PPTA
Plasma Protein Therapeutics Association

Navigating the Plasma Regulations

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Landscape

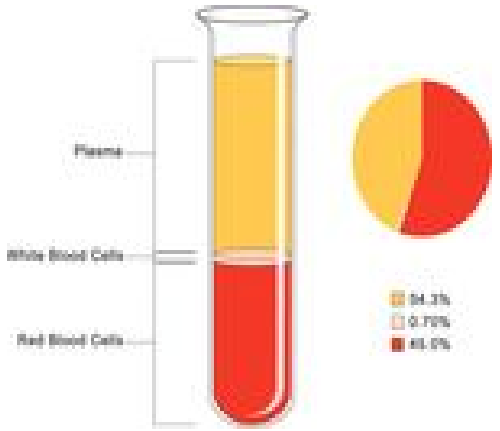
- United States
  - Structure
  - Products
- Europe
  - Structure
  - Products
- Rest of World
  - Tidbits
- PPTA Voluntary Standards

United States

- Players
  - Food and Drug Administration
    1. Statutes (FDCA and PHS Act)
    2. Regulations (Standards and cGMP)
    3. Guidance documents and blood memos
  - States
    1. No Federal pre-emption
    2. Some specific plasmapheresis requirements
  - Centers for Medicare and Medicaid Sciences
    1. Clinical Laboratory Improvement Act
    2. Total Protein Test for Source Plasma

United States

- Plasma products for manufacturing
  - Recovered Plasma
  - Source Plasma
    1. Frequent
    2. Infrequent
  - Alternatives to Source Plasma
    1. Concurrent—Coming soon!!??
       a. 2015 Guidance Agenda
       b. Draft Guidance for Industry: Relabeling of Apheresis Plasma Intended for Transfusion to Concurrent Plasma for Further Manufacture
    2. Component—highly unlikely



Recovered Plasma

- Recovered Plasma
  - Prepared from WB or by product/intended for manufacturing use (CPG 7134.12)
  - Not US licensed product
  - Shipped for fractionation under Short Supply
    1. 21 CFR 601.22
    2. Guidance for Industry: Cooperative Manufacturing Arrangements for Licensed Biologics

Source Plasma

- ". . .defined as the fluid portion of human blood collected by plasmapheresis and intended as source material for further manufacturing use." [21 CFR 640.60]
- Frequent—every 2 days/not more than twice per week. All requirements of 21 CFR Subpart G apply
- Infrequent—1995 Blood Memorandum: variance to 21 CFR 640.63 and 640.65 made in accordance with FDA regulations provided in 21 CFR 640.120. Exemptions from PE, TP/SPE if frequency no more than every 4 weeks

Possible Alternatives

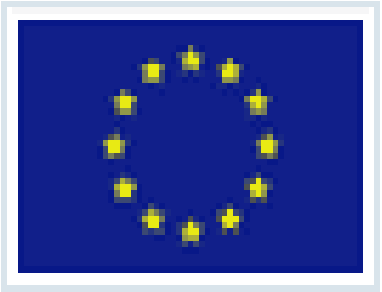
- AABB Interorganizational Plasma Task Force
  - Plasma for manufacturing prepared in blood establishments in-line with blood requirements
  - Proposed names:
    1. Concurrent—plasma collected by apheresis with another transfusible component
    2. Component—stand alone plasma for manufacturing use prepared by plasmapheresis
- BPAC considerations
- ABC outreach via Congress and FDA Commissioner

Europe

- Players
  - European Union/European Commission (EU/EC)
  - Council of Europe/European Directorate for Quality of Medicines/European Pharmacopeia (CoE/EDQM/Ph.Eur.)
  - European Medicines Agency (EMA)
  - National Competent Authorities (NCA)
  - Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-operation Scheme (PIC/S)

Europe

- European Union
  - Legal body established by treaties: the 'Maastricht' Treaty on European Union in 1993 and the Treaty of Amsterdam in 1999
  - Functioning entities: European Commission, European Parliament, Council of the European Union
  - 28 member states



Europe

- EU legislative acts—
  - Regulations: binding for member states; must be applied as is. Exp. Orphan medical products, pharmacovigilance
  - Directives: goal that member states must achieve. “How” left to member states.
  - Decisions: binding on member state addressed
  - Recommendations: not binding
  - Opinions: not binding

EU Directives

- Substances of human origin—directives for blood, tissues/cells, organs
- Blood Directive (2002/98/EC) Setting standards of quality and safety for blood and blood components (Mother)
- Daughter Directives
  - 2004/33/EC. Certain technical requirements. Annex III. Donor eligibility requirements.
  - 2005/62/EC. Community standards and specs for quality system.
  - 2005/61/EC. Traceability/notification of serious adverse reactions.

Directive 2004/33/EC

- Whereas: (4) Blood and blood components imported from third countries, including those. . .starting material. . medicinal products. . .human plasma, should meet quality and safety. . .this Directive.
- Annex III
  - Permanent deferral. Sexual behavior. Persons whose sexual behaviour . . .high risk. . .
  - Temporary deferral. Persons whose behaviour or activity. . .high risk: defer after cessation. . .for period. . . .

Member State implementation example

- Males who have sex with males
  - Permanent deferral: Austria, Belgium, Croatia, Denmark, France, Germany
  - Temporary deferral: UK, Sweden, Hungary, Finland
  - No specific mention: Italy, Poland, Spain

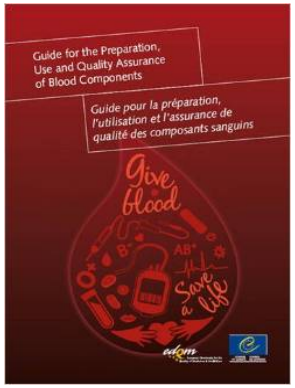
- Q: Will I be able to implement anticipated FDA policy relaxation?
- A: It depends—Fractionator contract/communication essential!!

Council of Europe

- After WWII, Winston Churchill called for a "kind of United States of Europe" and creation of Council of Europe
  - Founded 1949 (Treaty of London)
  - 47 member states/co-operate
- Secretariat for blood transferred to EDQM in 2007
- EDQM—Quality in Medicines
  - Batch release
  - Quality standards/reference materials
  - European Pharmacopeia

Council of Europe/EDQM

- Guide to the Preparation, Use and Quality Assurance of Blood Components—
  - Not mandatory but adopted by some NCAs
  - Primarily blood for transfusion



- European Pharmacopoeia
  - Monograph: Human Plasma for Fractionation
  - Mandated via Directives
  - Authority for freezing plasma among others

European Medicines Agency

- Agency of the European Union
- Responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union
- Operating since 1995-20th Anniversary this year

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Medicines Agency

- Operates through committees/working parties with representation from NCAs
- Responsible for scientific review of products seeking marketing authorization via centralized procedure
- Various other functions, including inspections
- Issues scientific guidance
  - Not mandatory
  - “strongly encouraged”

European Medicines Agency

- Link to plasma as a starting material
  - Guideline on plasma-derived medicinal products (EMA/CHMP/BWP/706271/2010)
    1. Manufacture of plasma-derived medicinal products starts at plasma pool
    2. Starting material concerns
       a. Risk factors
       b. Selection and exclusion criteria
       c. Testing
       d. Traceability
       e. Post-collection measures/lookback

European Medicines Agency

- Applicable guidance documents
  - Guideline on the scientific data requirements for a plasma master file (PMF) (EMEA/CHMP/BWP/3794/03)
    1. PMF a fractionator responsibility
       a. Separate from MAA dossier
       b. Concept established in 2003
    2. Guideline lists information needed by collectors for fractionator to complete the PMF
       a. Facility information/Inspection
       b. Donor/donation characteristics
       c. Testing
       d. Traceability

European Medicines Agency

- Applicable guidance documents
  - Guideline on epidemiological data on blood transmissible infections (EMA/CHMP/BWP/548524/2008)
    1. Information to be submitted in PMF
    2. Requires donor viral marker data
       a. First time tested
       b. Repeat tested
    3. HIV, HCV, HBV
    4. Prevalence/incidence rates
    5. Trending
    6. Risk assessment

PIC/S

- Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S)
  - two international instruments between countries and pharmaceutical inspection authorities
  - provide together co-operation (harmonization) in the field of GMP
  - GMP standards/guidance documents; training competent authorities/inspectors; assessing inspectorates
  - 46 participating authorities

PIC/S

- PIC/S Guide to inspections of source plasma establishments and plasma warehouses (Inspection Guide)
  - September 2007
  - Provides guidance for GMP inspectors
  - Available to facilities collecting and/or storing plasma for fractionation

Rest of World

- More emerging markets are setting up their own regulatory functions
- Most mimicking European system, not FDA
- Copying most often the PMF concept
  - Insist on independent review
  - Add additional requirements
  - Not harmonized
- Soooooooo, even if US and European requirements met, there may be others
- Fractionator contracts/communications essential

PPTA Voluntary Standards

- PPTA has certification programs for source plasma collectors and fractionators

IQPP Standards

- Donor Management/Health
  - Use of National Donor Deferral Registry (U.S.)
  - Community-based Donor Standard
  - Qualified Donor Standard (no one-time donors)
  - Donor Education Standard
  - Cross-Donation Management Standard
  - Donor Adverse Event Recording Standard
- Center Management
  - Personnel Education and Training Standard
  - Professional Plasma Collection Facility Standard
  - Viral Marker Standard (acceptable rates/qualified donations)
  - Quality Assurance Standard

QSEAL Standards

- Controls on Incoming Plasma Standard*:* Places manufacturer controls on incoming plasma, regardless of its source
- Recovered Plasma Specification: Addresses facilities that manufacture therapies using Recovered Plasma
- NAT Testing Standard
- Intermediates Standard
- 60 day inventory hold
- Qualified plasma donor – same as IQPP
- Viral marker standard – same as IQPP

Certification

- Facilities audited/ companies certified
- Certification of adherence to PPTA's voluntary standards
- All Global member companies are QSEAL Certified

Baxter

Biotest

KEDRION

GRIFOLS

CSL Behring

Summary

THANK YOU

Blood is local. Plasma is global.

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