Navigating the Plasma Regulations

Mary Gustafson
Vice President, Global Regulatory Policy, PPTA

ABC Annual Meeting
March 21, 2015
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
• 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      b. Draft Guidance for Industry: Relabeling of Apheresis Plasma Intended for Transfusion to Concurrent Plasma for Further Manufacture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 transfusable 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
  – Functioning entities: European Commission, European Parliament, Council of the European Union
  – 28 member states
• 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
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
  – 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!!
• 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
• **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

• 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
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
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
• 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 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

[Images of IQPP and QSEAL logos]
• **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

Biostest

GRIFOLS

KEDRION

CSL Behring

March 21, 2015 America’s Blood Centers www.pptaglobal.org
THANK YOU
Blood is local. Plasma is global.

Mary Gustafson
mgustafson@pptaglobal.org