Key steps to improve quality of plasma for further processing

Online Workshop
Working Party for Global Blood Safety (GBS) of ISBT
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No Disclosure

I have no actual or potential conflict of interest in relation to this congress or this presentation

Background

Plasma is a component for transfusion or for fractionation, prepared either from whole blood or from plasma collected by apheresis, frozen within a specified period of time and to a temperature that adequately maintains the protein levels

*Modified from Council of Europe *Guide to the preparation, use and quality assurance of blood components*

Background

Plasma is a component for transfusion or for fractionation, prepared either from whole blood or from plasma collected by plasmapheresis, frozen within a specified period of time and to a temperature that adequately maintains the protein levels

- Plasma for fractionation is intended for recovery of either:
  - labile proteins (coagulation factors)
  - non-labile proteins

More stringent requirements

Introduction

Introduction

Consequences for many Blood Establishments (BEs) in low & middle income countries (LMICs):

- Limited resources are directed towards manufacture of:
  - red cell concentrates
  - platelets - predominantly whole blood derived, occasionally single donor via plateletpheresis
  - small volume of fresh frozen plasma for clinical use
- Volume of unused residual plasma from whole blood or plateletpheresis can be significant

Introduction

- Unused residual plasma does not meet quality & safety standards for fractionation → discarded
- Drives up costs:
  - purchase of plasma-derived medicinal products (PDMPs)
  - wastage of plasma
- BEs in LMICs that plan to utilise residual plasma as starting material for fractionation must improve the quality & safety of their plasma

Introduction

- Improvements need to be made across the whole manufacturing process:
  - Donor selection
  - Collection – whole blood & plasmapheresis
  - Processing
  - Testing
  - Handling, storage & transport
  - Quality Assurance/Quality Control (QA/QC)

Good Manufacturing Practice (GMP)

Quality Management System + Manufacturing Principles

GMP

- Implementation of GMP is essential
- Sets out requirements for:
  - organisational & manufacturing responsibilities
  - good documentation systems & records (traceability)
  - staff training & competency
  - ensuring qualification &/or validation of:
    - materials
    - equipment
    - processes
    - facilities
  - performance monitoring & improvements

GMP

- GMP establishes a quality framework for BEs that should be applied to all blood collection activities
- Implementation therefore improves the safety & quality of all components manufactured by the BE, including other "fresh" plasma components eg:
  - pathogen-reduced plasma
  - standard & mini-pool SD-cryoprecipitate
  - mini-pool IgG
- In addition to GMP, BEs should select an appropriate Standard that sets out specifications for the components produced

Standards

- Specifications for plasma for fractionation are set by fractionator
- Based on international Standards such as:
  - European Pharmacopoeia – *Human plasma for fractionation*
  - European Medicines Agency – *Guideline on plasma-derived medicinal products*
  - FDA 21 CFR 640.30 & 640.60 – *Plasma; Source Plasma*

Quality & Safety Improvements

Donor selection

Only a carefully selected, healthy donor who, as far as can be ascertained after medical examination, laboratory blood tests and a study of the donor's medical history, is free from detectable agents of infection transmissible by plasma-derived medicinal products may be used. *

** European Pharmacopoeia*

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Donor testing

- Every donation from every donor should be screened for transfusion transmissible infections
- At a minimum, these should include:
  - antibodies to HIV-1 & HIV-2
  - hepatitis B surface antigen
  - antibodies to hepatitis C virus
- Fractionators may require additional testing to be performed – these will be specified in the contract

Collection

- Risk of bacterial contamination:
  - venepuncture for WB & plasmapheresis collections
  - connection of blood packs/reagents for plasmapheresis
  - contaminated work surfaces
- Prevention of contamination:
  - validated arm disinfectant & procedure
  - integrated collection packs - CLOSED SYSTEM
  - regular cleaning of surfaces

Collection

- Whole blood (WB) collection process should result in a donation that is:
  - well mixed with no clots
  - correct volume with no under- or over-dilution
  - timed to ensure appropriate use of plasma

- Automated blood mixer for WB collection:
  - mixes collection pack continuously
  - calculates volume from weight, clamps off blood flow at target
  - records time of collection

Collection

- Plasmapheresis collection process – key factors:
  - qualified machines
  - integrated collection system (packs)
  - controlled rate of flow
  - control over use of saline vs anticoagulant
  - validated process
- Transport of WB & plasma to Processing department:
  - avoid delays
  - maintain temperature

Need to monitor time & temperature

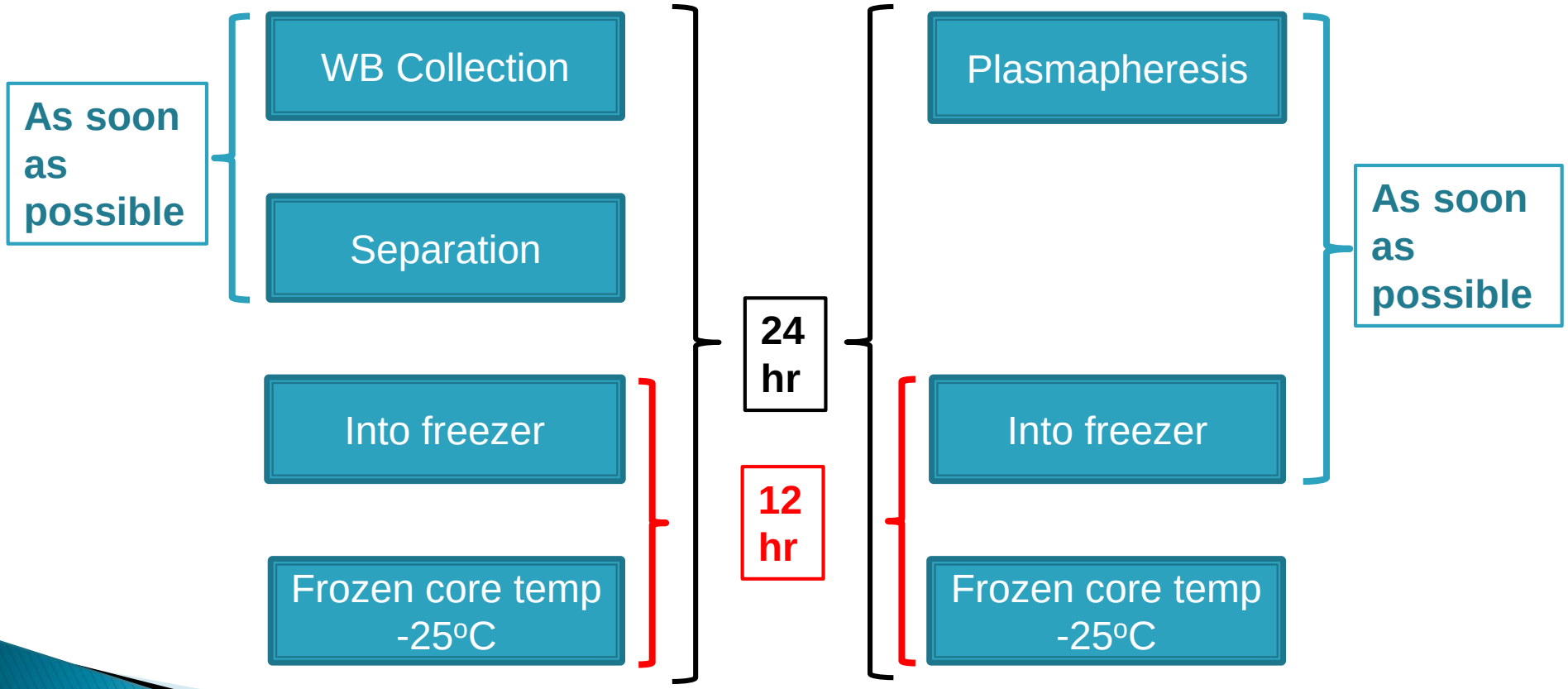
Processing

- The “processing” step includes:
  - centrifugation of WB
  - separation of plasma from red cells +/- platelets
  - freezing of plasma (from WB or plasmapheresis)

- The process should result in plasma that:
  - is free from microbial contamination
  - has minimal cellular contamination
  - has optimal levels of coagulation factors or non-labile proteins (depending on intended PDMP)

Processing

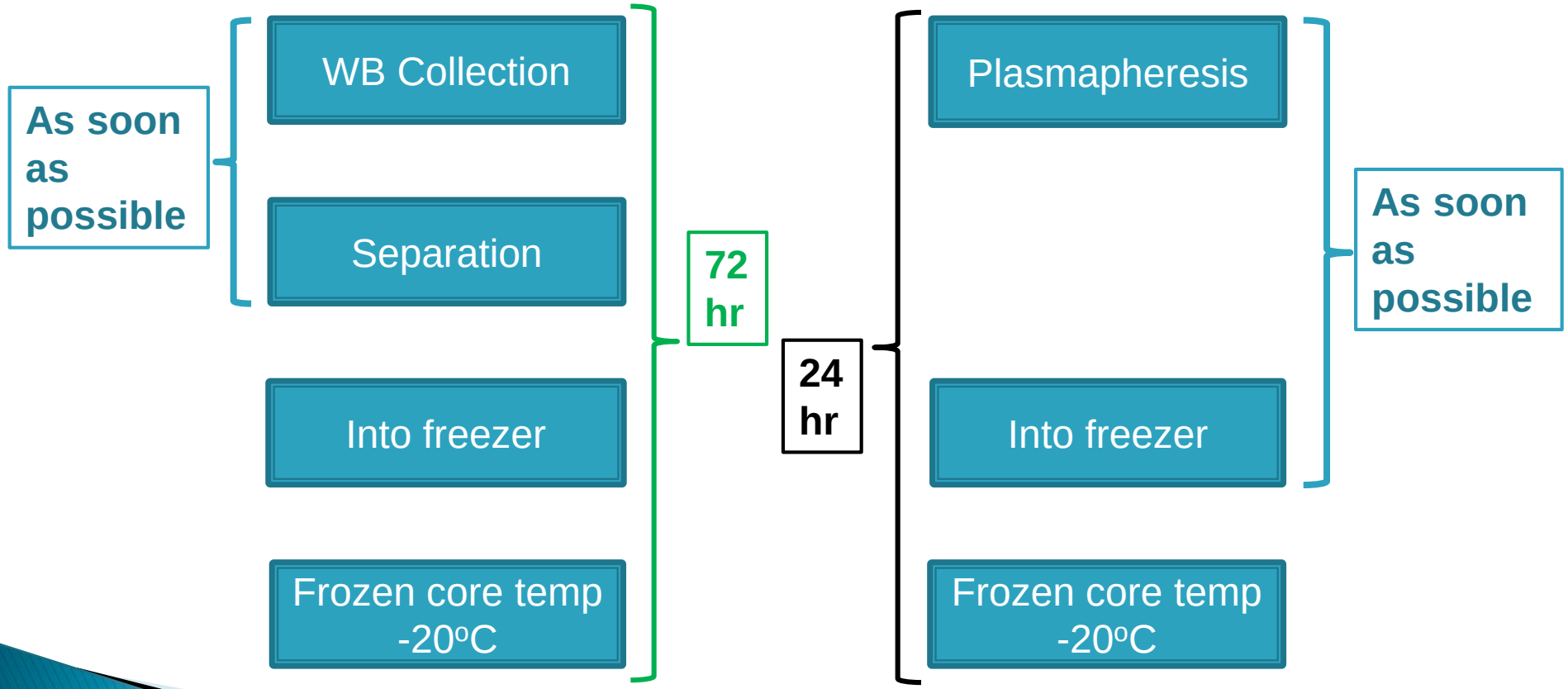
- Processing times for labile (coagulation) proteins*:



* *European Pharmacopoeia*

Processing

- Processing times for non-labile proteins*:



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Processing

- Therefore key factors for Processing (1):
  - traceability → Ensures timeframes met for processing, freezing
  - controlled work environment → Ensures optimal handling temperature
  - closed blood pack system
  - regular cleaning all surfaces

  (closed blood pack system, regular cleaning all surfaces) → Reduce risk of microbial contamination

Processing

- Key factors for Processing (2):
  - use of reliable equipment:
    - centrifuges
    - rapid freezer
    - heat sealers
    - sterile docking equipment

Equipment:
- Qualified & validated
- Regularly:
  - Serviced
  - Calibrated
  - Cleaned
  - Performance monitored

  - Automated blood separator:
    - ensures consistency of plasma quality

Handling, storage & transport

- Processes for handling, storage & transport of plasma should ensure that:
  - traceability is maintained
  - integrity & protein levels are not compromised
  - risk of microbial contamination is minimised
  - pack is not damaged or breached at any stage
  - stored plasma is secure

Handling, storage & transport

- Key factors for handling, storage & transport (1):
  - controlled environment
  - regular cleaning of all work surfaces including freezers & transport containers
  - careful handling or use of padded packets during transport of frozen plasma (brittle)
  - security of storage:
    - restricted access to freezers
    - use of quarantine facilities until all acceptance testing is complete & plasma is “released”

Handling, storage & transport

- Key factors for handling, storage & transport (2):
  - use of reliable equipment:
    - storage freezers
    - transport containers for WB or plasma to processing
    - transport containers for frozen plasma from storage to fractionator
    - Dataloggers for monitoring Temperature during transport

Equipment:
- Qualified & validated
- Regularly:
  - Serviced
  - Calibrated
  - Cleaned
  - Performance monitored

QC testing & monitoring

- Regular monitoring of quality & safety & processes is a key GMP requirement:
  - confirms requirements are met (records - evidence)
  - identifies problems at an early stage (management of nonconforming product & root cause analysis)
  - allows corrective actions to be taken as soon as possible
  - identifies improvements that can be made

QC testing & monitoring

- Final plasma component should:
  - not be haemolysed or lipaemic
  - not contain clots
  - be free of cellular contamination
  - have FVIII levels that meet specified requirements (plasma for labile proteins)
- Additional requirements may be set by the fractionator

QC testing & monitoring

- Key factors for QC testing in final plasma:
  - all plasma packs should be inspected for presence of visible:
    - haemolysis / red cell contamination / lipaemia
    - clots
  - statistically significant sample of plasma packs should be tested for
    - cellular contamination
    - FVIII levels (plasma for labile proteins)
  - additional testing if required by the fractionator

Summary

- Implementation of GMP provides a foundation for managing quality & safety that will facilitate improvements across the whole manufacturing process
- These improvements, together with key steps outlined in this presentation, will enable plasma quality to meet standards for fractionation
- The ability to send their plasma for fractionation will bring BEs in LMIC significant cost benefits & enable them to move towards self sufficiency in PDMPs

Thank You