notify fractionators of potentially affected shipments, and assess risk to recipients of manufactured products.

Lookback must be triggered by confirmed positive TTI test results on any donor, diagnosis of CJD or vCJD in a donor, receipt of information indicating a donor received infected blood transfusion, or other information indicating potential infectious risk.

The lookback process systematically identifies all previous donations from the affected donor using the traceability system, determines the disposition of all units whether they remain in inventory, have been shipped to fractionators, or have been destroyed, immediately notifies fractionators for any released units so they can assess impact on their plasma pools and products, quarantines any units still in inventory to prevent release, and thoroughly documents all actions taken and parties notified.

The lookback period typically encompasses all donations within twelve months prior to the positive test, though this may be extended based on risk assessment, disease characteristics, and regulatory requirements. The robust traceability system enables rapid lookback queries to identify affected units quickly.

16.4 Traceback and Traceforward

Traceback represents investigation from a recipient of plasma-derived medicinal products backward to identify the plasma donor or donors whose plasma may have been involved. Traceforward represents investigation from a donor forward to identify all plasma-derived medicinal product recipients who may have received products made from that donor's plasma. Both directions of tracing require robust traceability systems with complete records. Close cooperation with fractionators and health authorities is essential to enable effective investigations across organizational boundaries.

16.5 Product Recalls

Formal recall procedures must be established for plasma still under the establishment's control before shipment and plasma that has been shipped to fractionators. Recall decisions consider the nature and severity of the quality issue that has been identified, risk to recipients if the plasma is used for manufacturing, regulatory requirements mandating recalls for certain defects, and fractionator assessment of whether the plasma can still be safely used given the nature of the problem.

The recall process systematically identifies affected plasma units using the traceability system, quarantines units remaining in inventory to prevent release, immediately notifies fractionators of shipped units providing complete information about the problem, coordinates with fractionators on disposition decisions, documents all actions taken with complete records, reports to DRAP as required by regulations, investigates root causes to understand why the problem occurred, and implements CAPA to prevent recurrence.

Recall effectiveness must be verified by confirming all affected units are accounted for and confirming appropriate disposition has occurred.

16.6 Communication with Donors

Donors who receive confirmed positive results for transfusion-transmissible infections must be handled with sensitivity and professionalism. They must be notified by a qualified healthcare professional with appropriate training in counseling, provided with appropriate counseling about the implications of the positive result, referred

for medical follow-up and treatment as appropriate, advised about permanent deferral from all future blood or plasma donation, and informed about prevention of transmission to others.

Strict confidentiality must be maintained throughout this process to protect donor privacy. Procedures must comply with all applicable laws regarding disclosure of health information, patient rights, and ethical requirements. The notification and counseling process recognizes that learning of an infection diagnosis is traumatic and donors need compassionate support.

17. AUDITS AND INSPECTIONS

17.1 Internal Audits

Regular internal audits must be conducted as an integral part of the quality management system. These audits provide independent assessment of GMP compliance, evaluate quality system effectiveness, identify opportunities for improvement, and ensure adherence to established procedures across all areas of operation. Internal audits should be conducted by trained auditors who are independent of the areas being audited to ensure objectivity, with audit frequency determined by risk assessment and previous findings, thorough documentation of all observations and findings, development of action plans to address identified issues, and systematic follow-up to verify completion and effectiveness of corrective actions.

17.2 Supplier and Contract Audits

Suppliers and contractors providing critical services or materials must be carefully qualified before approval and periodically re-audited to ensure continued compliance. Initial audits before supplier approval verify that the supplier has adequate quality systems, facilities, and capabilities to meet requirements. Periodic re-audits at risk-based frequencies ranging from annually to every three years depending on the criticality of the supplier and their performance history provide ongoing assurance. Regular review of quality agreements and supplier performance metrics supplements audits. All audit findings must be thoroughly documented and systematically followed up to ensure resolution of identified issues.

17.3 Audits by Fractionators

Plasma establishments must facilitate audits conducted by their fractionator customers, recognizing that these audits serve important purposes. Fractionator audits verify compliance with quality agreements that establish requirements for plasma supply, assess GMP compliance to ensure plasma is produced according to appropriate standards, evaluate adequacy of plasma quality relative to fractionator specifications, verify traceability systems function correctly, and evaluate effectiveness of corrective actions for previous findings.

Establishments should cooperate fully with fractionator auditors, providing access to all relevant areas, unrestricted access to all relevant records and data, opportunities to interview personnel involved in operations, and transparent responses to all questions and observations. Audit findings must be carefully reviewed, understood, and addressed within agreed timeframes, typically thirty to ninety days depending on the severity of the findings. Fractionator audit outcomes may affect continued business relationships if significant deficiencies are not adequately resolved.

17.4 DRAP Inspections

DRAP conducts inspections of licensed establishments to verify regulatory compliance and assess quality systems. Inspections may be conducted for initial licensing before operations begin, license renewal at periodic intervals and routine surveillance to monitor ongoing compliance, for-cause inspections in response to quality problems or complaints, or pre-approval for new processes, equipment, or products.

Inspections comprehensively assess compliance with licensing conditions established at the time the license was granted, these requirements and all applicable technical requirements, GMP requirements applicable to plasma collection and processing, and all regulatory requirements under the Drugs Act and DRAP Act, and Rules framed thereunder .

Serious GMP deficiencies identified during inspections may result in regulatory actions including issuance of warning letters detailing deficiencies, license suspension preventing operations until corrections are made, license revocation permanently canceling authorization, or other regulatory actions deemed appropriate to protect public health.

18. REFERENCES

18.1 Regulatory References

These requirements are grounded in Pakistani legislation and regulations that establish the legal framework for plasma collection and distribution. The foundational Drugs Act of 1976, designated as Act No. XXXI of 1976, provides broad authority for regulation of drugs and biological products throughout Pakistan. The DRAP Act of 2012, formally Act No. I of 2013, established the Drug Regulatory Authority of Pakistan and defined its powers and responsibilities for ensuring drug quality and safety. The National Blood Policy of 2025, promulgated by the Ministry of National Health Services, Regulations and Coordination, establishes overarching principles for blood and plasma donation throughout Pakistan.

18.2 PIC/S Requirements

The Pharmaceutical Inspection Co-operation Scheme has developed comprehensive requirements that form the technical foundation for these requirements. PIC/S PE 005-4 dated 1 June 2021 provides Good Practice Requirements for Blood Establishments and Hospital Blood Banks. PIC/S PE 009-17 dated 25 August 2023 is the Guide to Good Manufacturing Practice for Medicinal Products, with particular attention to Annex 14 addressing Manufacture of Products Derived from Human Blood or Plasma. PIC/S PI 011-3 provides Recommendations on Computerised Systems that inform requirements for electronic record systems.

18.3 European Union Directives and Requirements

The European Union has developed a comprehensive regulatory framework for blood and plasma safety that has strongly influenced these requirements. Directive 2002/98/EC of the European Parliament and of the Council dated 27 January 2003 sets standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components. Commission Directive 2004/33/EC dated 22 March 2004 implements Directive 2002/98/EC regarding certain technical requirements for blood and blood components. Commission Directive 2005/61/EC dated 30 September 2005 implements Directive 2002/98/EC regarding traceability requirements and notification of serious adverse reactions and events. Commission Directive 2005/62/EC dated 30 September 2005 implements Directive 2002/98/EC regarding Community standards and specifications relating to quality systems for blood establishments. Directive 2001/83/EC of the European Parliament and the Council

establishes the Community Code relating to medicinal products for human use. The EMA Guideline EMEA/CPMP/BWP/5619/03, Revision 1.3, addresses Scientific Data Requirements for a Plasma Master File.

18.4 Council of Europe

The Council of Europe through the European Directorate for the Quality of Medicines & HealthCare publishes the Guide to the Preparation, Use and Quality Assurance of Blood Components, currently in its 21st Edition, which provides comprehensive technical guidance for blood establishments.

18.5 World Health Organization

The World Health Organization has published important technical standards for blood establishments. WHO Technical Report Series 941, Annex 4 from 2007 addresses Good Manufacturing Practices for Blood Establishments. WHO Technical Report Series 961, Annex 4 from 2011 provides updated Good Manufacturing Practices for Blood Establishments. WHO Requirements on Drawing Blood: Best Practices in Phlebotomy published in 2010 provide technical guidance for blood collection procedures. The WHO Model Regulatory Framework for Good Reliance Practices informs the approach to reliance on foreign regulatory authorities.

18.6 Pharmacopoeias

The European Pharmacopoeia Current Edition includes the Monograph for Human Plasma for Fractionation (0853) that establishes quality standards for plasma used in pharmaceutical manufacturing. The United States Pharmacopeia Current Edition also provides relevant standards.

18.7 Industry Standards

The Plasma Protein Therapeutics Association has developed the International Quality Plasma Program Standards, Version 5.0, which include detailed standards for various aspects of plasma collection including the IQPP Donor Education Standard, IQPP Cross Donation Management Standard, IQPP Qualified Donor Standard, IQPP Use of National Donor Deferral Registry (NDDR) Standard, and IQPP Viral Marker Standard.

The International Society of Blood Transfusion publishes the ISBT 128 Standard that establishes global standards for identification and labeling of blood products.

18.8 International Requirements

The International Council for Harmonisation has published relevant requirements including ICH Q7 on Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients, ICH Q8 on Pharmaceutical Development, ICH Q9 on Quality Risk Management, and ICH Q10 on Pharmaceutical Quality System.

18.9 Transport Regulations

The International Air Transport Association publishes the IATA Dangerous Goods Regulations, Current Edition, which governs air transport of biological materials. The International Maritime Dangerous Goods Code, Current Edition, establishes requirements for sea transport of dangerous goods including biological substances.

18.10 Other References

The United States Code of Federal Regulations Title 21, Parts 600-680 addresses Biologics and provides regulatory standards used internationally. Title 21, Part 1271 addresses Human Cells, Tissues, and Cellular and Tissue-Based Products. The US FDA has published various guidance documents including Recommendations for Assessing Donor Suitability and Blood and Blood Product Safety in Cases of Known or Suspected West Nile Virus Infection. WHO Recommendations for the Production, Control and Regulation of Human Plasma for Fractionation provide additional technical guidance applicable globally.