

SESSION 7: QUALITY CONSIDERATIONS FOR PLASMA FOR FRACTIONATION

GPG/GMP SPECIFIC REQUIREMENTS FOR PLASMA FOR FRACTIONATION

IPFA/EBA Workshop on Plasma Collection

January 15, 2019

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OVERVIEW

- EU Regulatory environment of GPGs/GMPs
- GPGs for Blood establishments
  - Legal status
  - Focus: Personnel, PQR, Change control
- EU GMPs
  - Annex 14
  - Focus on audits, qualification, RBA, quality agreements

EU REGULATORY ENVIRONMENT OF GPG/GMP





EU REGULATORY ENVIRONMENT

BLOOD ESTABLISHMENTS

Plasma for fractionation (PfF)

- EU Blood Legislation

Mother directive (2002/98/EC) and technical directives (2005/62/EC, 2005/61/EC, 2004/33/EC, 2016/1214)

- Guide to the preparation, use, QA of blood components (Appendix to R(95)15) – recommendation)
- GPGs=part of Blood components EDQM Guide (binding)

FRACTIONATORS

Plasma-derived Medicinal Products (pdMPs)

- EU Pharmaceutical legislation (Directive 2001/83/EC)
- GMPs (directive 2003/94/EC)
  - Part I, Part II, Annexes 14, 15
- GDPs
- EU Pharmacopoeia (Ph. Eur. monograph n°0853 on PfF)

GOOD PRACTICES

- Definition: a procedure that has been shown by research and experience to produce optimal results and that is established or proposed as a **standard** suitable for widespread adoption
- Fields: Food industry, Pharmaceuticals etc…
- GXPs
  - M: Manufacturing
  - D: Distribution

  → cGMDPs
  - L: Laboratory → Non clinical laboratory studies (toxicology)
  - C: Clinical → Clinical trials
- cGMPs

  ↑ Current

GOOD PRACTICE GUIDELINES (GPG) FOR BLOOD ESTABLISHMENTS





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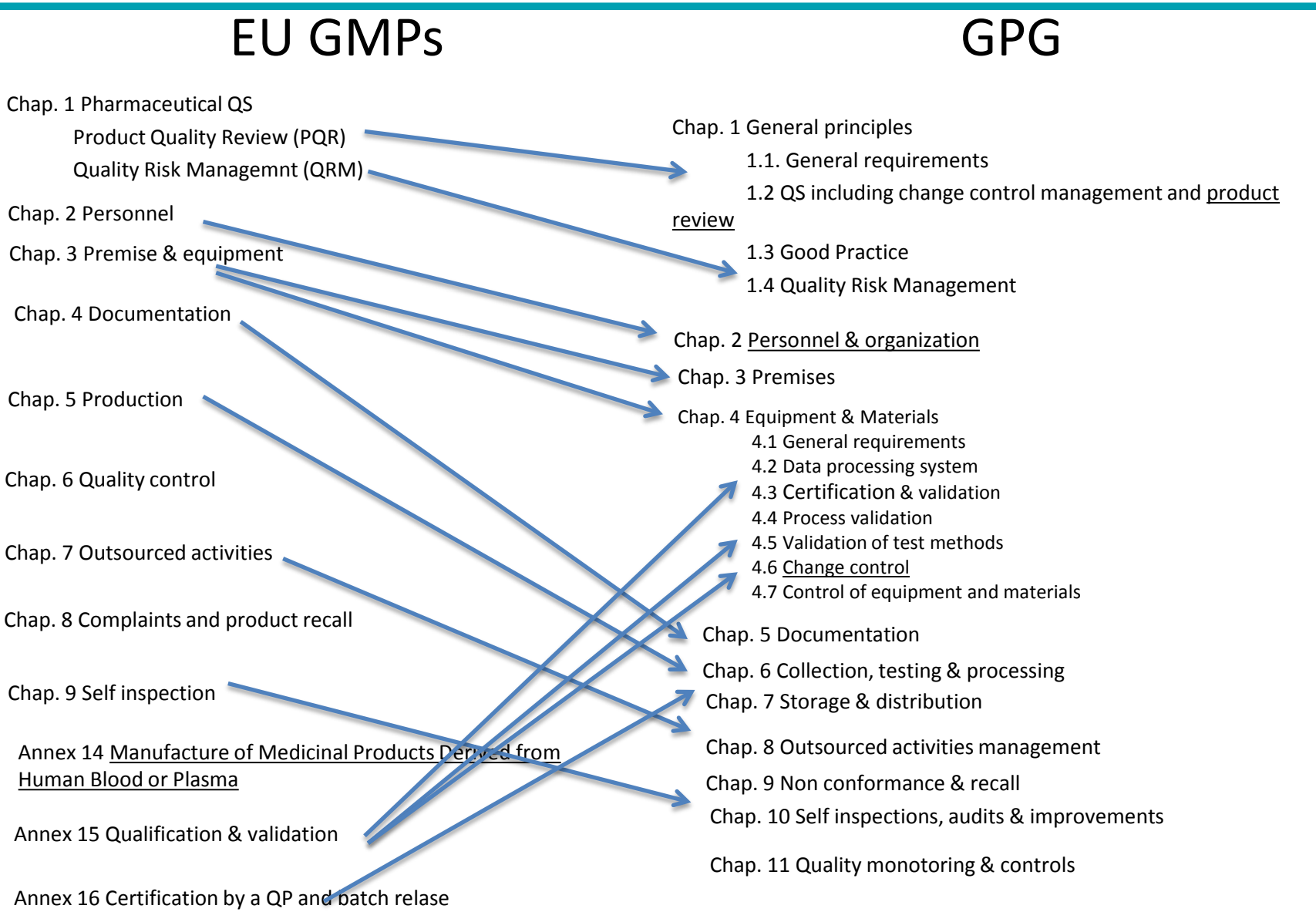
GOOD PRACTICE GUIDELINES

- Legal status:
  - EC directive 2016/1214
  - Member States should take into account the GPG as of 15 February 2018 at the latest
    - Dynamic reference
    - No need for regular revisions
  - Transposition and implementation
    - Incorporation of the EU law in the national law
      - Legally binding guidances
- Derived from the detailed principles of GMPs
  - Specificities of the Quality System (QS) directly applicable to Blood Establishments (BEs)

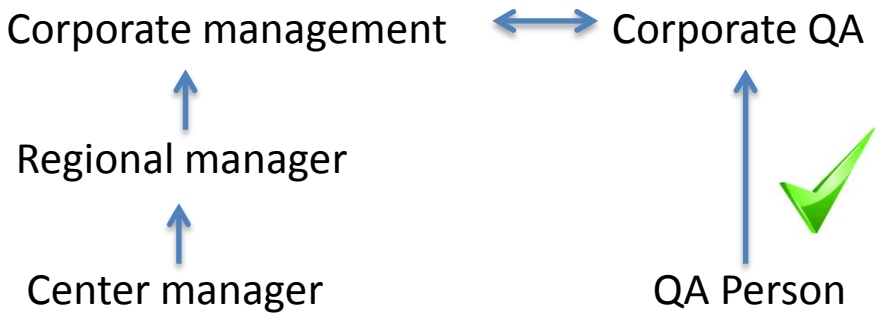
GPG ARE DIRECTLY DERIVED FROM GMP



GPG - PERSONNEL

- Executive management has the ultimate responsibility to ensure that an effective QS is in place and resourced adequately.
- Executive management's leadership and active participation in the QS is essential.
- Responsibility for processing management and QA must be assigned to **different** individuals and function **independently**.

Organisational charts



GPG – PRODUCT QUALITY REVIEW

- Product quality reviews (PQR)
  - Generally an annual process, so-called Annual Product Reviews (APR) in USA
  - PQR should be conducted with the objective of verifying the consistency of the existing process and the appropriateness of current specifications in order to highlight trends and to identify improvements in both components and process
  - Should be documented
- PQR may consist of reviews:
  - Starting materials
  - Critical IPCs
  - Results of QC and Quality monitoring
  - All changes
  - Qualification status of equipments
  - Technical agreements and contracts
  - Significant deviations, non conformances and corrective actions
  - Internal and external audits and inspections and corrective actions
  - Complaints and recalls
  - Donor acceptance criteria
  - Donor deferall
  - Lookbacks

GPG – PQR BENEFITS

- Benefits of PQRs
  - Annual overview, review of key parameters
    - 1/ by operational staff
    - 2/ senior management -> Annual Quality meetings
  - Key documentation readily available for audits/inspections
  - Give an overall first overview of the QS of the BE
  - Identifications of specific trends/recurrences
  - And take appropriate measures

GPG - CHANGE MANAGEMENT

- Robust change management system should be in place
  - Importance of a robust Change Control process
    - Timely notification to fractionator
      - Regulatory leadtimes prior implementation
        - » Plasma Master File 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*

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)*

EXAMPLES OF CHANGES POTENTIALLY IMPACTING PLASMA FOR FRACTIONATION

- 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)

GOOD MANUFACTURING PRACTICES





EU GMP, LEGAL BASIS

- **EudraLex, The Rules Governing Medicinal Products in the European Union, Volume 4, EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary**
  - **Part I - Basic Requirements for Medicinal Products, 9 Chapters**
  - Part II - Basic Requirements for Active Substances used as Starting Materials
  - **Annexes (19): Annex 14**

- **Legal basis for publishing the detailed guidelines:** Article 47 of Directive 2001/83/EC on the Community code relating to medicinal products for human use and Article 51 of Directive 2001/82/EC on the Community code relating to veterinary medicinal products. This document provides guidance for the interpretation of the principles and guidelines of good manufacturing practice (GMP) for medicinal products as laid down in Directive 2003/94/EC for medicinal products for human use and Directive 91/412/EEC for veterinary use.

ANNEX 14 SCOPE

- Scope: 1.1 The provisions of this Annex apply to medicinal products derived from human blood or plasma, fractionated in or imported into the EU/EEA. **The Annex applies also to the starting material (e.g. human plasma) for these products.**

- 2.5 For **all subsequent steps after collection and testing** (e.g. processing (including separation), freezing, storage and transport to the manufacturer) the requirements of Directive 2001/83/EC apply and must therefore be done in accordance with the principles and guidelines of Good Manufacturing Practice.

QUALIFICATION OF COLLECTION CENTERS BY FRACTIONATOR

- Blood/plasma collection centres are **authorized** by local NCAs 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 centers at a frequency between 1 to 5 years depending on scoring calculated yearly

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 to be 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 = intrinsec activity -> low risk, but if large volumes for fractionator transit through this site-> should be considered at higher risk
- Score = A+B+C+D etc…
  - Higher score is not associated to « low quality site », but to a site which require stronger monitoring (ie major changes recently implemented and which require on site audits)
- Scoring may be used to define audit frequency for already qualified sites

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

CONCLUSION

GMP culture: continuous improvements, quality risk management, change control management, risk analysis….

Implementations require investment, efforts

Return on investment is quick and obvious (after a few years): process effectiveness, cost effectiveness, Diminution of % of non compliance

A few years after implementation, everyone is convinced of benefits and assets of Continuous improvement culture!