




SPECIFIC REQUIREMENTS FOR PLASMA FOR FRACTIONATION

IPFA – KUALA LUMPUR

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OVERVIEW

Specific plasma requirements for plasma for fractionation.

Point of view from an EU fractionator

- Collection of plasma
- Quality and audit requirements
- Safety requirements
- Regulatory requirements
- Pros & Cons of recovered and source plasma
- How to facilitate integration of more recovered plasma for further manufacturing?

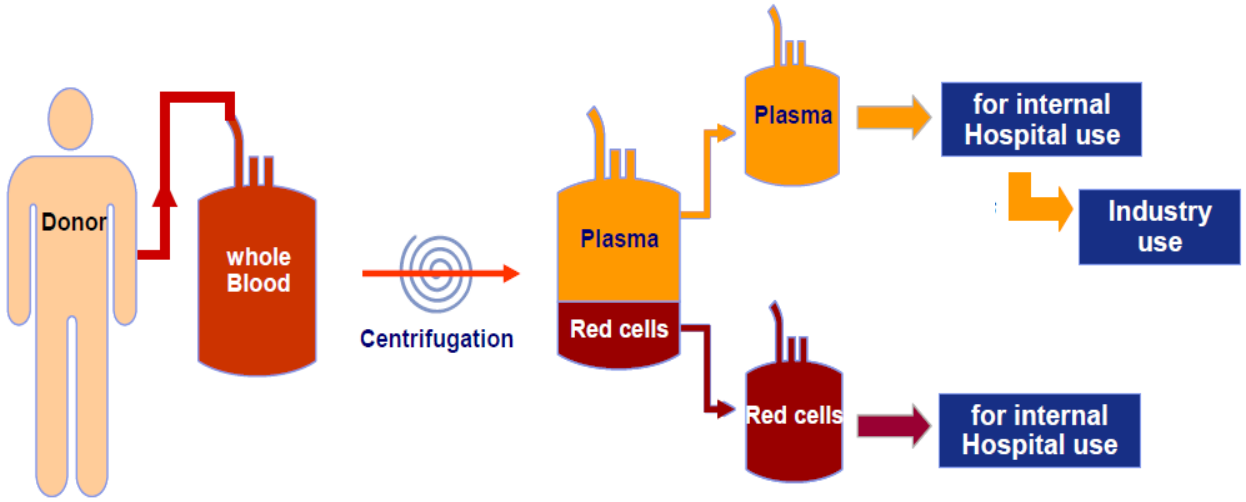
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COLLECTION OF PLASMA



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PLASMA COLLECTION FROM WHOLE BLOOD (FFP AND RECOVERED PLASMA)

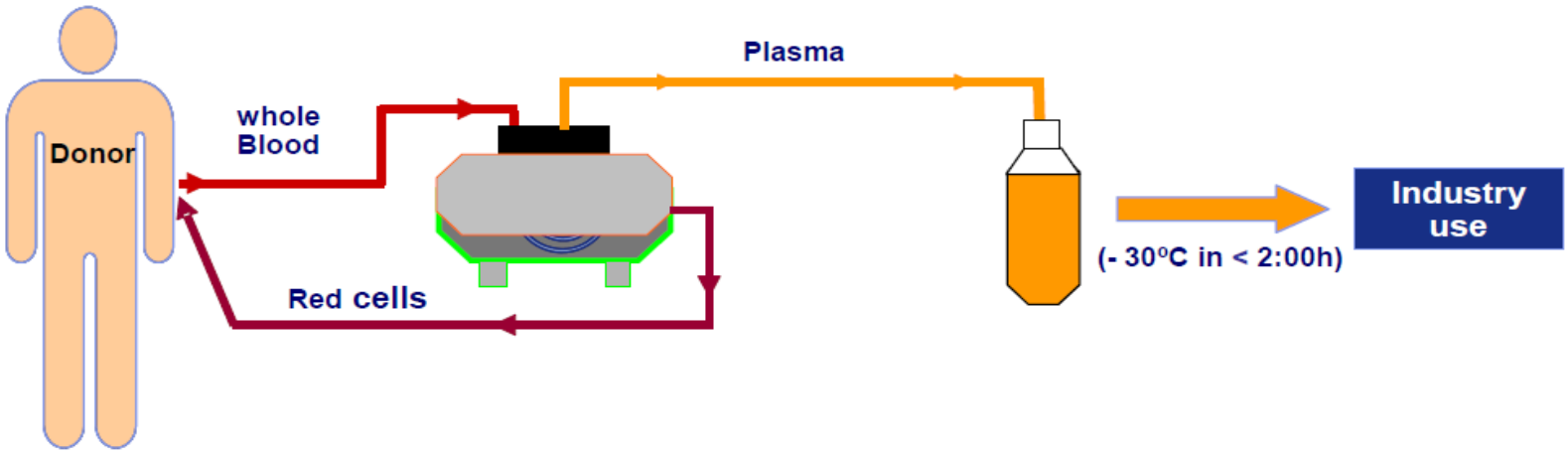


Source: Market Research Bureau

- Most common scheme:
  - Collection at multiple small-medium collection centres (few 1000 liters per year) and multiple mobile units
  - Separation and freezing in processing centres

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COLLECTION OF SOURCE PLASMA



Red cells are immediately re-injected into the donor

- Common scheme:
  - One collection/processing centre (can collect 30.000 - 70.000 liters per year)

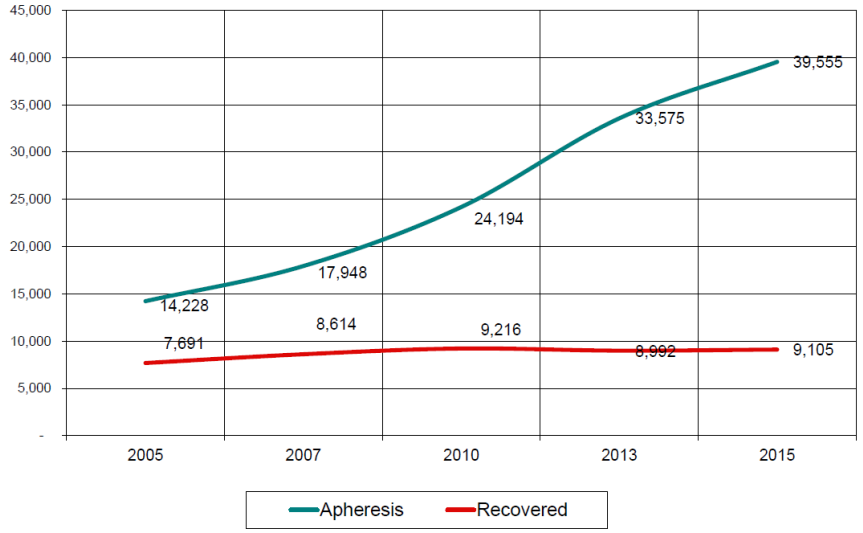
Source : Market Research Bureau

SOURCES OF PLASMA FOR FRACTIONATION

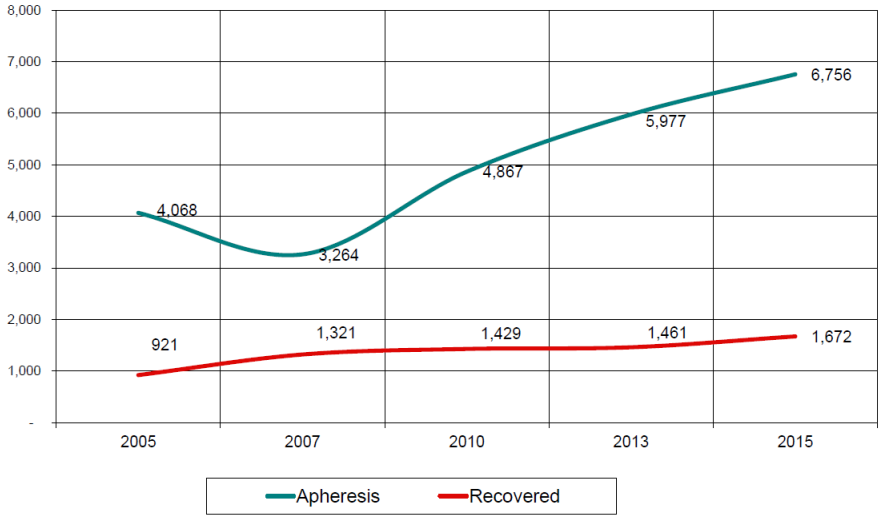
- Definitions:
  - Plasma separated from whole blood (so-called « *Recovered* ») and not used for ttransfusion is a 'waste' product from production of labile components

    Perspectives : worldwide limited volumes with limited growing perspectives because of smaller needs of red cells linked to medical improvements (surgery, innovation) and fewer crashes/accidents.
  - Plasma collected by aphaeresis (so-called « Source ») is collected for manufacturing.

Plasma for Fractionation - World
2005 - 2015 (Thousand Liters)



Plasma for Fractionation - Asia & Pacific
2005 - 2015 (Thousand Liters)



WORLDWIDE USE OF PLASMA FOR FRACTIONATION

- The world of plasma from fractionation is very diverse:

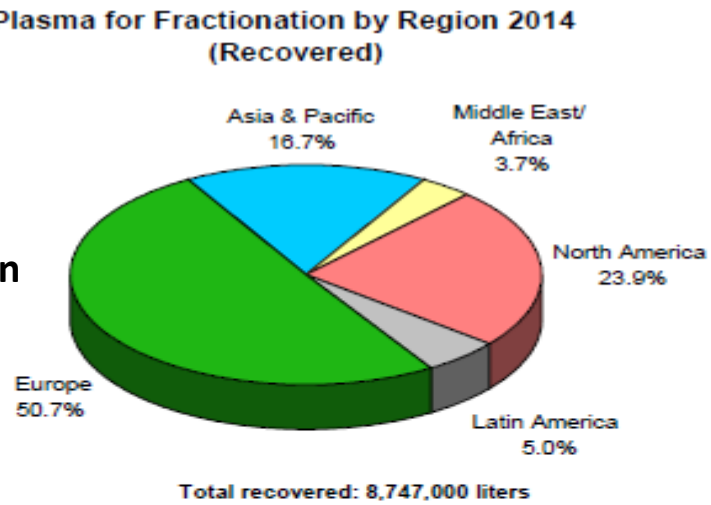
  Three big areas to consider:

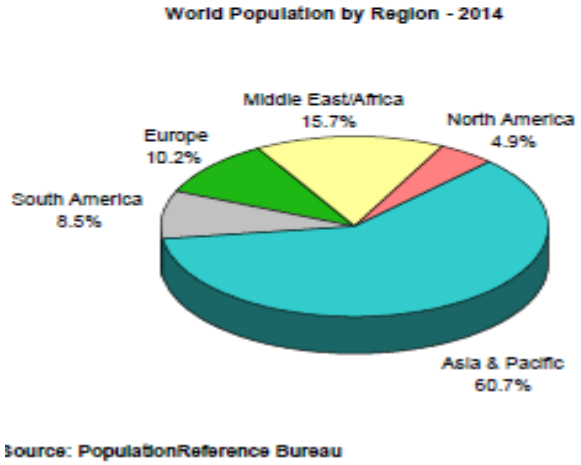
  - Europe: main source of '*recovered*' plasma,
  - USA: main supplier of '*source*' plasma,
  - Rest of the world: collected plasma not always strictly compliant with WHO Quality standards/ regulations for fractionation and any other local applicable regulations, and as a consequence **large amounts of plasma are wasted**.

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Recovered plasma for fractionation: mainly collected in EU

- **4,4 Ml collected in Europe**
- **Asia Pacific has 60% of the world population**
- **and produces 17% of recovered plasma**



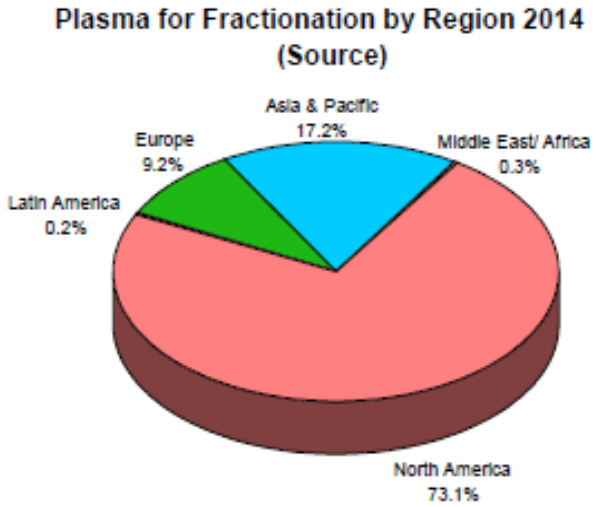


Europe has 10% of the world population and produces 51% of the world's recovered plasma for fractionation

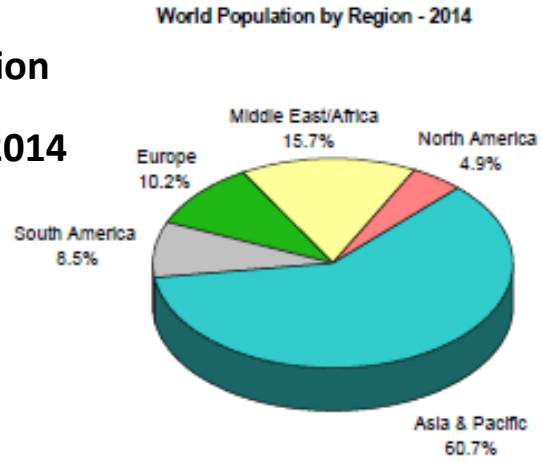
SOURCE PLASMA IS MAINLY COLLECTED IN USA

- **USA collect the majority of plasma for fractionation: 2 ML of recovered and 26 ML of source plasma, which corresponds to 2/3rd of the world production**

- **Asia Pacific has 60 % of the world population and collected 17 % of source plasma in 2014**



Total source 36,212,000 liters



Source: PopulationReference Bureau

North America has 5% of the world population and supplies 73% of the world's source plasma for fractionation

QUALITY AND AUDIT REQUIREMENTS



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QUALIFICATION OF COLLECTION CENTERS BY FRACTIONATOR

- Blood/plasma collection centres are **authorized** by local National Control Agencies and are regularly inspected
- Blood/plasma collection centres are **qualified** as supplier by PDMPs manufacturers
- **Audits** are part of the qualification process (EU GMPs Annex 14)

> 3.4 Supplier qualification, including audits, should be performed by the fractionation plant/manufacturer of the finished product according to written procedures. Re-qualification of suppliers should be performed at regular intervals taking a risk-based approach into account.

- Audits of collection centres at a frequency between 1 to 5 years, depending on scoring calculated annually

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RISK BASED APPROACH, FROM FRACTIONATOR VIEW

- Mandatory according to EU GMP, Annex I *Risk management methods and tools,* to be used to prioritize manufacturing sites for inspection/audit by regulators or industry.

- 3 to 6 risks factors (A, B, C…) are defined by plasma fractionator: take into account complexity of sites (collection, processing, storage, testing), major changes over the last year, GMP audit inspection records, volumes etc.…
  - Storage site only = intrinsic activity -> low risk, but if large volumes for fractionator transit through this site-> should be considered at higher risk

- Risk factors (A, B, C…) are rated using scale of 1-5 (1 being the lowest)

- Score = A+B+C+D etc.…
  - Higher score is not associated to « low quality site », but to a site which require stronger monitoring (i.e. major changes recently implemented and which require on site audits)

- Scoring are used to define audit frequency for already qualified sites

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AUDITS OF COLLECTION CENTERS

- New Blood Establishment
  - Pre-audit meeting
    - Optional but recommended
    - Meet supplier in person, address open questions
    - First check/impression about QS level
  - Initial Qualification Audit
    - In-depth assessment against all applicable guidelines and Quality Agreement linking the supplier to the manufacturer

AUDITS OF COLLECTION CENTERS

- Approved Blood Establishments
  - Requalification audit
    - In-depth reassessment
    - More detailed on specific topics
  - Follow-up audit
    - To ensure CAPA were implemented
  - Focused audits
    - To solve specific critical issues

AUDITS OF COLLECTION CENTERS

- Benefits of audits
  - Confirmation of compliance level by an external party
  - Readiness for Competent Authorities inspections
  - Opportunities for improvements
  - Win-win situation for both parties
  - Address open issues in persons

QUALITY CONTRACTS

- Quality Agreements
  - A regulatory requirement according to EU GMPs Annex 14

3.5 The fractionation plant/manufacturer of the finished product should establish written contracts with the supplying blood establishments. As a minimum the following key aspects should be addressed:

-definition of duties and respective responsibilities
-quality system and documentation requirements
-donor selection criteria and testing
-requirements for the separation of blood into blood components/plasma
-freezing of plasma
-storage and transport of plasma
-traceability and post donation / collection information (including adverse events).

  - Detailed « list of specifications », legally binding documents between the plasma supplier and the fractionator

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CHANGE MANAGEMENT

- Robust change management should be in place
  - Importance of a robust Change Control process
    - Timely notification to fractionator
      - Regulatory lead-times prior implementation
        - » PMF submission and approval
        - » Update of product licenses accordingly.
    - Impact assessment as part of Change Control process
      - Impact assessment of change on manufacturer operations

EXAMPLES OF CHANGES POTENTIALLY IMPACTING PLASMA FOR FRACTIONATION

- Change in donor deferral criteria
  - *May impact product allocation to certain markets*
- New plasma storage site, testing laboratories, center relocation
  - *Impact on plasma availability; hold until approval in the regulatory files: in particular Plasma Master Files (PMF)*
- Change to a new test system for viral markers (if not EC marked):
  - *Analytical validation must be submitted for PMF approval prior plasma can be fractionated*

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EXAMPLES OF CHANGES POTENTIALLY IMPACTING PLASMA FOR FRACTIONATION

- New plastic material for plasma bags
  - *Evaluation of compliance to regulations, extractables & leachables*
  - *Plasma bag properties (broken units; adherence of labels, impacts on cutting devices)*

- Change in plasma collection method, freezing process, anticoagulant ratio
  - Potential impact on plasma quality (i.e. activation of proteins)
  - Production yields
  - Manufacturing process performance (i.e. increased filter usage)

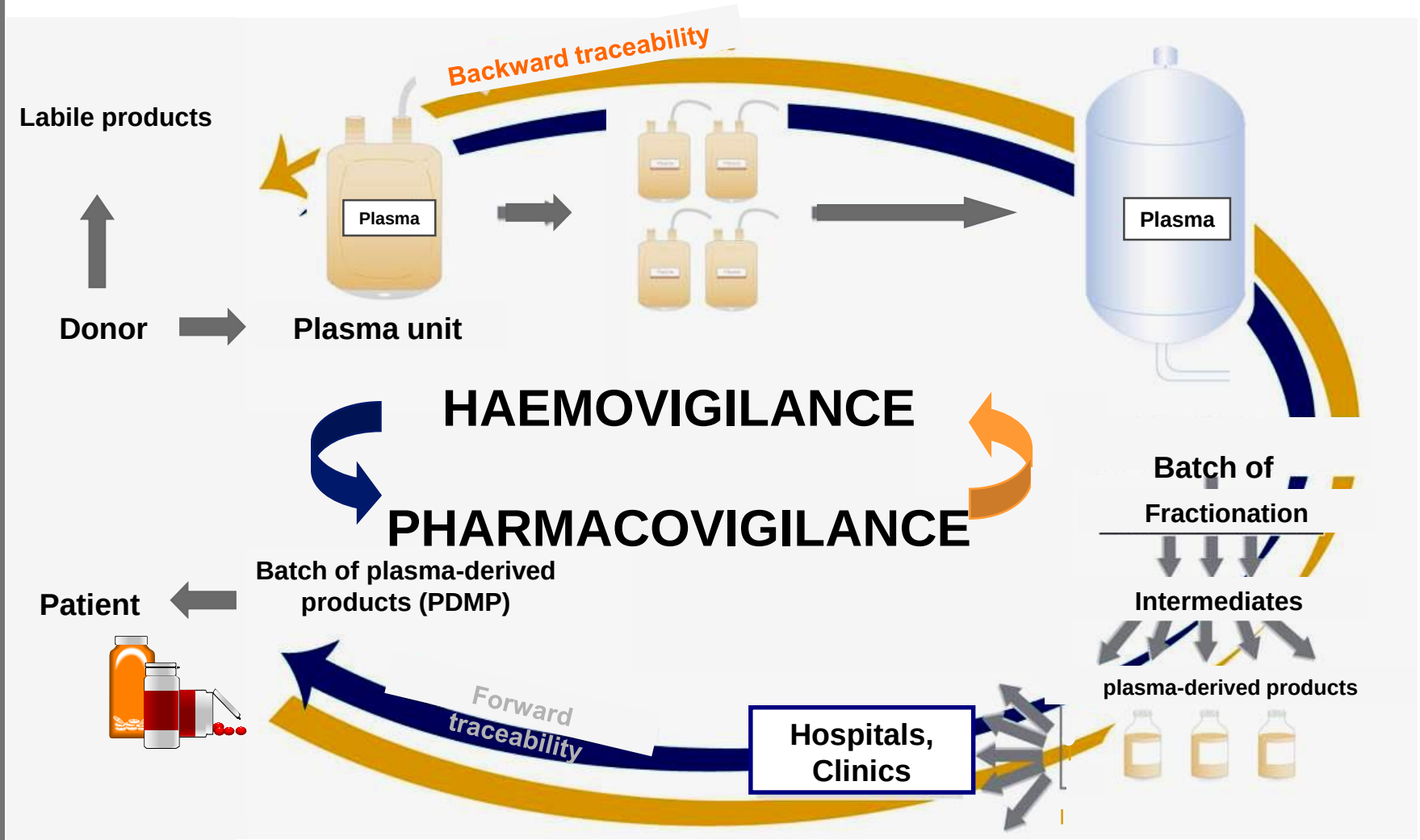
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SAFETY REQUIREMENTS

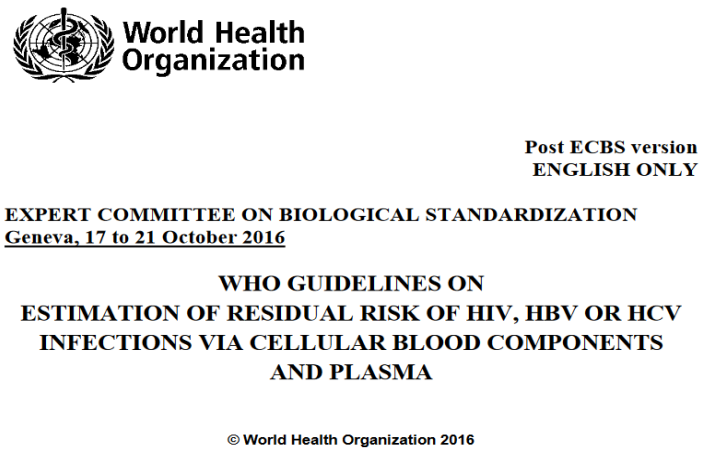


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HAEMOVIGILANCE = ADDITIONAL SAFETY FOR RECOVERED PLASMA THANKS TO VIGILANCE ON RECIPIENTS OF LABILE PRODUCTS



EPIDEMIOLOGICAL DATA



World Health Organization

Post ECBS version
ENGLISH ONLY

EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION
Geneva, 17 to 21 October 2016

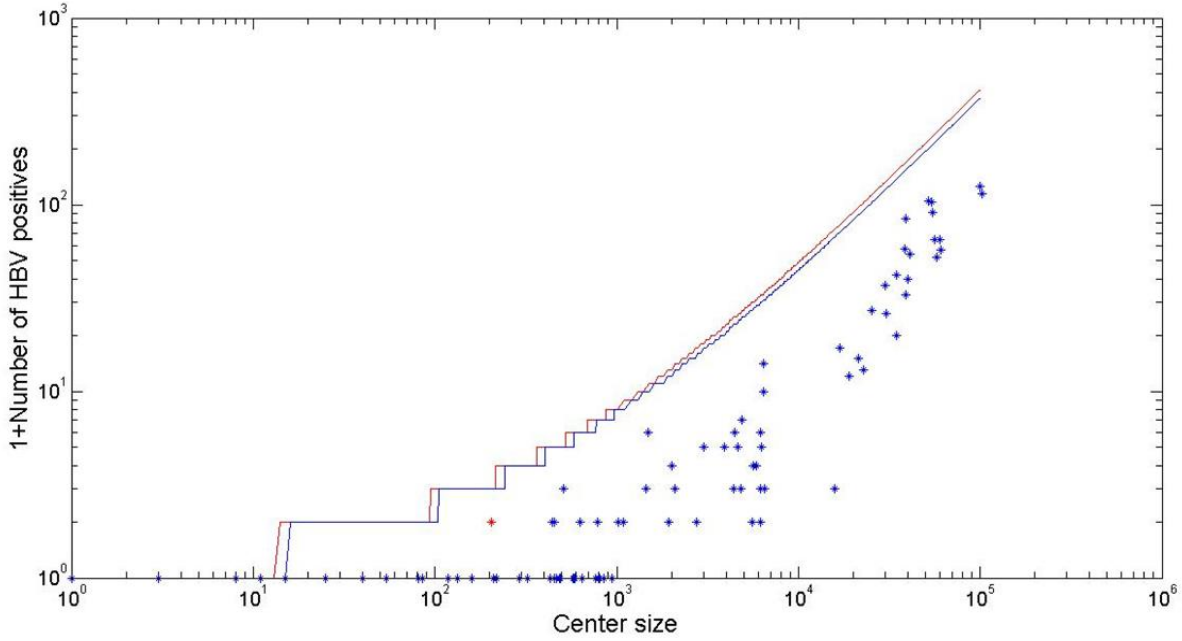
WHO GUIDELINES ON
ESTIMATION OF RESIDUAL RISK OF HIV, HBV OR HCV
INFECTIONS VIA CELLULAR BLOOD COMPONENTS
AND PLASMA

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- EMA and WHO guidelines on epidemiological data
- Requirements to report rates for HCV/HBV/HIV markers and provide statistical analysis
- Data to be reported at the level of centers (fixed address), not always relevant/possible for recovered plasma
- CAPAs to be initiated if alert limits are reached
  - Exchanges with plasma suppliers, root cause analysis

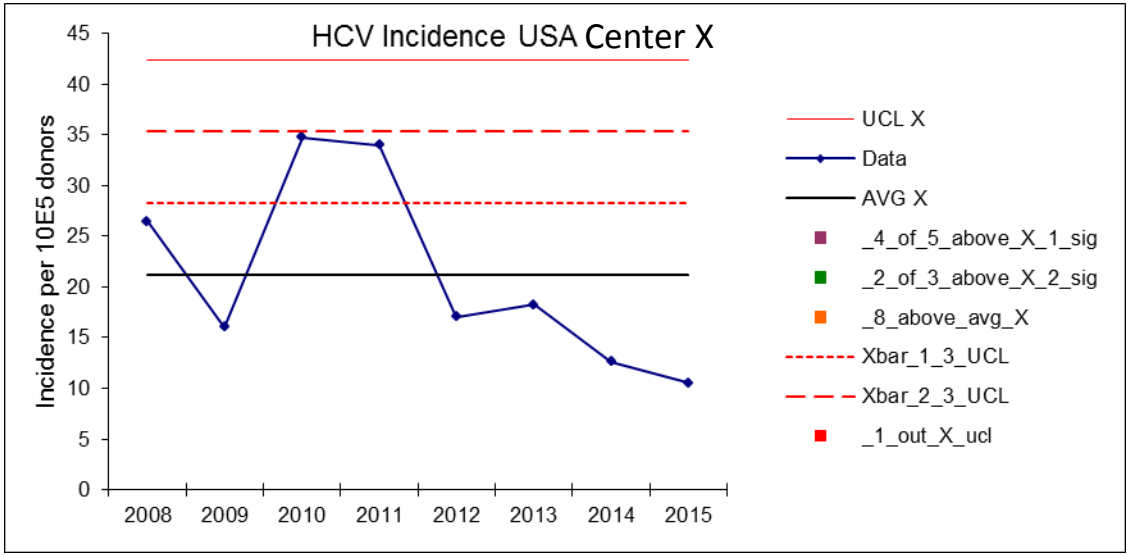
EPIDEMIOLOGICAL DATA

- Alert limits should be fixed (not acceptance limits):
- Reference rates per viral marker and per donation type (First time Tested Donations/Repeat Tested Donations):
  - Defined as the **99.5th percentile** of the Gamma distribution
  - Based on Poisson distribution Threshold Values are derived.



EPIDEMIOLOGICAL DATA

- Monitoring of trends (continuous improvement tool)
  – Control charts :



UCL: Upper Control Limit
AVG: Average

REGULATORY CONSTRAINTS

- If fractionation plant is located in EU, EU GMPs Annex 14 applies
  - Even for contract fractionation programs (parts thereof apply)

- Plasma Master File (PMF) registration in EU
  - Main issues with epi data (geographic areas are limited) and with regular inspections by Health Authorities (EU inspections are required worldwide)

- Additional local regulations
  - Traceability archives:

    30 years in EU from data of manufacturing,

    40 years for France from collection date,

    40 years in Japan from end of shelf-life of drug products

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PROS & CONS OF RECOVERED VS SOURCE PLASMA



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PROS & CONS – RECOVERED AND SOURCE

- Regulatory constraints to register collection sites of recovered plasma: regular inspections and availability of capacity in inspectors, epi-data follow-up at level of centres. Capacity of auditors for small centres.

  Basically, it is easier to qualify and register source plasma collection centres.
- But:
  - Recovered plasma: higher rates in key proteins especially in IgG
  - Price of recovered plasma is usually lower
  - Additional safety for recovered plasma which benefits from the haemovigilance system on recipients of labile products
  - Recovered generally associated to VNRD

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HOW TO FACILITATE INTEGRATION OF MORE RECOVERED PLASMA FOR FURTHER MANUFACTURING?



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WAYS TO MOVE FORWARD?

- Standardisation of Quality Standards: worldwide policies (WHO initiatives very welcome)

- Standardisation of Regulatory Policies:
  - Criteria for selection of donors
  - Recognition by other HAs of local HAs inspections

- Better recognition of recovered plasma by regulators:
  - Towards a status of licenced product in USA as source plasma
  - Future possibility to register recovered plasma in some countries (China….)

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SUMMARY

- Source plasma is currently the main provider of plasma for fractionation and is needed by the fractionation industries,
  but there is room for use of more recovered plasma for fractionation, in particular from Asia-Pacific region.

- Is it reasonable/sustainable to mainly rely on USA for plasma for fractionation?

- Key driver for the future: ability of Blood Transfusion Organisations to switch to collection of plasma by **apheresis dedicated to fractionation (especially through infrequent programs)?**

- In all cases, good **communication between plasma suppliers and fractionators** is paramount especially to anticipate and mitigate regulatory and quality constraints.

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