FDA Perspective on Plasma Quality and GMPs

Judy Ellen Ciaraldi
Food and Drug Administration
Division of Blood Components & Devices/OBRR/CBER

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Presentation Outline

• Legal Framework for the Regulation of Biological Products
  – Food, Drug and Cosmetic Act
  – Public Health Service Act
  – FDA Regulations
  – cGMP Regulations
  – Additional resources: Guidance Documents

• Regulation of Plasma for Further Manufacturing – Source Plasma (SP) & Recovered Plasma (RP)
  – Manufacturing Requirements for Source Plasma and Recovered Plasma
  – FDA Oversight of Manufacturing Practices
U.S. Collection Data

• About 15.7 million blood donations each year in US
  - Unknown – amount of RP made

• Licensed blood applicants – 1,447 collection centers

• Unlicensed blood collectors – 1,034

• About 29.4 million SP donations from over 1.5 million donors each year in US
  - PPTA website - 2013

• Licensed SP applicants – 450 collection centers

• Regulated by FDA and EMA (European Medicines Agency)
Legal Framework for the Regulation of Biological Products
Federal Food, Drug and Cosmetic Act (21 USC 302 et. seq.)

- Manufacturers must prove drug is safe and effective before marketing
- Prohibits interstate commerce of misbranded and adulterated drugs, foods, cosmetics and therapeutic devices
- Provides penalties for violations, including court injunction
- Requires manufacturing facility registration
- Authorizes manufacturing facility inspections
Public Health Service Act
(42 USC 262 et. seq.)

- Regulation of biological products and control of communicable diseases
- Defines biological product to include blood, blood components and derivatives (added in 1970)
  - Regulates blood and blood components like drugs
- Section 351 – stipulates requirements for licensure
  - Secretary establishes requirements for approval, suspension and revocation of a biologics license
  - Allows interstate commerce of approved products
- Section 361 – requires control of communicable diseases
FDA Regulations

• FDA promulgates regulations to implement the requirements in the PHS and FD&C Acts
• Codified in the Code of Federal Regulations (CFR)
• Are binding like laws on both agency and industry
• Difficult to amend or revoke; may become obsolete and need to be periodically reviewed and updated
• FDA regulations are found in Title 21 of the CFR
  – Biological product regulations are in 21 CFR parts 600 – 680
  – Blood component regulations are in 21 CFR parts 600 – 640
• Regulations ensure the safety of the biological products and donors and include current Good Manufacturing Practices (cGMP) requirements
cGMP Regulations

• Manufacturers must have systems in place to control the manufacturing process

• cGMP regulations provide direction for control and include concepts of:
  – Quality assurance
  – Quality control
  – Process validation

• Blood component cGMPs in 21 CFR 606.3 – 606.171

• Apply to blood components for transfusion and plasma for further manufacturing
cGMP Regulations (cont.)

• Contain requirements for:
  - Quality oversight
  - Personnel qualifications
  - Facility standards
  - Equipment, supplies and reagents qualification
  - Standard operating procedures
  - Labeling
  - Laboratory controls
  - Records
  - Adverse event (fatality) and product deviation reporting to FDA
Additional Resources for Biologics Regulation

- **Guidance documents**
  - Contain FDA’s recommendations (current considerations) on how to comply with statutes and regulations
  - Describe new policies and procedures
  - Do not bind FDA or industry
  - Alternative approaches can be used if they satisfy the requirements in applicable statutes and regulations
  - Found on CBER website
Regulation of Blood Products for Further Manufacturing

Source Plasma & Recovered Plasma
FDA’s Five Layers of Blood Safety

• **Donor Screening**
  - Donor questionnaire and deferral based on geographical, behavioral and medical risk factors

• **Blood Testing**

• **Donor Deferral Lists**
  - Blood establishments must maintain a list of deferred donors

• **Quarantine Controls**
  - Segregate untested and positive units from acceptable units

• **Problems and Deficiencies**
  - Blood establishments must investigate manufacturing problems and correct any deficiencies
Plasma for Further Manufacturing

- **Source Plasma (SP)**
  - Fluid portion of human blood collected by plasmapheresis and intended as source material for further manufacturing use (21 CFR 640.60)
  - Licensed blood component

- **Recovered plasma (RP)**
  - Plasma derived from single units of Whole Blood (WB) as a by-product in the preparation of blood components from WB collection and intended for further manufacturing (CPG 7134.12)
  - Unlicensed blood component
  - Interstate commerce under Short Supply Arrangement (21 CFR 601.22)
Current Sources of Plasma for US Plasma Derivative Manufacture

- Phlebotomy
- Whole Blood
- Source Plasma (Infrequent)
- Unlicensed recovered plasma

Whole Blood Donor Standards

Source Plasma Donor Standards

Making Recovered Plasma and Source Plasma

- Phlebotomy Whole Blood
- Automated Apheresis

Plasma Derivatives Or Non-injectable Products

- Plasma for Transfusion FFP, PF24
- Plasma for Transfusion Apheresis FFP, PF24 collected + RBC, Plts
- Source Plasma (Infrequent)

Convert anytime

1 year before conversion

Unlicensed recovered plasma

Automated Plasmapheresis

Source Plasma
## Source Plasma and Recovered Plasma

<table>
<thead>
<tr>
<th>Donor Selection</th>
<th>Source Plasma</th>
<th>Recovered Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Requirements in 21 CFR 640.63 &amp; 640.65</td>
<td>• Physical exam initially/annually</td>
<td>• RP made from Whole Blood donors; requirements for Whole Blood donors in 21 CFR 640.3</td>
</tr>
<tr>
<td>• Physical exam initially/annually</td>
<td>• Total protein</td>
<td></td>
</tr>
<tr>
<td>• Total protein</td>
<td>• SPE initially/every 4 months</td>
<td></td>
</tr>
<tr>
<td>• SPE initially/every 4 months</td>
<td>• Informed consent</td>
<td></td>
</tr>
<tr>
<td>• Informed consent</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Source Plasma and Recovered Plasma (cont.)

<table>
<thead>
<tr>
<th></th>
<th>Source Plasma</th>
<th>Recovered Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Collection Frequency</strong></td>
<td>• Frequent – 2 days apart; no more than 2x/week</td>
<td>RP is not a collected product; it is made from Whole Blood or plasma products used for transfusion</td>
</tr>
<tr>
<td></td>
<td>• Infrequent – once every 4 weeks or less frequent</td>
<td></td>
</tr>
<tr>
<td><strong>Collection/Preparation Method</strong></td>
<td>Automated (or manual) plasmapheresis</td>
<td></td>
</tr>
</tbody>
</table>
## Source Plasma and Recovered Plasma (cont.)

<table>
<thead>
<tr>
<th></th>
<th>Source Plasma</th>
<th>Recovered Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Shelf Life</strong></td>
<td>10 years</td>
<td>Not specified in regulations</td>
</tr>
</tbody>
</table>
| **Storage Temperature** | • Injectable – immediately after filling, store at -20C or colder  
• Non-injectable – store at temperatures appropriate for intended use | Not specified in regulations; must meet final product manufacturer’s specifications |
### Source Plasma and Recovered Plasma (cont.)

<table>
<thead>
<tr>
<th>Infectious Disease Testing</th>
<th>Source Plasma</th>
<th>Recovered Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• HIV-1/2 antibody and HIV-1 NAT</td>
<td>• HIV-1/2 antibody and HIV-1 NAT</td>
</tr>
<tr>
<td></td>
<td>• HCV antibody and NAT</td>
<td>• HCV antibody and NAT</td>
</tr>
<tr>
<td></td>
<td>• HBsAg and HBV NAT</td>
<td>• HBsAg and HBV NAT</td>
</tr>
<tr>
<td></td>
<td>• Syphilis initially/every 4 months</td>
<td>• Syphilis</td>
</tr>
</tbody>
</table>
## Source Plasma and Recovered Plasma (cont.)

<table>
<thead>
<tr>
<th>Source Plasma</th>
<th>Recovered Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infectious Disease Testing (cont.)</strong></td>
<td><strong>In-process -</strong></td>
</tr>
<tr>
<td>-</td>
<td><strong>HAV NAT</strong></td>
</tr>
<tr>
<td>-</td>
<td><strong>Parvovirus B-19 NAT</strong></td>
</tr>
<tr>
<td>-</td>
<td><strong>HB core antibody</strong></td>
</tr>
<tr>
<td>-</td>
<td><strong>HTLV-I/II antibody</strong></td>
</tr>
<tr>
<td>-</td>
<td><strong>West Nile Virus NAT</strong></td>
</tr>
<tr>
<td>-</td>
<td><strong>Chagas antibody</strong></td>
</tr>
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</table>
Ensuring Safety of Plasma Derivatives

- Plasma derivatives are made from plasma pooled from thousands of donors
- Must ensure safety of starting plasma product
  - Employ the five layers of blood safety and cGMPs
- Blood establishments and plasma derivative manufacturers have implemented mitigation measures to reduce risks
  - Voluntary industry standards
  - Pathogen inactivation and virus removal
- FDA’s regulatory oversight
FDA Oversight of Manufacturing Practices

• FDA Facility Registration and Product Listing
  - Required under the FD&C Act
  - Does not permit shipping of blood products in interstate commerce

• FDA Licensure of Biological Products
  - Required under Sec. 351 of the PHS Act
  - Allows shipment of approved product in interstate commerce

• FDA Facility Inspections
  - Required under the FD&C Act and PHS Act
  - Observe adherence to cGMP and manufacturing requirements for licensed and unlicensed products
FDA Facility Inspections

• Types of Inspections:
  – Routine (all registered facilities) – conducted @ 2 years by FDA field inspectors who observe all manufacturing operations
  – Pre-license – part of the license review; conducted by CBER and FDA field inspectors who observe all manufacturing operations related to the license application
  – For cause – conducted by FDA field inspectors; investigate fatalities and complaints

• Inspection Information
  http://www.fda.gov/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/default.htm
Summary

• FDA has authority to oversee the manufacture of plasma used for further manufacturing to ensure it is safe, pure, and potent
  - FDA also oversees the safety of the blood or plasma donor

• All blood and plasma establishments must follow FDA cGMPs

• In US, SP and RP are used for further manufacturing
  - SP is directly collected, has required donor and product standards, and must be licensed
  - RP prepared from plasma intended for transfusion, has fewer required standards, and is unlicensed
• Plasma derivative manufacturers have implemented additional safeguards, e.g., pathogen inactivation and virus removal

• FDA assesses compliance with FDA cGMPs and manufacturing requirements during:
  - Review of license applications
  - Inspections of blood establishments and plasma derivative manufacturers

• Objective: Ensure quality of plasma for further manufacturing

• GAO report (HEHS-98-205): Plasma Product Risks are Low if Good Manufacturing Practices are Followed
For More Info on Regulatory, Licensing, and Blood Product Standards

Office of Communication, Outreach and Development, CBER, FDA
10903 New Hampshire Avenue
Building 71, Room 3103
Silver Spring, MD 20993-0002
ocod@fda.hhs.gov
800-835-4709
Helpful Website Addresses

- **General FDA information**
  http://www.fda.gov/

- **General CBER information**
  http://www.fda.gov/BiologicsBloodVaccines/default.htm

- **Email Subscriber Service**
  - “What’s New”
  - Guidances, Proposed and Final Rules, Workshops and Meetings, Recalls
  - Enter your email address
  - It’s free!!
  http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm125685.htm
FDA

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