

National Regulatory Authority in Promoting Good Manufacturing Practice Compliance



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Executive Director



1^oI INTERNATIONAL CONGRESS ON BLOOD SAFETY AND HAEMOVIGILANCE

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ANTALYA, TURKEY

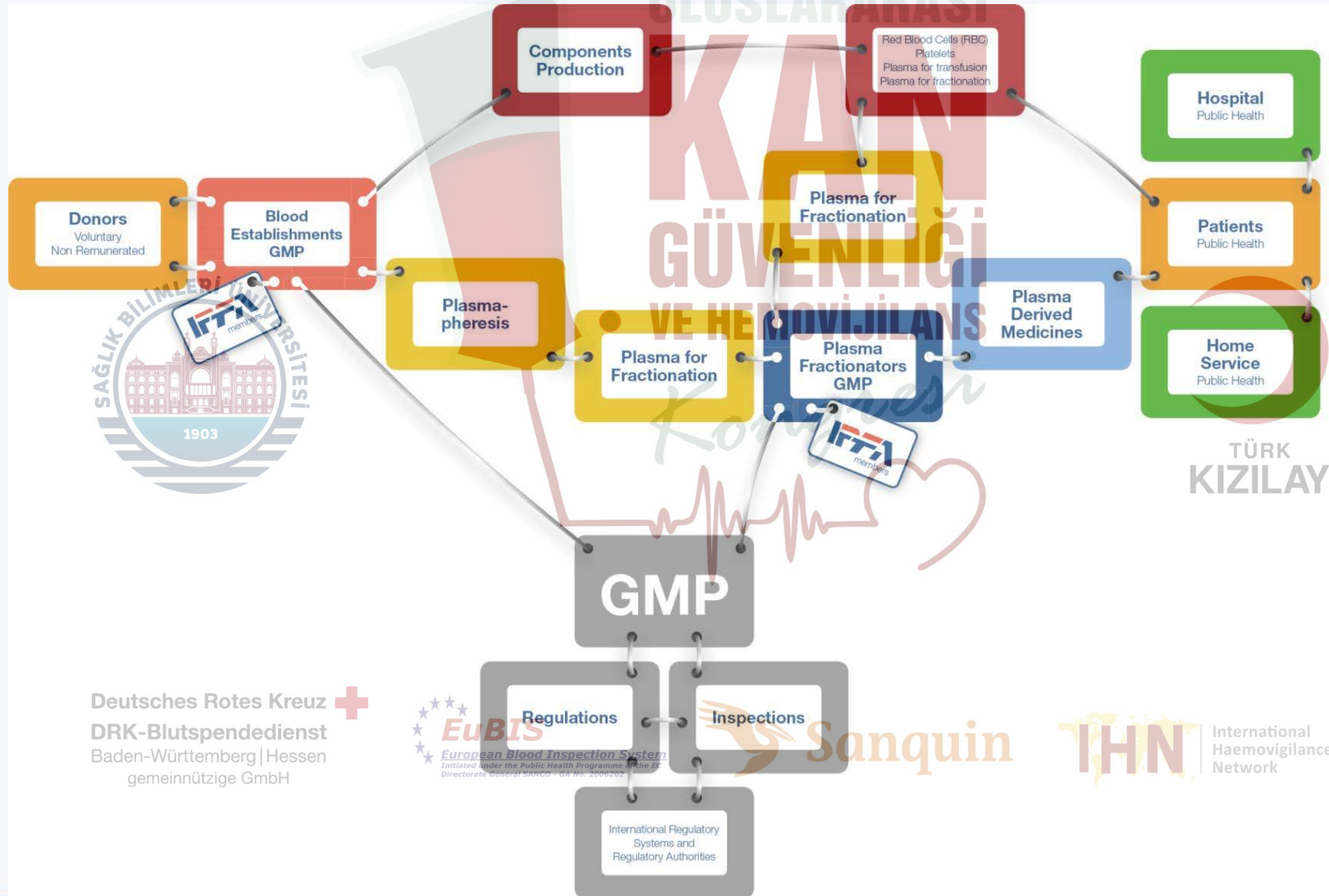
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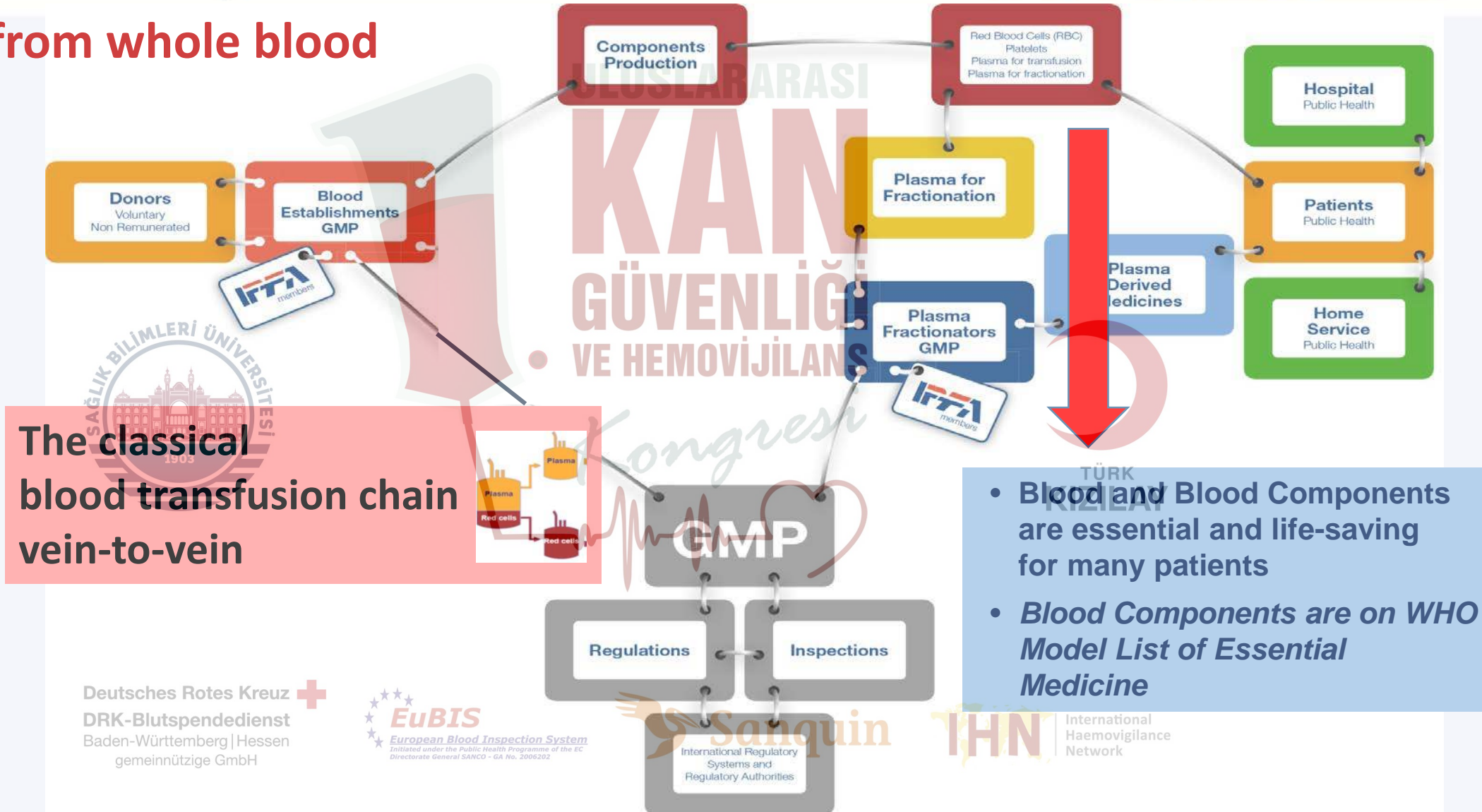

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Blood and Plasma Chain



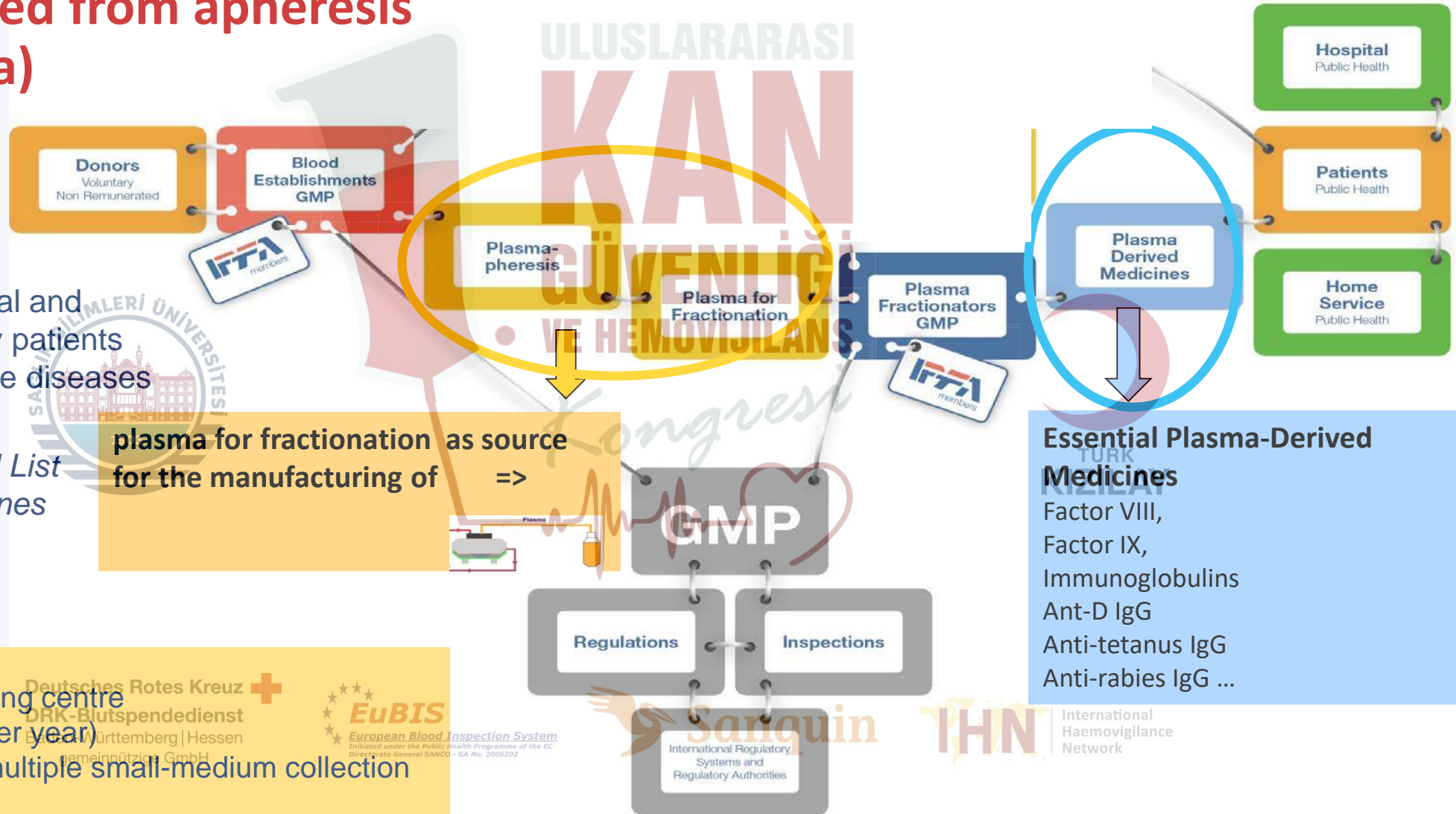
IPFA, embedded in community

Collection from whole blood



Plasma collected from apheresis (source plasma)

- PdMPs are essential and life saving for many patients with rare and severe diseases
- PdMPs are also on the WHO Model List of Essential Medicines



plasma for fractionation as source for the manufacturing of =>

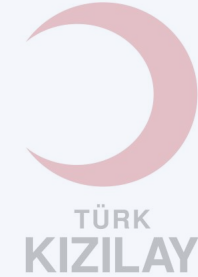
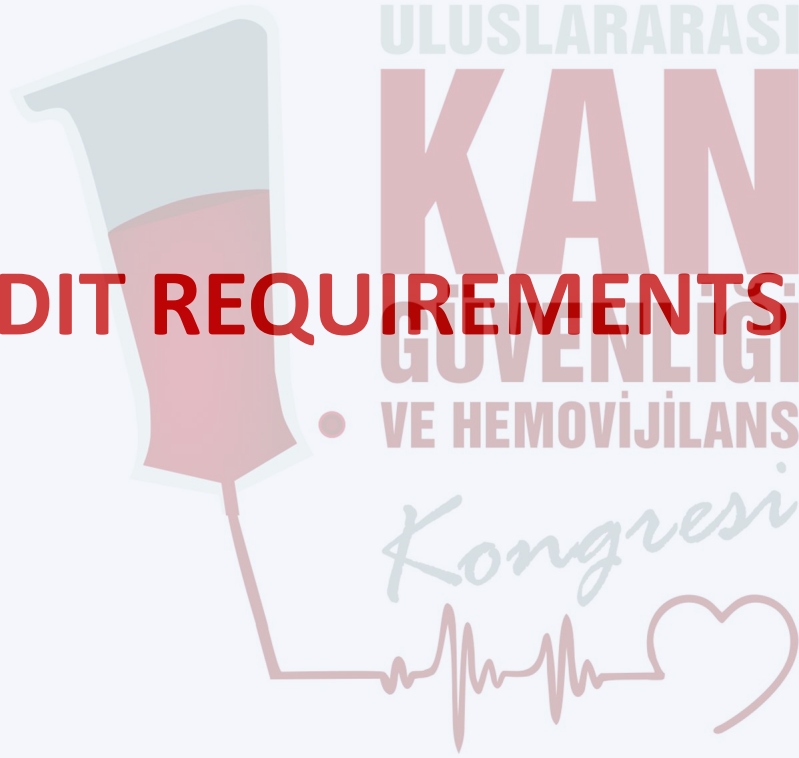
Essential Plasma-Derived Medicines
 Factor VIII,
 Factor IX,
 Immunoglobulins
 Ant-D IgG
 Anti-tetanus IgG
 Anti-rabies IgG ...

Usual scheme

- One collection/processing centre (can collect 30-70 kL per year)
- But also, collection in multiple small-medium collection centres (few kL per year) and multiple mobile units

IPFA, embedded in community

QUALITY AND AUDIT REQUIREMENTS



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Quality

In manufacturing, a state of being free from defects, deficiencies and significant variations.

Strict and consistent commitment to certain standards that achieve uniformity of a product within countries, regions, even cities in order to satisfy specific customer or user requirements.

ISO 8402-1986 standard defines quality as
"the totality of features and characteristics of a product ... that bears its ability to satisfy stated or implied needs."

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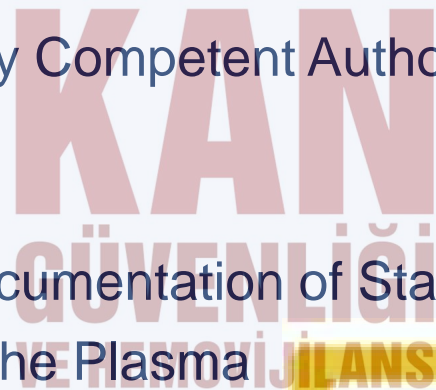
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Quality of Plasma PfF?

- PdMPs need to be registered by Competent Authorities to be available to patients
- PdMPs do satisfy GMPs
- PdMPs registration includes documentation of Starting Material
- Starting material for PdMPs is the Plasma



✓ Documentation of Plasma as Starting Material:
Scientific Data on Plasma (e.g. European PMF)

✓ Scientific Data on Plasma includes documentation of quality of plasma

➤ Plasma PfF needs to be at high quality level

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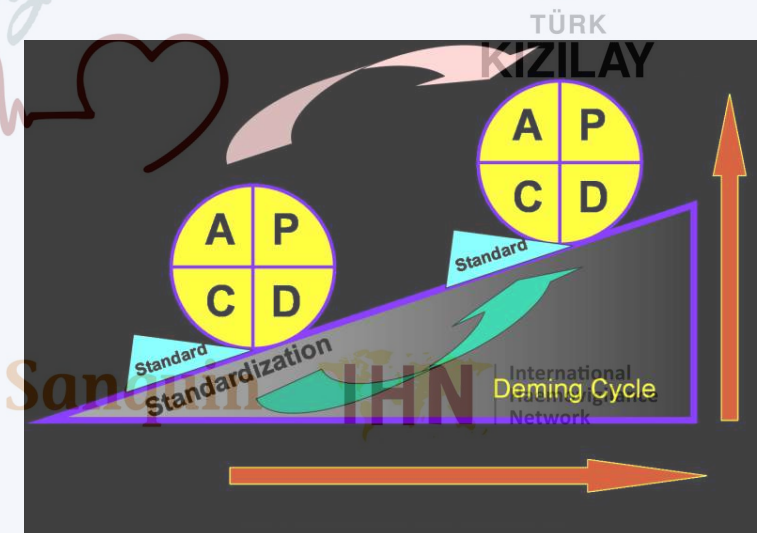
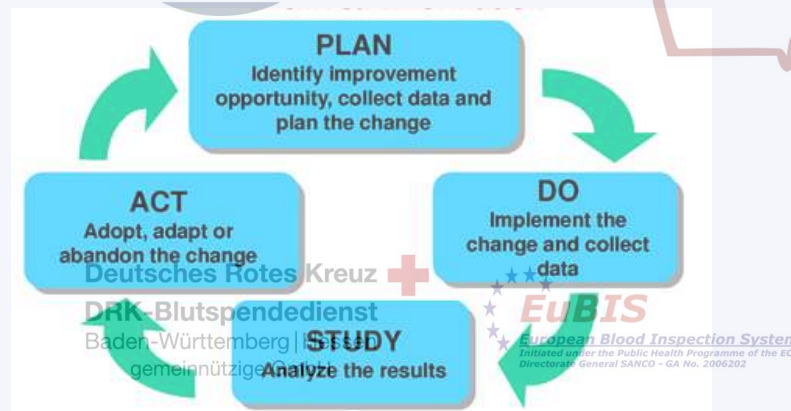
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Quality, a virtuous Process





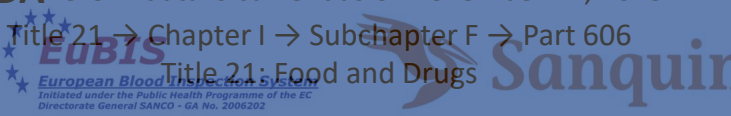

Define, Measure, Analyse, Improve and Control

to support Continual Improvement

PDSA/PDCA is a process through which new standards are set; to be challenged; revised and replaced by newer and better standards; **continuously**



Quality Reference Documents

| | | |
|---|--|--|
|  <p>World Health Organization</p> <p>NATIONAL STANDARDS FOR BLOOD TRANSFUSION SERVICE</p> <p>Edition 1-2013</p> | <p>© World Health Organization WHO Technical Report Series, No. 961, 2011</p> <p>Annex 4</p> <p>WHO guidelines on good manufacturing practices for blood establishments</p> | <p>Blood Safety Program, Health Care and Diagnostic Division Department of Medical Services Ministry of Health Thimphu: Bhutan</p> |
|  <p>SAĞLIK BİLİMLERİ ÜNİVERSİTESİ</p> <p>1903</p> | <p>The Rules Governing Medicinal Products in the European Union Volume 4</p> <p>EU Guidelines</p> <p>for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use</p> <p>Annex 14</p> <p>Manufacture of Medicinal Products Derived from Human Blood or Plasma</p> |  <p>TÜRK KIZILAY</p> |
| <p>Human Plasma for Fractionation Plasma Humanum Ad Separationem</p> <p>Eur. Pharmacopeia Monograph 01/2014:0853</p> | | |
| <p>Deutsches Rotes Kreuz  DRK-Blutspendedienst Baden-Württemberg Hessen gemeinnützige GmbH</p> | <p>FDA e-CFR data is current as of November 24, 2015</p> <p>Title 21 → Chapter I → Subchapter F → Part 606</p> <p>Title 21: Food and Drugs</p>  <p>EUBIS European Blood Inspection System Initiated under the Public Health Programme of the EC Directorate General SANCO - GA No. 2006202</p> <p>Sanquin</p> |  <p>THN International Haemovigilance Network</p> |

Quality

Quality management: Develop a culture of quality

Strict and consistent commitment to certain standards that achieve uniformity of a product to satisfy specific customer (patients) requirements.

- **Support from government is needed**
 - **Action plan with clear milestones**
 - **Dedicated key people working in coordination**
- **Regulatory needs**
 - **Implementation of National Regulatory Authority (NRA) for blood products**
 - **National blood policy and directives of plasma donations in order to set guidelines and assure homogeneity in the quality of the raw material, plasma**
- **Sufficient Inspection resources of National Competent Authorities for regular inspections of local collection centres**



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Political background

Developing a national blood programme

Requires a serious, **sustainable commitment of resources** (capital and operating budgets)

Senior management have the **responsibility** of securing sufficient resources for the work to be done.

This entails developing a **strategy, estimating budget** requirements, understanding the requirements of funding agencies and developing proposals accordingly

It is likely that a mix of fund providers, e.g. government plus external agencies, will be necessary, and that there will be a mix of cost recovery plus external subsidy

Development, execution and transparent reporting of costing are necessary to **demonstrate to funders that spending is appropriately managed** and will **help strengthen the case for funding support**

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ASSESSMENT CRITERIA FOR NATIONAL BLOOD REGULATORY SYSTEMS

SAĞLIK BİLİMLERİ ÜNİVERSİTESİ
1903

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The assessment criteria for national blood regulatory systems were adopted by the WHO Expert Committee on Biological Standardization at its sixty-second meeting, held in Geneva from 17 to 21 October 2011. The document contains the collective views of the WHO Blood Regulatory Network. It was developed in response to a request from WHO and the International Conference of Drug Regulatory Authorities for an assessment tool to assist capacity building of national regulatory authorities for the regulation of blood and blood products.

The tool is intended to help Member States to identify gaps and priorities when developing capacity building programmes, and support the introduction of regulation of blood products. Establishment of such regulation was recommended in the 2010 World Health Assembly resolution (WHA63.12) on the availability, quality and safety of blood products.

In the region

3. Recommendations

3.1 For Member States

1. **Establish/strengthen the national blood donor programme** to augment voluntary blood donations to meet the national requirements and allocate appropriate resources for its efficient implementation. Funding mechanisms available under Global Fund to fight AIDS, Tuberculosis and Malaria may be explored, if needed
2. Organize extensive public campaigns to mobilize communities for regular voluntary blood donations
3. **Forge sustainable partnerships among various partners**, especially NGOs operating at the community level, to educate, recruit and retain voluntary blood donors
4. **Build the capacity of blood transfusion services through infrastructure strengthening and training of staff to ensure the care of donors before, during and after blood donation.**
5. **Integrate the principles and practices of a quality system at all levels of the blood donation process**
6. Utilize modern **information technology tools in managing blood centres**, especially blood donor databases
7. Undertake operational research to improve the knowledge, attitude and behaviour of communities towards voluntary blood donations

3.2 For WHO

1. **Provide technical support** for developing and implementing national blood donor programmes as well as for their effective monitoring
2. **Develop generic standards for blood donor recruitment and disseminate the same to all Member States**
3. **Provide assistance in mobilizing resources to strengthen national blood donor programmes.**
4. **Assist in building the capacity of countries** for efficient management of blood donor programmes.
5. Facilitate intercountry information-sharing on advances and success stories in the area of blood donation



World Health Organization



PIC: Pharmaceutical Inspection Convention

Founded by The European Free Trade Association (EFTA) in October 1970
Is a legal Treaty between countries

Original Goals (18 EU MS only)

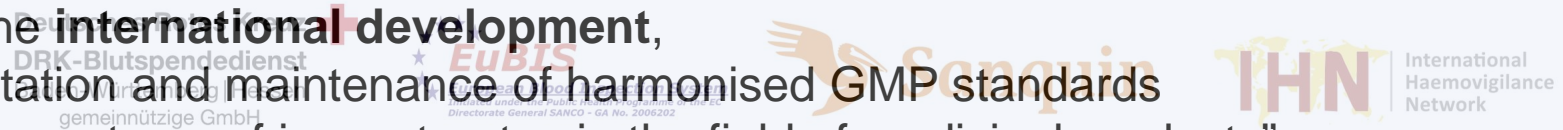
- Harmonised GMP requirements
- Mutual Recognition of Inspections
- Uniform Inspection Systems
- Training of Inspectors
- Mutual Confidence

*Only European Commission authorised
to sign agreements with other countries*

PIC Scheme Pharmaceutical Inspection
Cooperation Scheme

PIC/S Goal

“To lead the international development,
Implementation and maintenance of harmonised GMP standards
and quality systems of inspectorates in the field of medicinal products”.





Some PIC/S recommendation & Guideline Documents

- ✓ PIC/S GMP Guide (similar to EU GMP Guide).
- ✓ PIC/S GMP Guide for Blood Establishments.
- ✓ PIC/S Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments.
- ✓ Validation (master plan, IQ/OQ, process, cleaning).
- ✓ Validation of Aseptic Processes.
- ✓ Inspection of Isolator Technology.
- ✓ Quality Systems for Inspectorates.
- ✓ Sterility Testing.
- ✓ Validation of Computerised Systems.

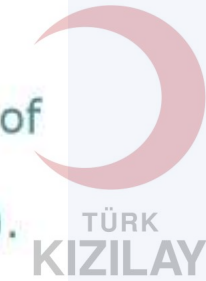
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General Quality Points for Blood Products

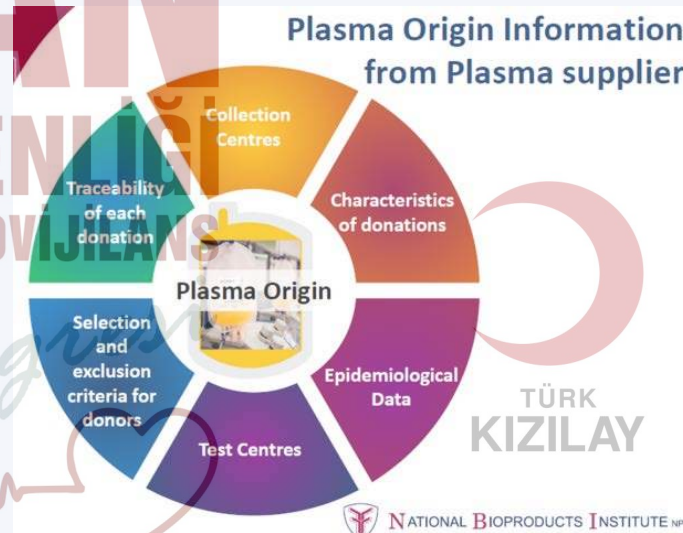
- Donor screening
- Validation of SOP's
- Documentation
- Training of personnel
- Virological screenings
- Traceability
- Maintenance of all equipment
- ...



Critical parameters for insuring quality of Plasma PfF

= **Acceptance Criteria by the Fractionator, whoever he is (you or them)**

- Selection of Blood Donors
- Collection time of the whole blood
- Centrifugation of whole blood
- Plasma Processing
- Minimum volume of plasma (recommended 200ml)
- Basic requirements for Donor's testing
- Temperature
- Kinetics and time of plasma freezing
- Physico-chemical Composition: Total proteins level, FVIII level, pH, ...
- Conservation/ Storage and Plasma Transport
- Traceability of plasma units and blood monitoring system (look-back management)



(see haemovigilance and pharmacovigilance)

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The Fractionator will perform Audits => Benefits for the Blood Establishment



Written Agreements and Audits, an opportunity to
Develop a culture of quality,



The Fractionator will perform Audits => Benefits for the Blood Establishment



Written Agreements and Audits, a win-win situation

Definition of Roles and Responsibilities (BE - Fractionator)

Increase Safety of Blood products

Building expertise within the BE

Audits of donation centers are a regulatory requirement for fractionators

Anticipate impacts of regulatory changes



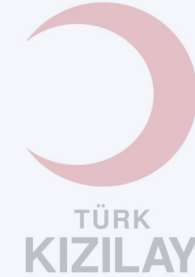
Readiness for Regulatory Competent Authority Regular Inspections

SAFETY REQUIREMENTS



ULUSLARARASI
KAN
GÜVENLİĞİ
VE HEMOVİJİLANS

Kongresi

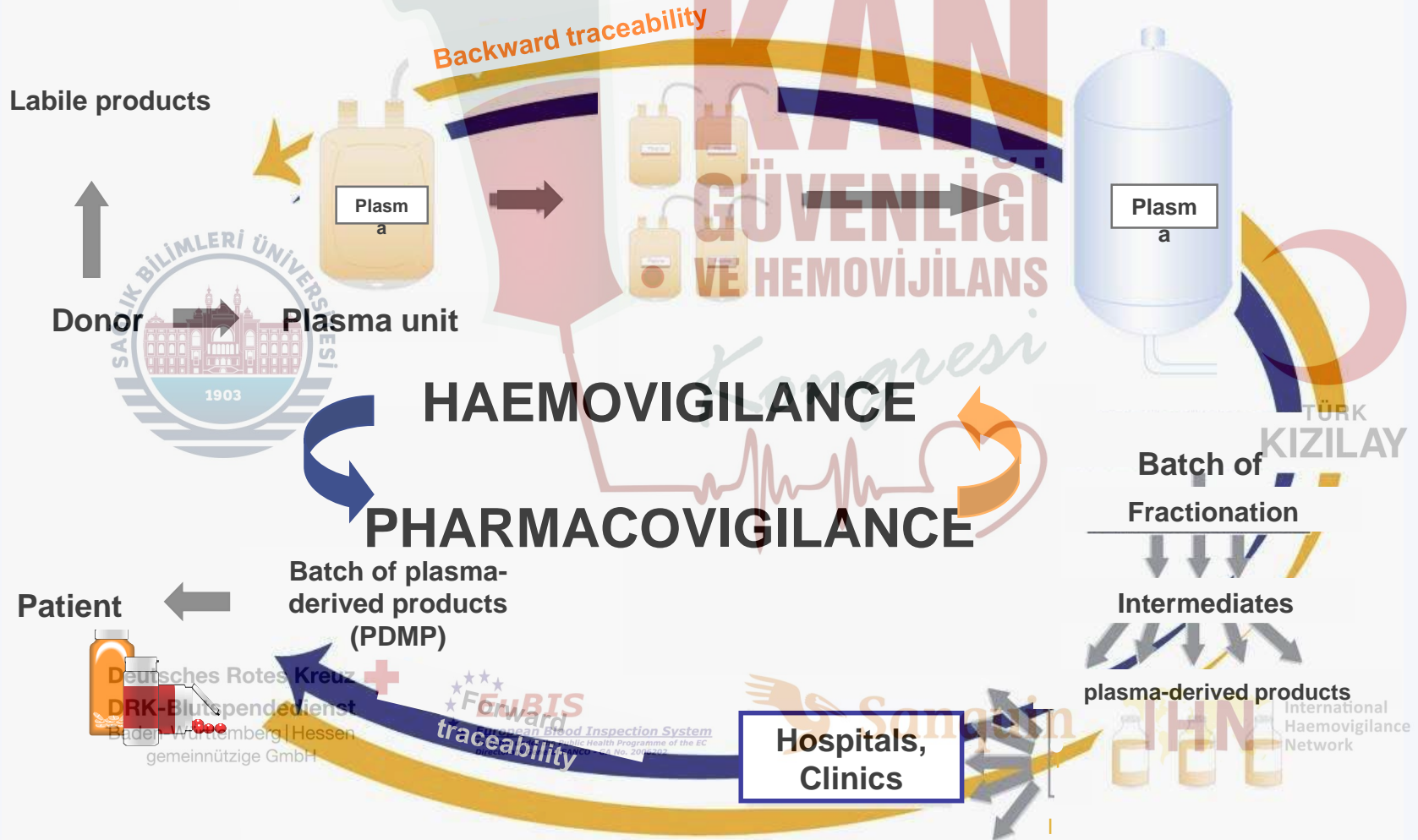


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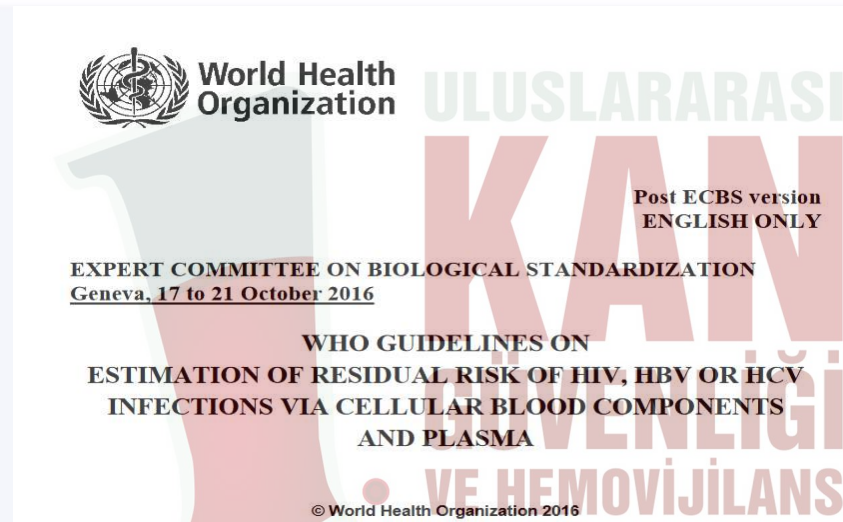


Haemovigilance

Additional Safety for recovered plasma, thanks to vigilance on recipients of labile products



Epidemiological Data



- 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 centres (fixed address), not always relevant/possible for recovered plasma
- Alert limits should be settled (not acceptance limits) First time and Repeat Tested Donations
- CAPAs to be initiated if alert limits are reached
 - Exchanges with plasma suppliers, root cause analysis

WAYS to MOVE FORWARD?

- Standardisation of Quality Standards: worldwide policies (WHO initiatives very welcome)
- European Directives
- Standardisation of Regulatory Policies:
 - Criteria for selection of donors
 - Recognition by other HAs of local HAs inspections
- Better usage of recovered plasma for fractionation
- Promotion of development of plasmapheresis collection of plasma for fractionation in blood establishments

Conclusion: Improving Quality of Blood Establishments


National Regulatory Authority in Promoting Good Manufacturing Practice Compliance

High positive impact on public health

Improving Quality of Blood Establishments

- => Improves Quality and Safety of Blood and Plasma
- => Allows less dependency on importations
- => Enhances Self-Sufficiency
- => Increases Availability of Blood and PdMPs for the Patients

- Drastic upgraded transfusion safety and viral epidemiology management by custom fractionation
- With a high positive impact on Public Health

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Plasma Chain

