



Specific Requirements for Plasma Fractionation



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Obituary Umberto Rossi



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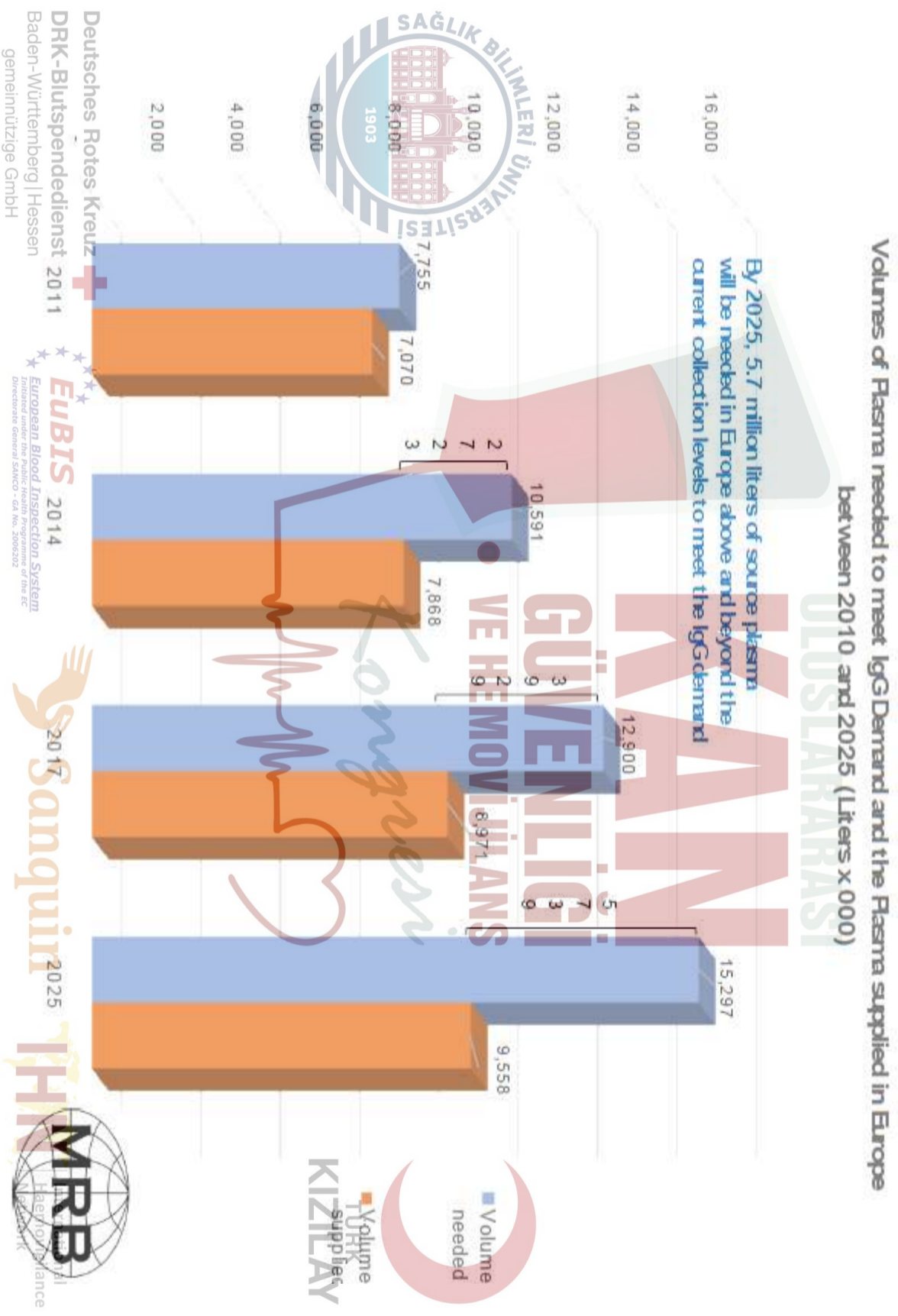

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- Umberto Rossi, founder and for long time President of the European School of Transfusion Medicine (ESTM), passed away in Milan, on September 6th, 2019
- The ESTM colleagues and friends express their gratitude for his extraordinary professional life devoted to education in Transfusion Medicine

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From P. Robert – MRB – IPPC Meeting – Amsterdam, March 19-20, 2019



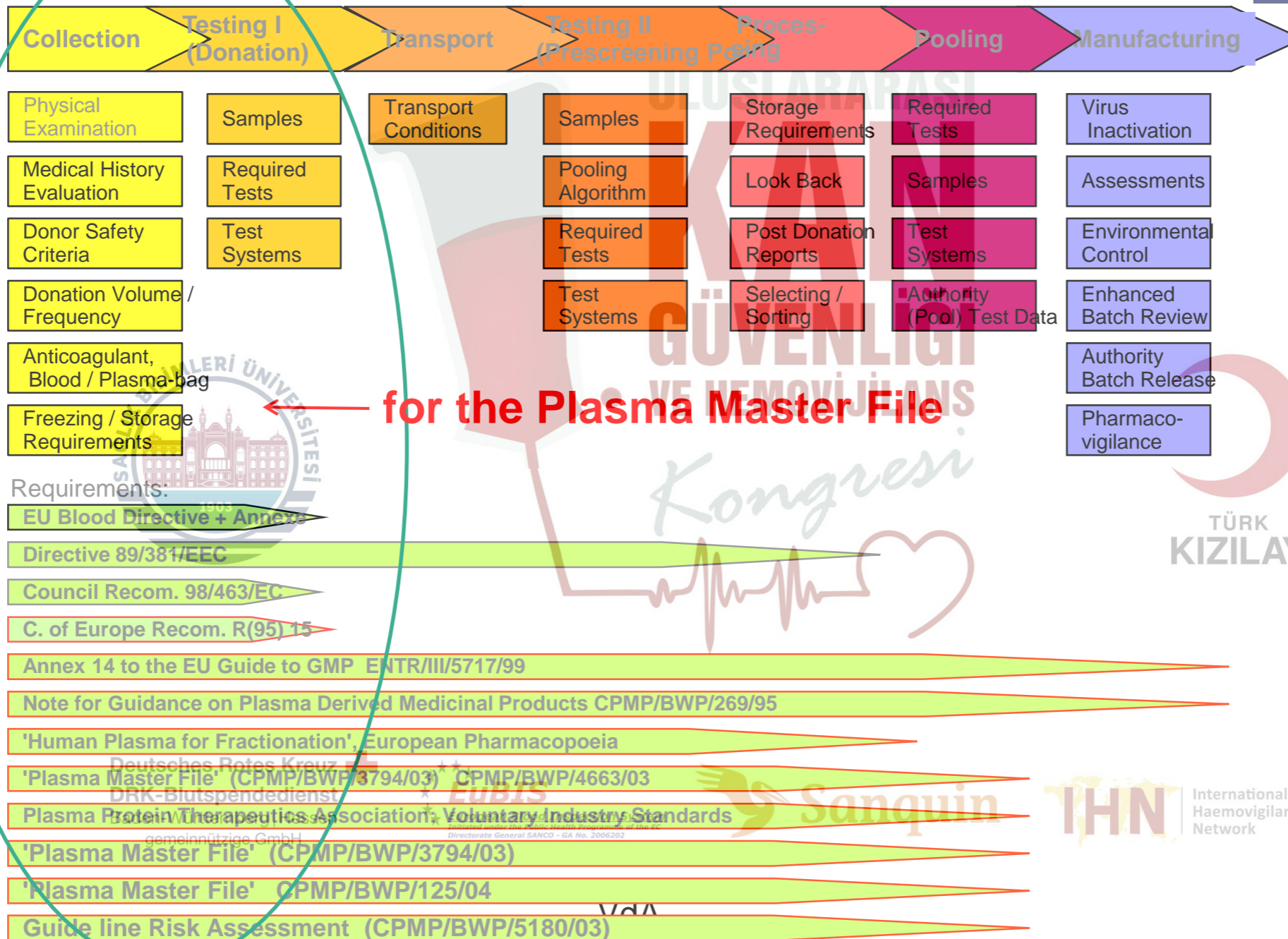
European regulations applicable to human plasma for fractionation

- DIRECTIVE 2001/83/EC Community code relating to medicinal products for human use.
- DIRECTIVE 2002/98/EC setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components.
- DIRECTIVE 2005/61/EC traceability requirements
- DIRECTIVE 2005/62/EC standards and specifications: quality system for blood establishments
- **DIRECTIVE 2016/1214/EU amending Directive 2005/62/EC: the “Good Practice Guidelines”**
- EU Guidelines for GMP for Medicinal Products - Annex 14 (Medicinal Products from Human Blood)
- CoE Recommendation No. R (95) 15 of the Committee of Ministers. Appendix: Guide to the preparation, use and quality assurance of blood components.

European regulations applicable to human plasma for fractionation

- “Guideline on plasma-derived medicinal products” EMA 21 July 2011 - EMA CHMP /BWP/ 706271/ 2010 CHMP
- “Guideline on the scientific data requirements for a Plasma Master File (PMF)” Rev 1 - EMA 15 November 2006 - EMEA/ CHMP/ BWP/ 3794/03
- “Guideline on epidemiological data on blood transmissible infections” EMA, 22 April 2010 - EMA/ CHMP/ BWP/ 548524/ 2008 - CHMP
- European Pharmacopoeia monograph “HUMAN PLASMA FPOR FRACTIONATION” n. 07/2008:0853

Human Plasma for Fractionation



Plasma production under GMP BUT: what is under GMP regulation?



- Chapter 1 - Pharmaceutical Quality Systems
- Chapter 2 - Personnel
- Chapter 3 - Premise and Equipment
- Chapter 4 –Documentation
- Chapter 5 - Production
- Chapter 6 - Quality Control
- Chapter 7 - Outsourced activities
- Chapter 8 - Complaints and Product Recall
- Chapter 9 - Self Inspection



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**DIRECTIVE 2016/1214/EU amending Directive 2005/62/EC:
the “Good Practice Guidelines”**

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GMP / GPG / ISO

GMP	GPG	ISO 9001
1. Pharmaceutical quality systems: pharmaceutical quality system, GMP for medicinal products, quality risk management	General principles 1.2. Quality systems 1.3 Good practice 1.4 Quality risk management	1. Scope 5. Quality policy, quality targets, context of the organisation 6. Planning, handling with opportunities and risks
2. Personnel	2. Personnel and organisation	5. Leadership: persons and responsibilities 7. Support, personnel
3. Premise and equipment	3. Premises 4. Equipment and materials	7. Support, premises, equipment
4. Documentation	5. Documentation	7. Support, documentation


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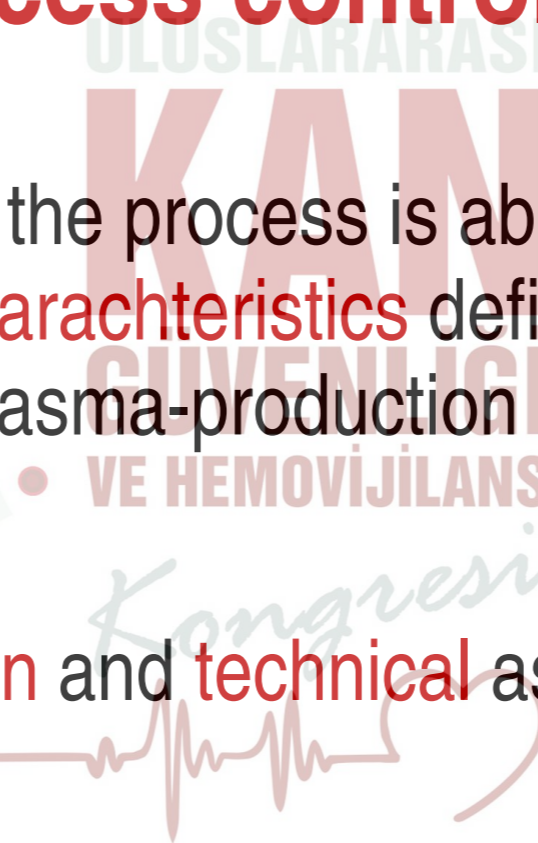

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GMP / GPG / ISO

GMP	GPG	ISO 9001
5. Production Good distribution practice (GDP)	6. Blood collection, testing and processing 7. Storage and distribution	8. Operation, manufacturing of products
6. Quality control 1. Product quality review	11. Quality monitoring and control	8. Operation, verification of product specifications
7. Outsourced activities	8. Contract management	8. Operation, control on extern processes
8. Complaints and product recall	9. Non-conformance 9.2. Complaints 9.3. Product recall	9. Performance evaluation, customer satisfaction
9. Self inspection	10. Self inspection, audit and improvements	10. Improvement

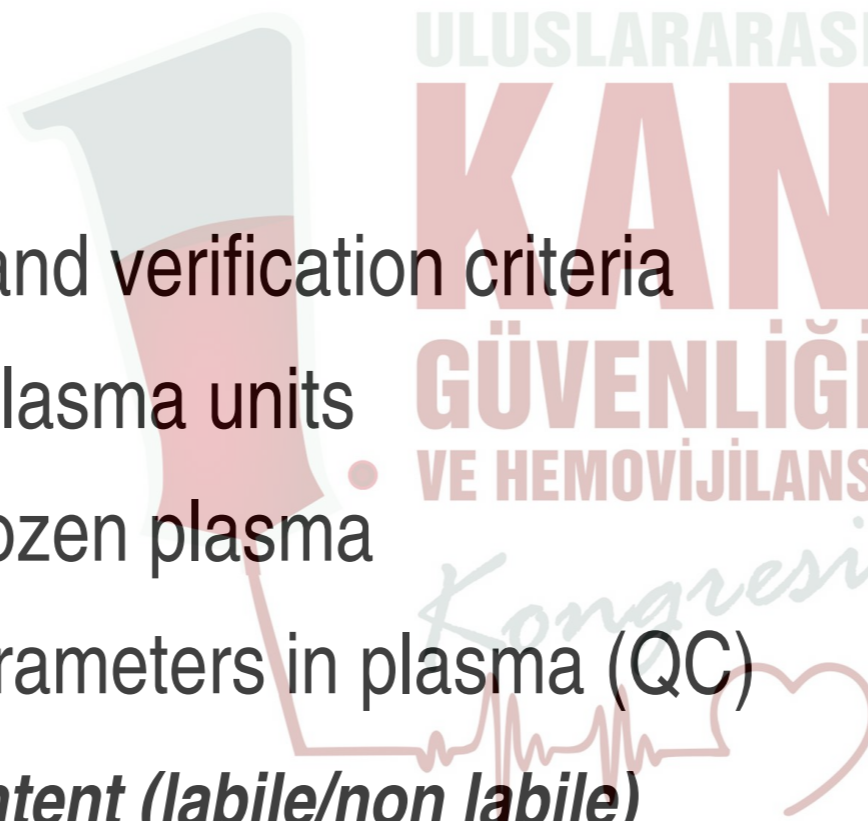
Production of plasma and process control:

- To demonstrate that all the process is able to **consistently meet properties and characteristics** defined by the standards for human plasma-production
- To consider **organization and technical** aspects
- To provide an **adequate documentation**



Steps of the process under control

1. Acceptance and verification criteria
2. Freezing of plasma units
3. Storage of frozen plasma
4. Biological parameters in plasma (QC)
 - ✓ ***protein content (labile/non labile)***
 - ✓ ***microbiological contamination***
5. Temperature during the chain of transport



Good Documentation Practice

Good Practice Guidelines (EU Directive 2005/62/EC e 2016/1214/CE)



«Records are made, manually and/or by recording instruments, during preparation which demonstrate that all the steps required by the defined procedures and instructions were in fact taken»

«Records of quality-control procedures must include identification of the person(s) undertaking the tests or procedures»

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AT THE PRODUCTION

1. Prepared in a way that removes cells and cellular debris
2. Separated from cells as to prevent microbial contamination
3. No antibacteric or antifungal agents added
4. Bags registered for blood and blood components storage; sealed as to prevent contamination

Inspection before freezing

- Volume
- Essentially free of red blood cells (no cloudy reddening visible) and without visible hemolysis
- No clots or other evident abnormalities
- No leakage (gentle squeezing)
- colour (from yellow to light green)



FREEZING (PLASMA AD SEPARATIONEM)

Plasma to fractionation	Time from collection to freezing	Freezing conditions	Reference
Intended for labile proteins production	When obtained by plasmapheresis or from whole blood (after separation from cellular elements), Plasma is frozen within 24 h of collection	Cooling rapidly in conditions validated to ensure that a temperature of -25°C or below is attained at the core of each plasma unit within 12 h of placing in the freezing apparatus	Eu. Pharmacopoeia. Human Plasma for Fractionation (Plasma ad separationem)
NOT Intended for labile proteins production	Separated from cellular elements and frozen at -20°C or below as soon as possible and at the latest within 72 h of collection	Conditions validated to ensure $\leq -20^{\circ}\text{C}$ in the core of the unit (no further specifications)	


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FEEZING PROCESS VALIDATION

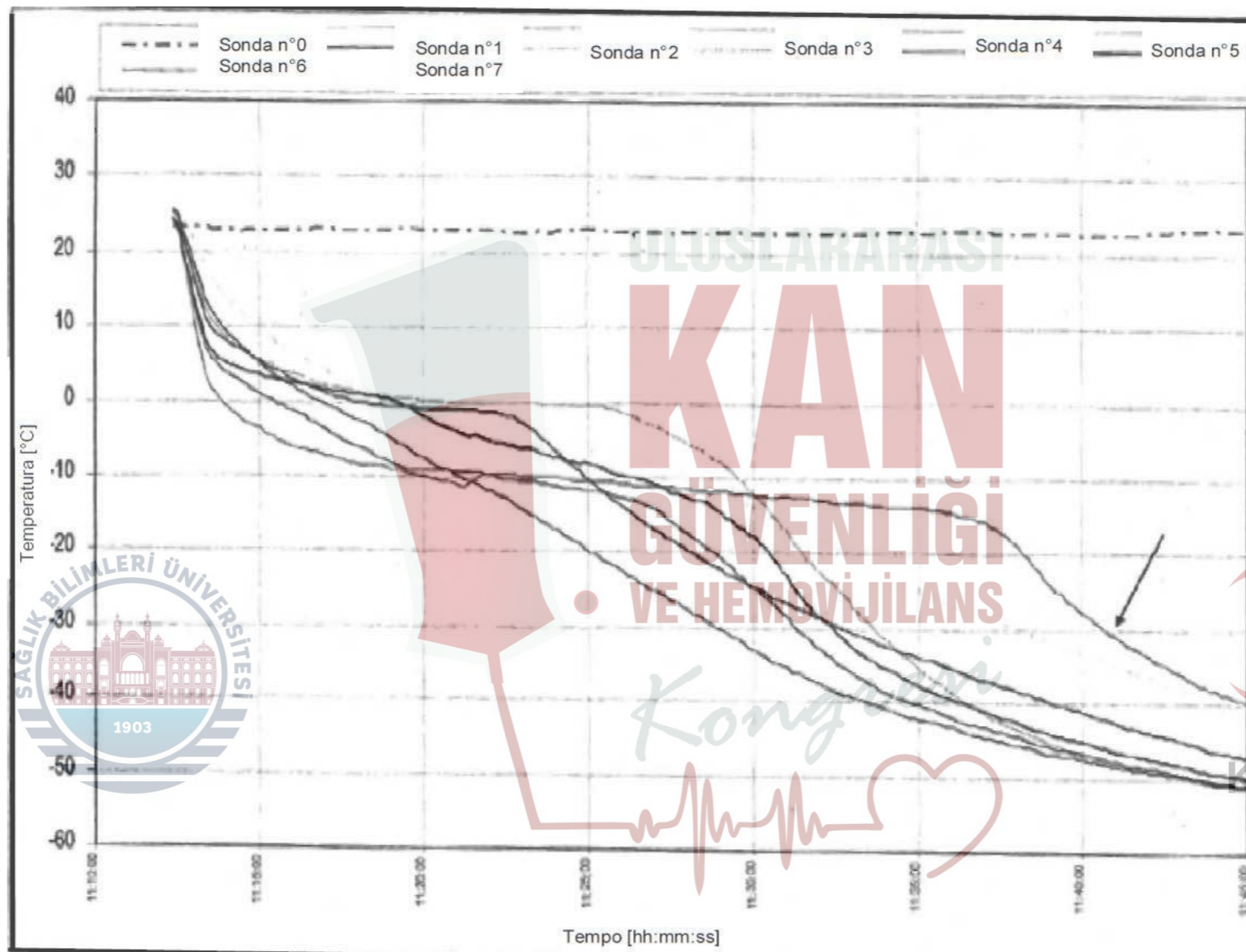
Do a Risk Assessment on critical steps of the process: logistic, materials, technologies, personnel

Define operational standards (parameters to be checked, SOPs...)

Clearly state expected results

VALIDATION TESTS

- Take into consideration critical factors influencing the result:
 - a. position of the unit in the apparatus
 - b. volume of the unit to be frozen
 - c. total volume of plasma in the apparatus
- To define the number of test needed, consider ALL THE FACTORS stratified which must fulfill standards in three consecutive batches



QC of freezing: the maintenance of the validation conditions can be controlled through (daily ?) monitoring of the temperature of a test bag to be positioned at the worse point of the freezer (i.e. the one where the longest time has elapsed before freezing during validation test)

Quality Control and Process control

EU Pharmacopoeia clearly states that the aim of GMPs is not that the QC be carried out on each unit of plasma.

They are rather given as guidelines for good manufacturing practice

The test for factor VIII is relevant for plasma intended for use in the preparation of concentrates of labile proteins.

(QC is intended to demonstrate the robustness of the process)

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Quality Control

Good Practice Guidelines (EU Directive 2005/62/EC e 2016/1214/CE)

«All quality control procedures must be validated before use.






Standard procedures for the quality control of blood components must be in place.

The suitability of each analytical method to provide the intended information must be validated.

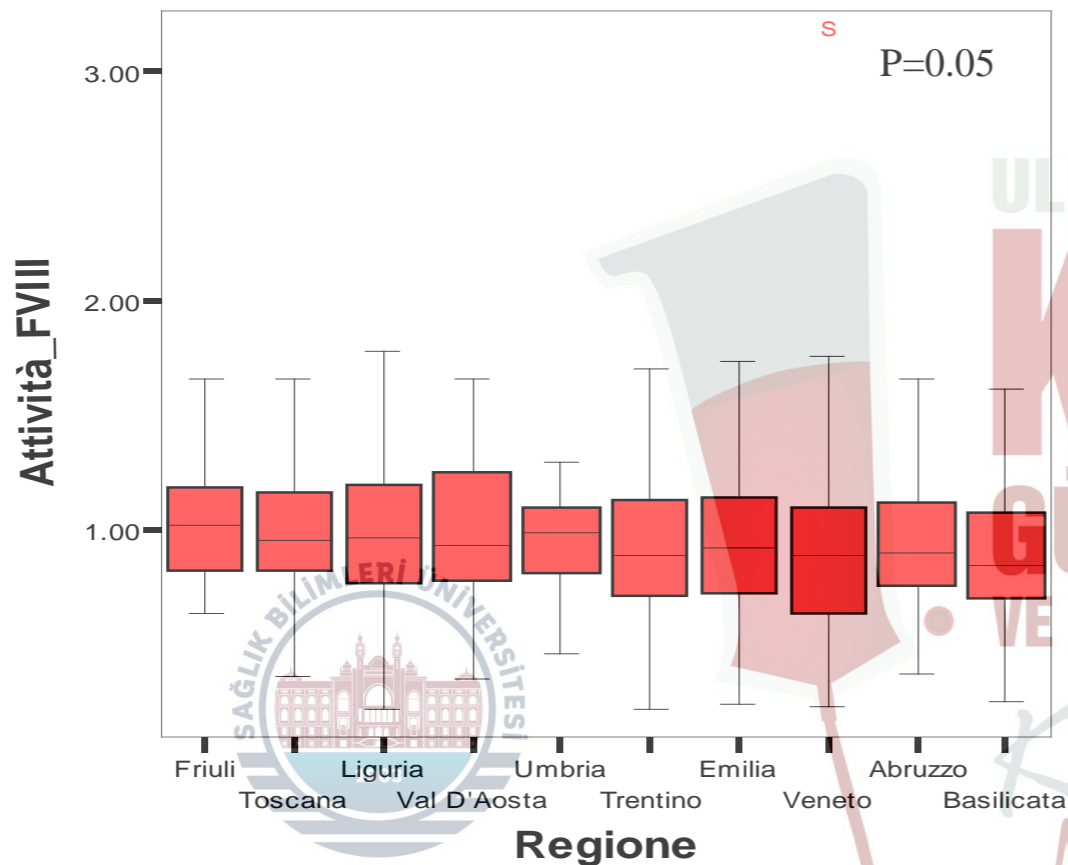
Quality control of blood and blood components must be carried out according to a sampling plan designed to provide the intended information.»



Biological properties requirements and standards

Parameter	Standard	Frequency of test	Reference	
Factor VIII	Not <math>< 0,7 \text{ U/ml}</math>	To be determined by statistical process control evaluation	EDQM Guide	
Total protein conc.	> 50 g/L		Eu.Pharmacopoeia. Human Plasma for Fractionation	
 Residual cells (PLASMA FOR CLINICAL USE)	RBC	<math>< 6.0 \times 10^9 / \text{L}</math>	 TÜRK KIZILAY EDQM Guide	
	WBC	<math>< 0.1 \times 10^9 / \text{L}</math> <math>< 1 \times 10^6 / \text{unit if leucodepletes}</math>		1% of the units (minimum 10 units/month)
	PLT	<math>< 50 \times 10^9 / \text{L}</math>		
 Sterility DRK-Blutspendedienst Baden-Württemberg Hessen gemeinnützige GmbH	 No bacterial growth <small>Initiated under the Public Health Programme of the EC Directorate General SANCO - GA No. 2006202</small>	To be determined by statistical process control evaluation	 IHN International Haemovigilance Network	

F VIII: a worst case surrogate for everything else !!



Dependent Variable: Attività_FVIII

Regione	Mean	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
Abruzzo	.937	.033	.872	1.003
Basilicata	.907	.034	.841	.974
Emilia	.949	.033	.884	1.015
Friuli	1.056	.033	.991	1.121
Liguria	1.018	.033	.953	1.083
Toscana	1.021	.033	.956	1.086
Trentino	.955	.033	.890	1.020
Umbria	.972	.033	.907	1.037
Valle D'Aosta	1.018	.074	.871	1.164
Veneto	.943	.033	.877	1.008

	Count	Mean	Median	Max	Min	Std Dev	Perc 05	Perc 25	Perc 75	Perc 95
Abruzzo	100	.94	.90	1.75	.38	.28	.55	.75	1.13	1.61
Basilicata	96	.91	.85	2.02	.25	.31	.48	.70	1.08	1.60
Emilia	100	.95	.93	2.28	.24	.35	.44	.72	1.15	1.74
Friuli	100	1.06	1.03	2.22	.28	.31	.66	.83	1.19	1.66
Liguria	100	1.02	.97	2.06	.22	.36	.49	.76	1.20	1.78
Toscana	100	1.02	.96	2.20	.36	.34	.58	.82	1.17	1.76
Trentino	100	.96	.89	2.14	.22	.34	.54	.71	1.13	1.70
Umbria	100	.97	.99	1.82	.46	.25	.57	.81	1.11	1.30
Valle D'Aosta	20	1.02	.94	2.04	.35	.40	.36	.78	1.27	2.02
Veneto	100	.94	.90	3.15	.23	.41	.46	.64	1.10	1.68

How to perform QC

Parameter	Method	Time of control
Volume (weight)	Scale (controlled)	After collection/ separation and before freezing
Aspect (colour, integrity,...)	Visual Inspection	
Factor VIII	Pool not less than 10 units(*)	2 aliquots frozen together with the units
Total Proteins		T1: 1 month after collection T2: 4 month after collection

QC Organization

Provide adequate resources, skill, technologies and reagents for biochemical test (proteins, F VIII...)

Choose appropriate analytical methods for tests (e.g. F VIII coagulation or chromogenic?)

EQAS = External Quality Assessment Schemes: Assess the integrity of the entire testing process for infectious disease markers from sample receipt through to final interpretation of test result:

- ✓ *Indicator of personnel efficiency / performance review*
- ✓ *Indicator for test precision and reproducibility*

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Strategy for statistical sampling

- The **number and frequency of components sampled** for quality control should be based on:
 1. Tolerance of failure (need to establish a 'target failure rate')
 2. Confidence level: for the detection of an actual failure rate that lies above the 'target failure rate'.

Statistical Process Control (SPC)

- A tool that enables an organisation to detect changes in the processes and procedures by monitoring data collected over a period of time in a standardised fashion.
- It became mandatory in 2005 for blood establishments in the EU (Directive 2004/33/EC)
- It must be included in the quality system of the facility

Frequency of control sampling

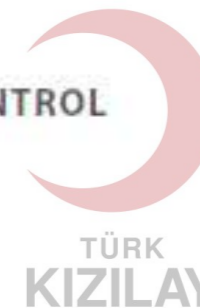
- A number of challenges arise in framing statistically based quality control testing programs.
- Issues include the: large variation in volumes of blood components at different blood establishments; need to minimise losses in blood components through testing at small centres; very low expected rate of non-conformance for some processes, and the number of discrete conditions that arise in the manufacture of otherwise similar components



ULUSLARARASI
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APPENDIX 4.
STATISTICAL PROCESS CONTROL

Kongress



European Committee
(Partial Agreement)
on Blood Transfusion
(CD-P-TS)

EDQM
19th Edition
2017

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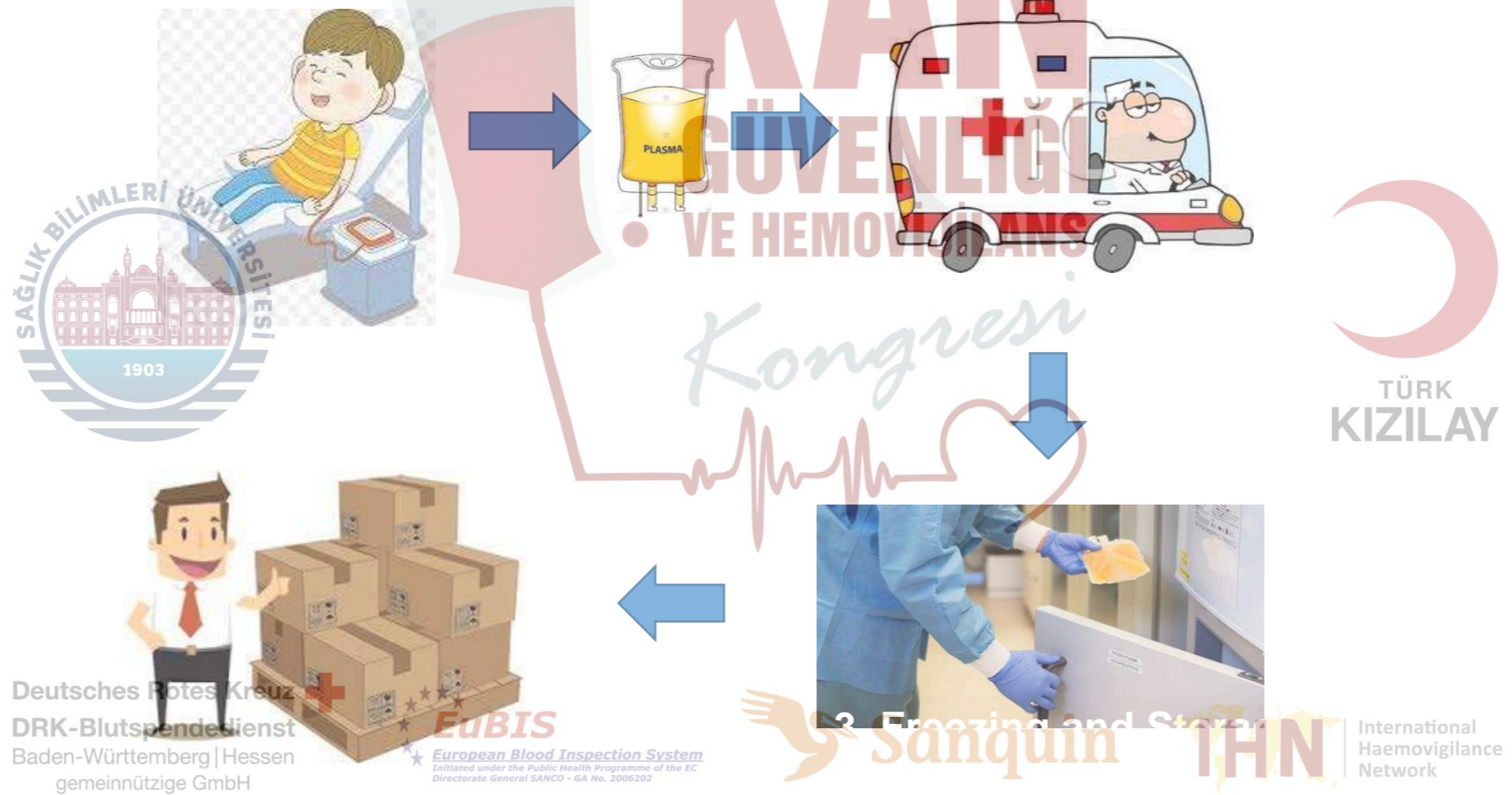


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Temperature Deviation Management

The temperature at which plasma is exposed is a critical factor in its quality



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3 Freezing and Storage
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Requirements

Plasma for Fractionation has to be stored and shipped at minus 20° C or colder (Eu.Pharmacopoeia)

The storage and transport temperatures must be recorded and documented

STORAGE AND TRANSPORT
Frozen plasma is stored and transported in conditions designed to maintain the temperature at or below - 20 °C; for accidental reasons, the storage temperature may rise above - 20 °C on one or more occasions during storage and transport but the plasma is nevertheless considered suitable for fractionation if all the following conditions are fulfilled:

- the total period of time during which the temperature exceeds - 20 °C does not exceed 72 h;
- the temperature does not exceed - 15 °C on more than 1 occasion;
- the temperature at no time exceeds - 5 °C.

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Temperature deviations

Differentiate between deviation related to **freezing** or **storage/transport**

Freezing: within your deviation management do a risk assessment

based on your own validation and European Pharmacopoeia,
and consider the impact to the product shipped to the Fractionator.

Storage and transport: within your deviation management do a risk
assessment and consider the requirements according the European

Pharmacopoeia

Only in case you assess no negative impact for the product you can ship
but the Fractionator must be notified through corresponding
documentation (temperature monitoring docs as graphs and tables)
prior shipping.



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