Federal Institute for Vaccines and Biomedicines

Paul-Ehrlich-Institut

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Plasma for Fractionation

Regulatory & Quality Standards in the EU

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Inspection Services for Biological Medicinal Products

IPFA Workshop Stellenbosch

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Plasma for Fractionation
- Involvement of the Paul-Ehrlich-Institut -



- **Inspections**
  - Lead and/or Co-inspector → PMF inspections: USA (EMA inspections)
  - Expert → Inspections by German National Competent Authorities: Germany and 3rd country (incl. contract fractionation programs)



- **Plasma Master File (PMF) assessment** procedure:
  - Coordinator 1 (3 PMFs), Coordinator 2 (2 PMFs)

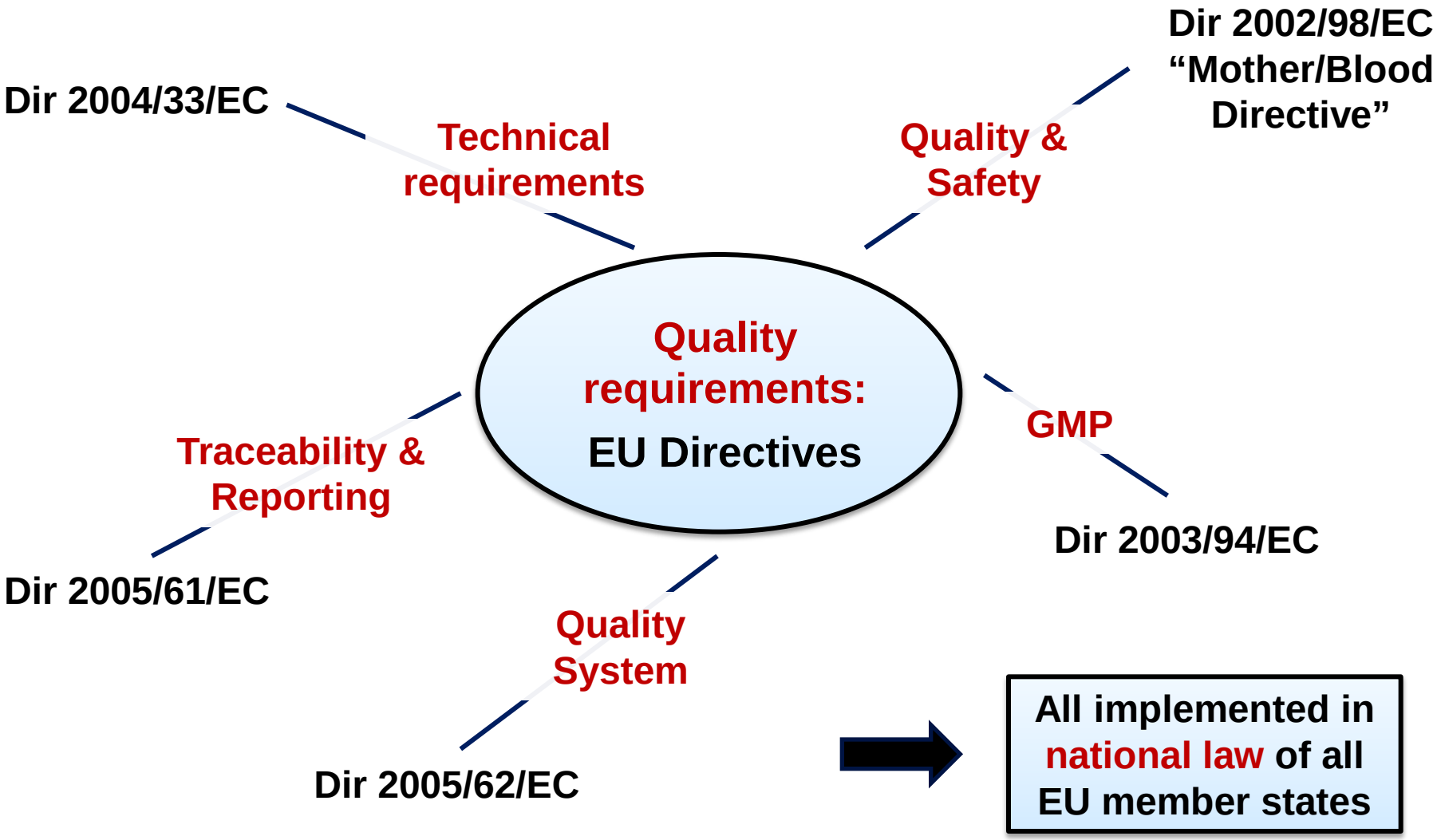


- **WHO Collaborating Centre for Blood Products & IVD devices**
  - Workshops on GMP implementation in blood establishments (Indonesia & South Africa)



- **Drafting group members for various guidelines**, e.g.
  - Annex 14 of the EU GMP guide (last revision 2011)
  - Good Practice Guidelines for Blood Establishments & Blood Banks

Quality Requirements in the EU
- Overview -



Quality Requirements in the EU
- Mother/Blood Directive 2002/98/EC -

- Amends Directive 2001/83/EC „Community code relating to medicinal products for human use“ → Quality, safety & efficacy requirements of medicinal products derived from human blood/plasma
- Sets standards of quality & safety for the collection, testing
  (and for processing, storage & distribution for human blood/blood components intended for transfusion)
- Defines responsibilities & qualification requirements for responsible person of the blood establishment → Compliance with laws in force
- Labelling requirements → Official component name, unique identifier, expiration date, storage temperature, …
- Testing requirements (donations) → HBsAg, anti-HCV, anti-HIV 1/2



Quality Requirements in the EU
- Mother/Blood Directive 2002/98/EC -

- Obligations to EU member states:
  - Establish technical requirements for
    - Donor suitability & donation screening
    - Traceability: donor ↔ recipient
    - Quality System

Implementation through amending directives!

- Obligations to competent authorities of each EU member state:
  - Organize inspection & control measures → Max. interval of 2 years
  - Licensure/approval of blood establishments
- Documentation to be submitted by the blood establishment for licensure, e.g.
  - Identification of blood establishment
  - Details on responsible person (name, qualification, contact details)
  - Description of the quality system

Quality Requirements in the EU
- Dir 2004/33/EC: Technical Requirements -

- Information to be provided to the donors → Educational material, risks associated with the collection procedure, etc.
- Information to be received from the donors → Identification, medical history, informed consent, etc.



- Donor eligibility & deferral criteria → Age, haemoglobin levels, deferral criteria & periods, etc.
- Import of blood & blood components from 3rd countries shall meet standards equivalent to this directive



- Storage & transport conditions → Maintain integrity of product
- Quality control requirements → Microbiological monitoring



Requirements for testing, quality control and storage are further detailed in the European Pharmacopoeia!

Quality Requirements in the EU
- Dir 2005/61/EC: Traceability & Reporting Requirements -

- Obligations to blood establishments:
  - Tracing of blood component to donor, donation, location, processing stage, blood component, final destination → Unique identifiers
  - Records of units received and their final destinations
  - Notification of competent authority → Reporting formats for serious adverse reactions & events
  - Record retention system → Traceability data: 30 years



- Obligations to member state authorities:
  - Annual report of member states to the EU Commission → Serious adverse reactions & events
  - Communication system between Member States → Withdrawal & disposition of affected blood/blood components



- Import of blood & blood components from 3rd countries shall meet standards equivalent to this directive

Quality Requirements in the EU
- Dir 2005/62/EC: Quality System -



- Quality system
  - Responsibility of all personnel
  - Management → implementation & maintenance (e.g. regular review)
- Main principles include
  - Personnel → Training
  - Premises & equipment → Suitable, calibrated, qualified, maintained
  - Documentation → Up-to-date, legible & in orderly fashion
  - Collection, testing & processing → Defined procedures, traceability
  - Storage & distribution → Process validated, cold chain maintained
  - Handling of non-conformances → Deviations, complaints, recalls
  - External & internal auditing → Schedule, trained auditors
- Import of blood & blood components from 3rd countries shall meet standards equivalent to this directive

Quality Requirements in the EU
- Dir 2003/94/EC: Principles of GMP -



- Applies to all steps after collection and testing (plasma for fractionation only) → processing, storage, transport
- Obligations to competent authorities of EU member states:
  - Organize inspections
- Obligations to manufacturers:
  - All manufacturing operations in compliance with GMP & marketing authorization (if applicable)
  - Specifies basic requirements for pharmaceutical quality assurance system, personnel, premises & equipment, documentation, production, quality control, non-conformances, self-inspections, etc.

Further interpreted in EU-GMP Guide and its Annexes!

Quality Requirements in the EU
- European Pharmacopoeia -

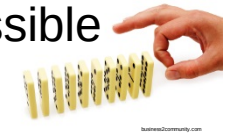


- **Monograph 0853 – Human Plasma for fractionation**
  - Donor selection → Dir 2004/33/EC & Council of Europe Recommendation No. R (95) 15
  - Immunization of donors → WHO Technical Report Series, No. 840
  - Record retention/labelling → Traceability (donor ↔ plasma pool ↔ acceptance procedures ↔ laboratory tests)
  - Donation testing: anti-HIV 1/2, HBsAg, anti-HCV → Repeat reactive donations are not acceptable
  - Freezing → Different requirements apply for whole blood collection & plasmapheresis as well as for the recovery of labile & non-labile proteins
  - Quality control (donations) → Total protein & FVIII
  - Storage & transport requirements → ≤ -20°C
  - 1st homogeneous pool testing → anti-HIV, HBsAg, HCV-RNA

Legally binding in all EU member states

Quality Requirements in the EU
- EMA Guidelines -

- Referenced in Annex 14 of the EU-GMP Guide
- Example: Guideline on Plasma-Derived Medicinal Products (EMA/CHMP/BWP/706271/2010)
  - Donor selection, testing, traceability → Directive 2002/98/EC & amending directives, Ph. Eur. Monograph 853, EU-GMP Annex 14
  - Management of post-collection measures
    - Triggers, e.g. reactive test results, donor develops transmissible infectious disease, donor did not meet other health criteria



    - Notification of manufacturer and/or national authorities
    - Identification of Look Back units: 6 months from last negative donation



Legally binding in all EU member states

Quality Requirements in the EU
- National Law & Guidelines -

- Implement EU requirements
- May define additional & more stringent requirements
- Examples for Germany



  - Medicinal Products Act (Drug Law)
  - Transfusion Law → Physician present during donation activities
  - German Medical Association Guidelines, e.g. “Hemotherapy Guideline” → Donation volumes (apheresis: 650ml/750ml/850ml) & frequency (apheresis: 45/year)
  - Votes of the Blood Working Group at the RKI → Votes 34, 35 & 42 (*Look Back* & re-entry requirements)
  - Specific requirements in particular epidemiological situations, e.g. disease outbreaks

Legally binding in respective EU member states

Quality Requirements in the EU
- Additional Guidelines -

- **WHO** guidelines (www.who.int), e.g. Technical Report Series
  - No. 941 (Production, control & regulation of plasma for fractionation)
  - No. 961 (GMP Guidelines for blood establishments)
  - No. 840 (Collection, processing & quality control of blood, blood components and plasma derivatives)
- **PIC/S** Guidelines (www.picscheme.org), e.g.
  - PIC/S GMP Guide for Blood Establishments
  - PIC/S Guide to Inspections of Source Plasma Establishments & Plasma Warehouses
- **EDQM/Council of Europe** guidelines (www.edqm.eu), e.g.
  - Guide to the Preparation, Use & Quality Assurance of Blood Components (Council of Europe Recommendation No. R (95) 15)
  - Good Practice Guidelines for Blood Establishments & Hospital Blood Banks Required to Comply with EU Directive 2005/62/EC

Additional Guidelines

Plasma Fractionation Programs in the EU
- Regulatory Requirements -

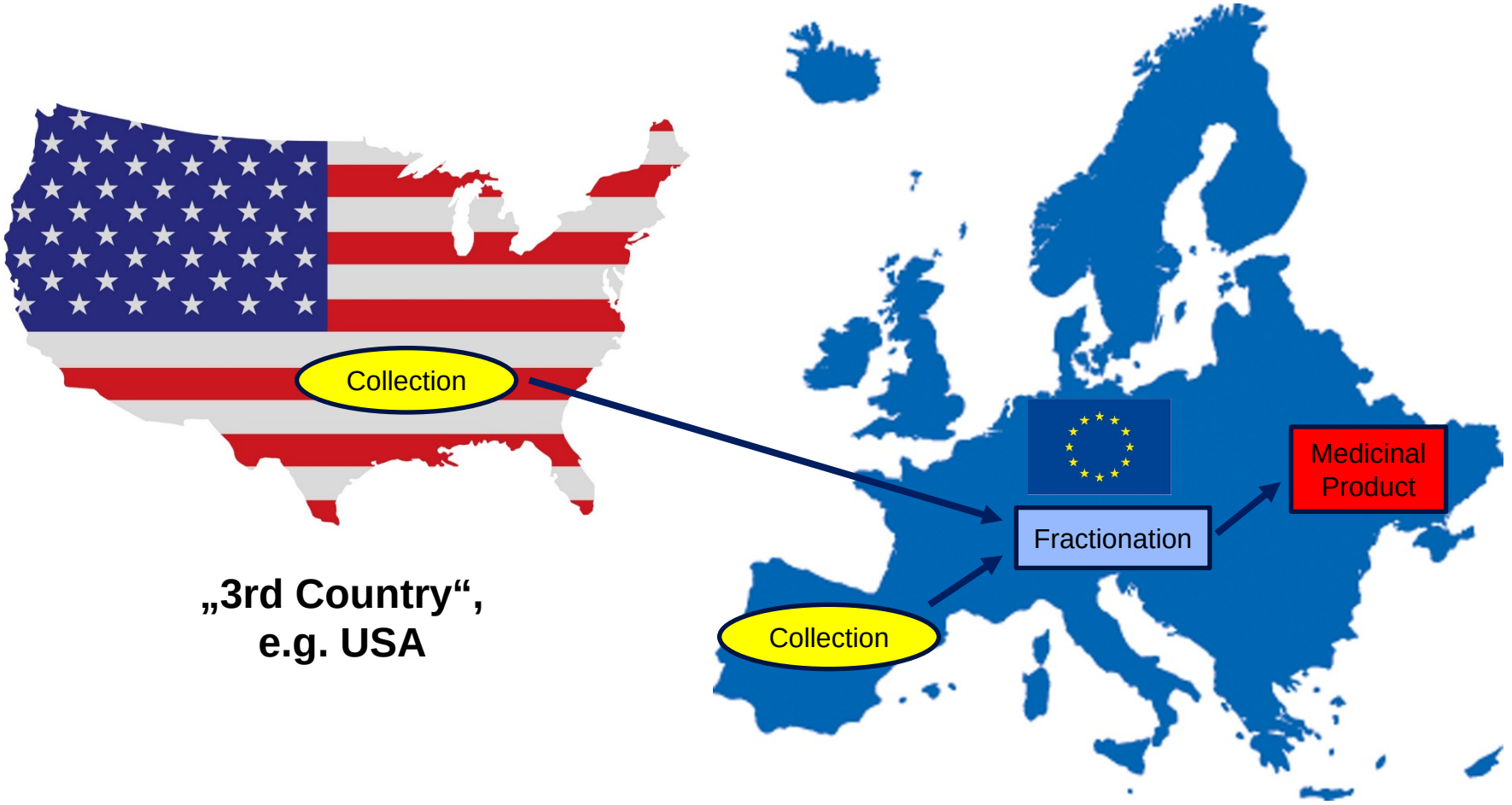


Plasma Fractionation Programs in the EU
- Regulatory Requirements -

- **Different requirements depending on:**
  - Where the plasma is collected → Country of plasma origin
  - Where the final medicinal product is marketed → Country of final product marketing

→ **EU-GMP Guide Annex 14**

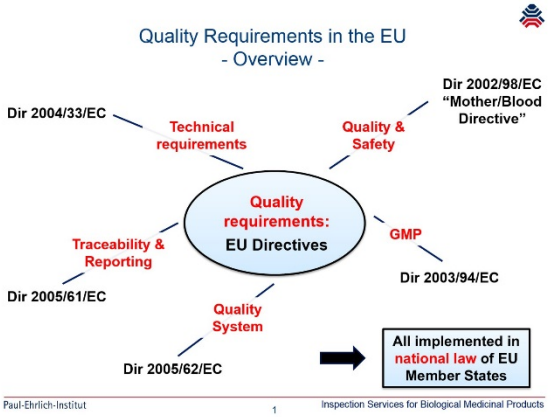
Plasma Collection & Manufacture of Plasma Derivatives for the EU Market



Plasma Collection & Manufacture of Plasma Derivatives for the EU Market
- **Quality Requirements** -

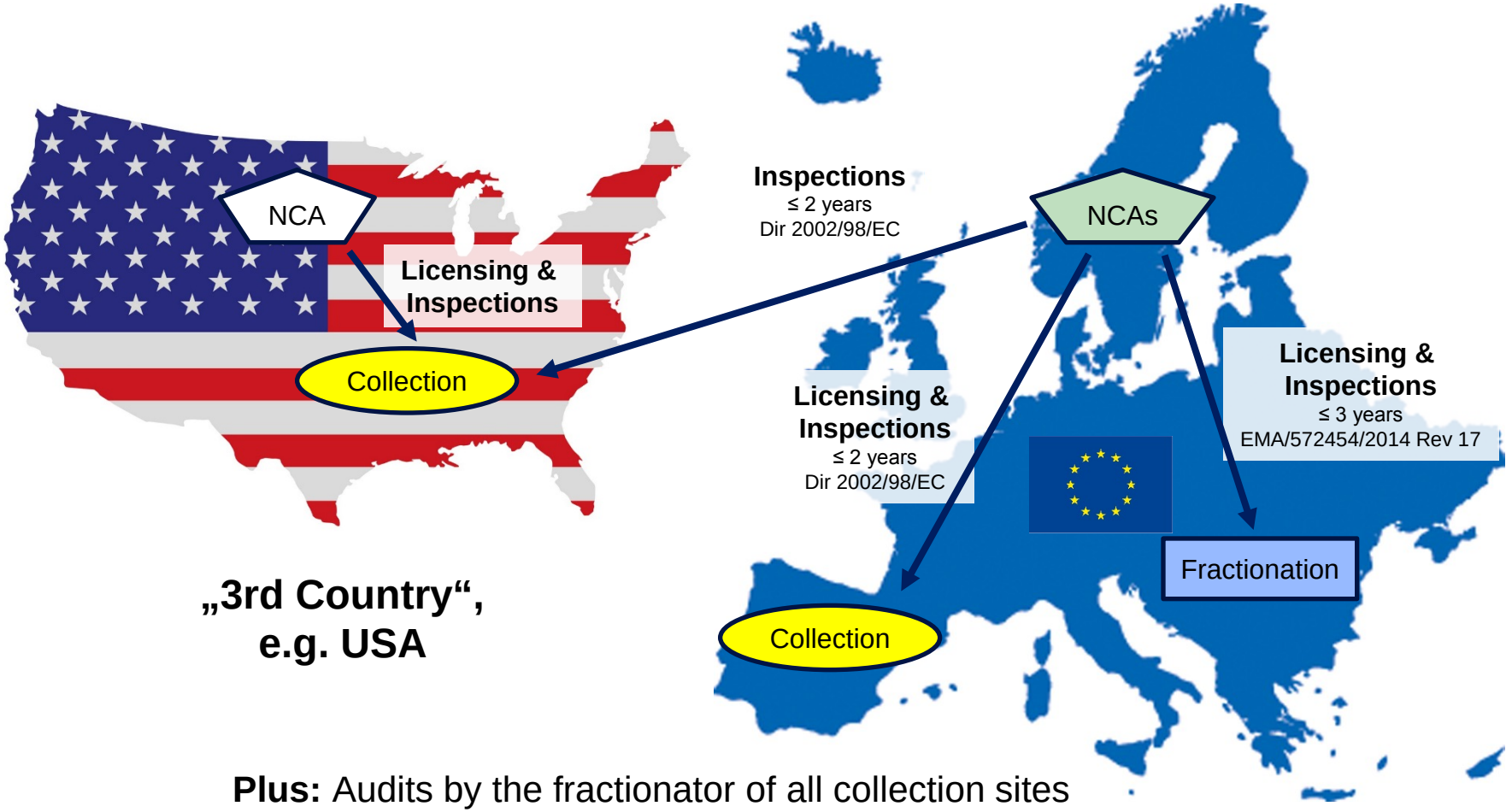


- **All EU-requirements**, e.g.
  - EU Directives



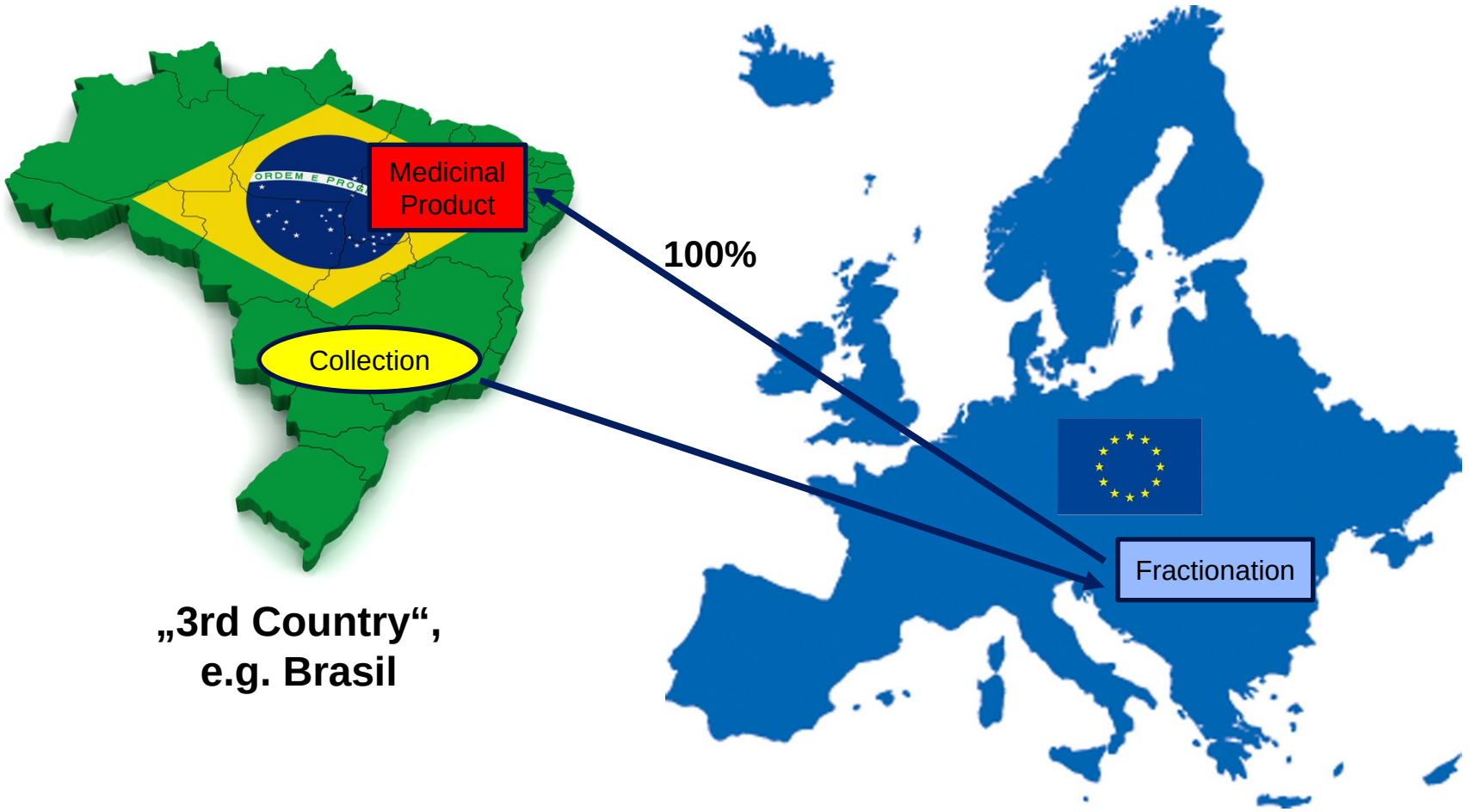
  - EU-GMP & Annexes
  - Ph. Eur. – Monograph 0853 “Human Plasma for Fractionation”
- **National** requirements of EU member states
- **Quality agreements** → Requirements between fractionator & blood establishment

Plasma Collection & Manufacture of Plasma Derivatives for the EU Market
- **Inspections & Licensing Requirements** -

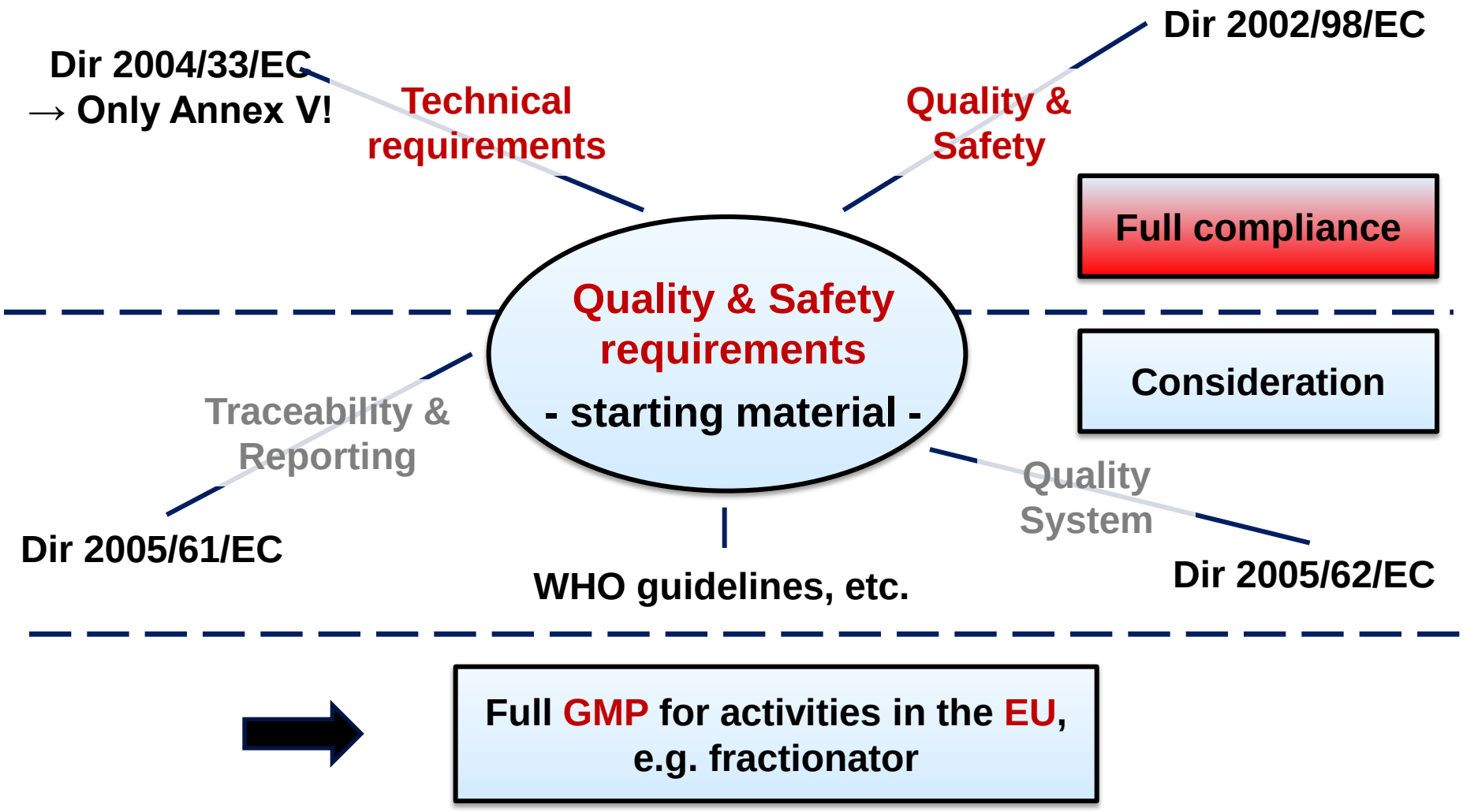


Plus: Audits by the fractionator of all collection sites

3rd Country Contract Fractionation Programs



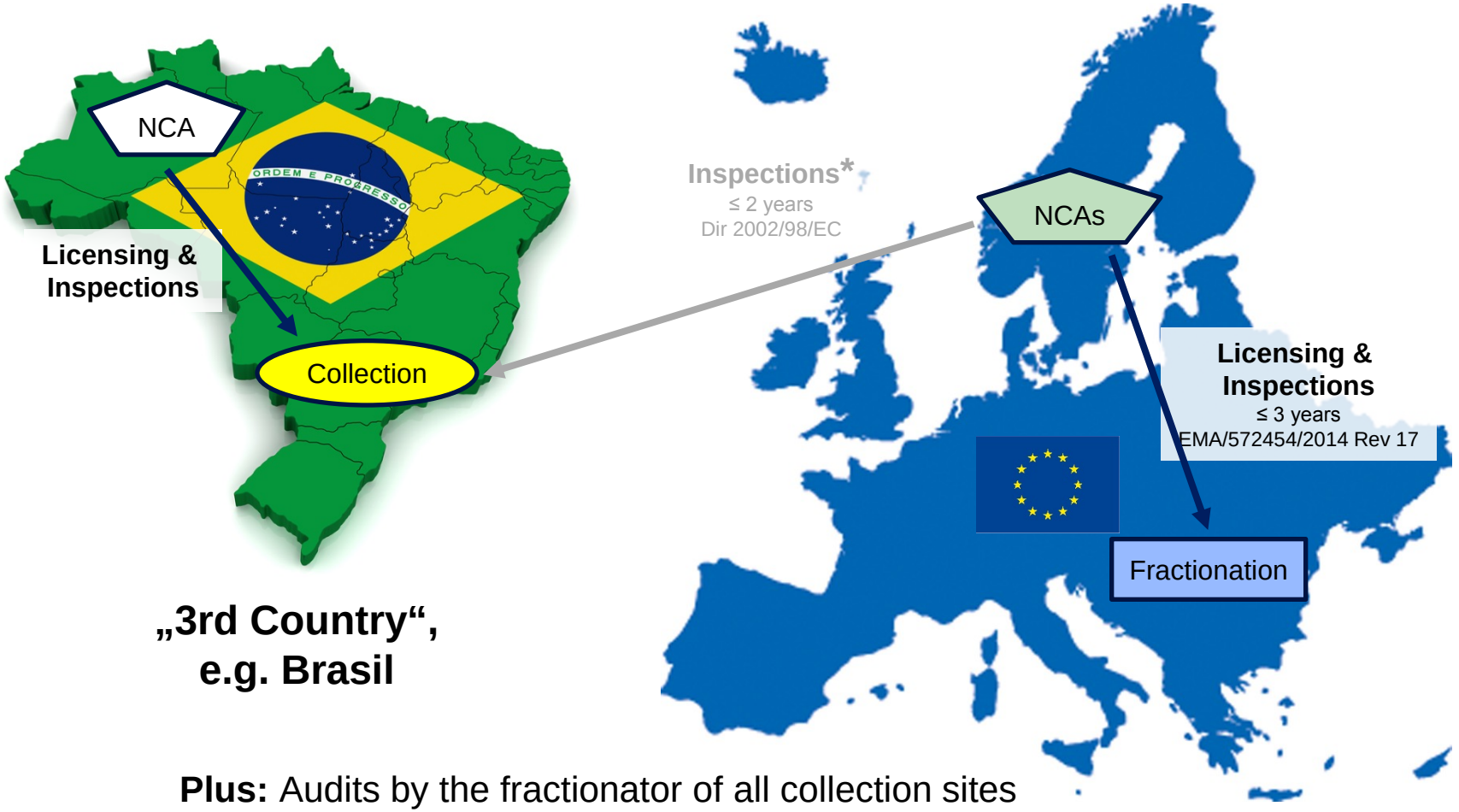
3rd Country Contract Fractionation Programs
- **Quality Requirements** -



3rd Country Contract Fractionation Programs - **Quality Requirements** -

- Directive 2002/98/EC
  - Donor identification system → Traceability
  - Traceability system → equivalent level
  - Testing → HBsAg, anti-HCV, anti-HIV 1/2
- Directive 2004/33/EC – Annex V only!
  - Equivalent standards to quality & safety as defined in this directive → e.g. full compliance with donor deferral criteria not required
  - Appropriate microbiological monitoring of collection & manufacturing process
  - Quality measurements for blood components → WB & FFP
- Program needs to be notified to the EU competent authority of the manufacturer

3rd Country Contract Fractionation Programs
- **Inspections & Licensing Requirements** -



„3rd Country“, e.g. Brasil

Plus: Audits by the fractionator of all collection sites

* Depending on national regulatory requirements

Conclusion

- Quality requirements for human plasma for fractionation are
  - Defined at EU level
  - Transcribed in national law of EU member states
- National law of EU member states may define additional requirements
- Inspections by national competent authorities ensure adherence to quality requirements → Licensure of blood establishments
- Mutual recognition of inspections/licenses by national competent authorities within Europe
- Quality & regulatory requirements depend on the fractionation concept → Multiple players involved
  - National competent authorities in countries of plasma origin, fractionator, final product marketing



  - Fractionator → Quality agreements

Thank you for your attention!



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Section 1/1 – Inspection Services for Biological Medicinal Products