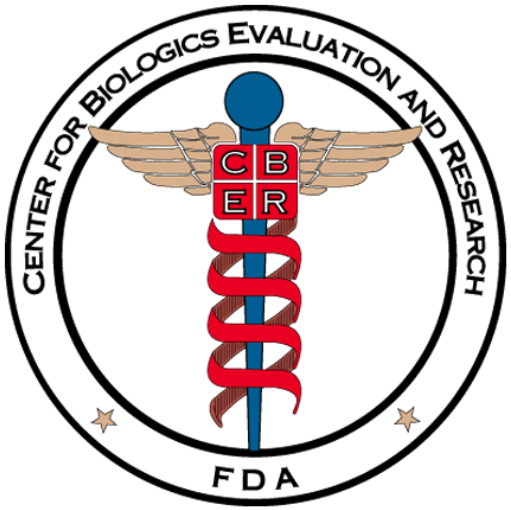

FDA Review of Apheresis Submissions

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Outline

- Resources for FDA Apheresis Review Criteria
- FDA Apheresis Review Checklists
- General Content of Apheresis Submissions
- Review Criteria for Specific Apheresis Products
- Shipping Products to CBER
- Comparability Protocol Submissions

Resources for FDA Apheresis Review Criteria

- **Regulations in the Code of Federal Regulations (CFR)**
- **Recommendations in FDA guidance documents**
- **Device Operator's Manuals**
- **Package Inserts for Reagents and Supplies**
- **Published scientific literature**

Regulations* used for Apheresis Reviews

- **Donor selection – 640.3, 640.21, 640.31, 640.63**
- **Collection procedure – 640.4, 640.22**
- **Testing – 610.40, 640.5**
- **Product standards (including QC) – 600.15, 610.53, 640.11, 640.25, 640.32, 640.34**
- **Labeling – 610.60, 606.121, 606.122**
- **GMPs – 210.1, 210.2, 211.1, 211.22**
- **Submission content – 601.12**

***Title 21 CFR**

GMP Regulations* used for Apheresis Reviews

- **Personnel – 211.25, 211.28, 606.20**
- **Equipment, Supplies and Reagents – 211.68, 606.60, 606.65**
- **SOPs – 211.80, 211.100, 211.111, 211.198, 606.100, 606.110**
- **Laboratory controls –211.103, 211.160, 211.165, 606.140**
- **Records –211.180, 211.186, 211.192, 211.194, 606.160, 606.165**
- **Adverse events – 606.170, 606.171**

***Title 21 CFR**

FDA Guidance Documents used for Apheresis Reviews

http://www.fda.gov/cber/blood/bldguid.htm

- Guidance for Industry: Recommendations for Collecting Red Blood Cells by Automated Apheresis Methods, Feb. 2001; Technical Correction – 2/13/2001
- Guidance for Industry: Use of Sterile Connecting Devices in Blood Bank Practices, 11/22/2000
- Revised Guideline for the Collection of Platelets, Pheresis, 10/7/1988
- Guideline for Quality Assurance in Blood Establishments, 7/11/1995

FDA Guidance Documents used for Apheresis Reviews

http://www.fda.gov/cber/blood/bldguid.htm

- Guidance for Industry: Recognition and Use of a Standard for Uniform Blood and Blood Component Container Labels, 9/22/2006
- Guidance for Industry: Bar Code Label Requirements Questions and Answers, 10/5/2006
- Guidance for Industry: An Acceptable Circular of Information for the Use of Human Blood and Blood Components, 12/9/2003
- Guideline for the Uniform Labeling of Blood and Blood Components, Aug. 1985

FDA Guidance Documents used for Apheresis Reviews

http://www.fda.gov/cber/blood/bldguid.htm

- Guidance for Industry: Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture, 8/7/2001
- Guidance for Industry For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Blood and Blood Components Intended for Transfusion or for Further Manufacture and For the Completion of the Form FDA 356h "Application to Market a New Drug, Biologic or an Antibiotic Drug for Human Use" 5/10/1999

FDA Guidance Documents used for Apheresis Reviews

http://www.fda.gov/cber/memo.htm

- Recommendations and Licensure Requirements for Leukocyte-Reduced Blood Products, 5/29/1996
- Revision of FDA Memorandum of 8/27/82: Requirements for Infrequent Plasmapheresis Donors, 3/10/1995
- Donor Deferral Due to Red Blood Cell Loss during Collection of Source Plasma by Automated Plasmapheresis, 12/4/1995
- Volume Limits for Automated Collection of Source Plasma, 11/4/1992

FDA Guidance Documents used for Apheresis Reviews

- Guidance for Industry: General Principles of Software Validation; Final Guidance for Industry and FDA Staff, 1/11/2002

  http://www.fda.gov/cber/blood/bldguid.htm

- FDA Guideline on General Principles of Process Validation, May 1987, reprinted Feb. 1993

  http://www.fda.gov/cder/guidance/pv.htm

Operator's Manuals and Package Inserts for Apheresis Reviews

- Operator's Manuals and Package Inserts
  - Apheresis instruments
  - Sterile connecting devices
  - Platelet and WBC counters
  - Collection bags
  - Leukocyte reduction filters
- How we use operator's manuals and package inserts
  - Donor selection
  - Collection procedures
  - Processing procedures
  - Product specifications

FDA Apheresis Review Checklists

http://www.fda.gov/cber/blood/checklist.htm

Last updated: October 13, 2006

- **Apheresis RBC Review**
- **Leukocyte Reduction Review**
- **Platelet Pheresis Review**
- **Infrequent Plasma Donors**
- **SOPs and Labeling**
- **QC sheets**
- **Each device manufacturer's directions/specifications (ALYX, MCS Plus LN 8150, MCS Plus LN 9000, Trima Version 5.1, Amicus)**

General Content of Apheresis Submissions

- FDA form 356h
- Cover letter
- SOPs
- Records and Forms
- Product Quality Control Logs
- Labeling
- Products (for some submissions)
- May reference previously approved SOPs, forms and labeling (include STN)

General Submission Content

- **Cover Letter**
  - **Products requested for licensure, including anticoagulants**
  - **Collection, processing and testing device(s) (model, version no.)**
  - **List of blood centers preparing products (address, registration number)**
  - **Description of operator training**

General Submission Content

- **SOPs**
  - **Donor suitability, including donor deferral, donation interval (eg, RBC loss)**
  - **Collection procedures, including arm prep, donor monitoring**
  - **Donor history forms, including informed consent**
  - **Product manufacturing procedures, including QC, labeling, splitting, leukocyte reduction, storage, shipping, equipment calibration, etc.**
  - **Adverse event and failure investigation**
  - **Quarantine and disposition of unsuitable products**

General Submission Content

- Records and Forms
  - Donor selection, including questionnaire, informed consent, education materials
  - Product processing, collection information
  - Product quality control logs
- Completed records and forms
  - 2 consecutive months quality control
    - Red Blood Cells
    - Platelets, Pheresis
    - Each type of device at each center
  - Validation summary, including failure investigation

General Submission Content

- **Product Quality Control Logs**
  - **Product description (eg, product name, leukocyte reduced)**
  - **Type of collection (eg, single, double)**
  - **Collection and testing dates**
  - **Product specifications**
  - **Product testing results, including WBC counts, platelet yields, absolute RBC volume, pH, RBC recovery, product volume, etc.**

General Submission Content

- **Product Quality Control Logs (cont.)**
  - **Collection device (manufacturer, model number)**
  - **Product identification number**
  - **Collection center**
  - **Technologist identified**
  - **Evidence of QA oversight**

General Submission Content

- **Labeling**
  - **FDA form 2567**
  - **Circular of Information**
  - **Base label and product overlay labels for each product**
  - **606.121((c)(13) – machine readable information**
    - **Unique facility identifier**
    - **Lot number relating unit to donor**
    - **Product code**
    - **ABO/Rh of donor**
  - **ISBT 128 or Codabar**
    - **ISBT – request 640.120 alternative procedure to 606.121(e)(1)(ii)**
  - **“Apheresis” in product name or attributes**

Review Criteria for Apheresis Red Blood Cells

- **Donation interval**
  - **After 1 RBC (with/without platelets, plasma) – 8 weeks**
  - **After 2 RBCs – 16 weeks**
- **RBC loss during incomplete procedure**
  - **< 200 mL – no deferral**
    - **Second loss < 100 mL within 8 weeks – 8 weeks**
    - **Second loss ≥ 100 mL within 8 weeks – 16 weeks**
  - **Between 200 mL and 300 mL – 8 weeks**
  - **> 300 mL – 16 weeks**

Review Criteria for Apheresis Red Blood Cells

- **Validation**
  - **100 consecutive units from all devices**
  - **Include single and double RBC collections**
  - **95% meet product standards or repeat validation**
- **Monthly QC (Submit 2 months)**
  - **50 units at each site**
  - **Include single and double RBC collections**
  - **Include all devices**
  - **95% meet product standards or repeat QC**

Review Criteria for Platelets, Pheresis

- **Donation interval**
  - **48 hours, no more than 2 in 7 days, maximum 24 per year**
  - **After 450 mL WB loss during plateletpheresis procedure – 8 weeks, unless extracorporeal RBC loss is < 100 mL**
- **RBC loss**
  - **Maximum per year not exceed RBC loss allowed for Whole Blood collections**
- **Donor criteria**
  - **Pre-donation platelet count – 150,000 platelets/uL**
  - **May also use post count from previous donation**
  - **Or as directed by the device operator's manual**

Review Criteria for Platelets, Pheresis

- **Validation, include sterility testing**
- **Monthly quality control (Submit 2 months)**
  - **4 units per machine type, per product type at each site**
  - **Platelet count – ≥ 3.0 x 10e11, 75% must meet standard**
  - **pH - ≥ 6.0, 100% must meet standard**
  - **Product volume**
  - **Done at expiration or time of issue**
  - **Test 1 bag of multiple bag collection**

Review Criteria for 7-d Platelets, Pheresis

- Gambro 7-day ELP Platelet Storage System using COBE Spectra and Gambro Trima
- Baxter 7-day PL 2410 Collection Container using Baxter Amicus
- Both tested with BacT/Alert Microbial Detection System (aerobic and anaerobic)
- Platelets, Pheresis, Leukocytes Reduced only
- Approval required before distribution of product

Review Criteria for 7-d Platelets, Pheresis

- Licensed firms request exemption to 610.53(c) under 610.53(d)
- Unlicensed firms request alternative procedure to 610.53(c) under 640.120
- Participate in post-marketing surveillance study
- Submit SOPs, forms
- Submit data to FDA 1 year after approval
- Licensed firms only – submit labels, products to CBER

Review Criteria for Leukocyte Reduced Products

- **Product standards**
  - **≥ 85% product recovery**
  - **Platelets, Pheresis - < 5.0 x 10e6 WBC per container**
    - **Do not need to count "baby" bags if collection container is < 5.0 x 10e6 WBC**
    - **Investigate if collection container > 5.0 x 10e6 WBC; optional - count "baby bags"**
  - **RBCs – < 5.0 x 10e6 WBC per container**
- **Monthly quality control (Submit 2 months)**
  - **1% of collection (4 units if less than 400 per month)**
  - **Test each product type each month**
  - **95% meet product standards**
  - **Other as specified by device manufacturer**

Review Criteria for Apheresis Fresh Frozen Plasma

- **Collection volume**
  - **FDA nomogram**
  - **Per year - ≤ 175 lbs – 12.0 L, > 175 lbs – 14.4 L**
  - **Not exceed bag or operator's manual specifications**
- **Infrequent plasma collections**
  - **Requested as alternative procedure to 640.3(a) under 640.120**
  - **Donate plasma every 28 days or less frequent**
  - **Donor weight - ≥ 110 lbs**
- **Frequent plasma collection must follow donor criteria in 640.63 and 640.65**

FDA Inspections for the Review

- **Centers applying for an original BLA**
- **Licensed applicant with an approved apheresis program, but collecting apheresis products at new/additional centers**
- **As requested by CBER to facilitate the review**

- **Confirm that center is in compliance with laws (FD&C Act and PHS Act), regulations and commitments in submissions**

Comparability Protocol (CP)

- **What is a CP?**
  - **Described in 601.12(e)**
  - **Submission option**
  - **Highly specific, well-defined plan for implementing a change in manufacturing**
  - **Specific for the change and for the applicant**
  - **Not appropriate for all changes**
  - **Approval of CP may allow a reduced reporting category for future implementation of the specific change in the CP**

Comparability Protocol (CP)

- **When is CP used?**
  - **Product manufactured using the change will meet approved product standards**
  - **Manufacturing process has been validated and all equipment has been qualified**
  - **Appropriate validated assays are available to detect effect of the change on the product**
  - **Implementation of single change in multiple locations operating under the same license using SOPs, forms, labels, etc. approved in CP**

Comparability Protocol (CP)

- **When should CP not be used?**
  - **Broad plan covering any conceivable change**
  - **Change has potential to adversely effect product**
  - **Pre-specified acceptance criteria are not available to determine effect on product**
  - **Change results in newly defined product that is not licensed**
  - **Use of new manufacturing facility needing pre-license inspection**
  - **Change in process, equipment or facility that may need pre-approval inspection**

Comparability Protocol (CP)

- **CP Submissions**
  - **Submit as PAS under 601.12(b)**
  - **Once approved, CP must be implemented exactly as described in CP**
  - **Subsequent supplements reporting implementation of change described in CP may be reported in lower category specified in approval letter (eg, PAS to CBE30)**
  - **Supplements reporting implementation of CP should include information committed to in approved CP**
  - **Submit a new CP or a change to an existing approved CP as a PAS**

Comparability Protocol (CP)

- **Contents of CP Submission**
  - **Description of the change**
  - **Implementation plan, including description of training**
  - **Specific tests and validation protocols**
  - **Product acceptance criteria**
  - **Supportive data obtained from testing and validation**
  - **QC testing procedures, including sampling plan**
  - **Description of actions if acceptable results not achieved**
  - **QA program oversight**

Shipping Products to CBER

- **What products are shipped**
  - **Platelets, Pheresis**
- **When to ship products**
  - **Centers applying for original BLA**
  - **Centers with an approved BLA but supplementing to include apheresis platelets**
  - **As requested by CBER to facilitate the review**
  - **After validation has been completed**
  - **After 2 months of QC has been completed**
  - **After all labeling and testing has been completed**

Shipping Products to CBER

- **Scheduling the shipment**
  - **Call CBER (Division of Hematology, Laboratory of Cellular Hematology (LCH)) at 301- 827- 3413**
  - **LCH operating hours: Monday through Friday between 8:30am and 4:00pm, excluding Federal holidays**
  - **Follow your existing SOPs for collecting, processing and testing, packing and shipping products intended for transfusion**
  - **Products should arrive during LCH operating hours**
  - **Products should arrive at LCH before they expire**

Shipping Products to CBER

- **Shipping address**

  Center for Biologics Evaluation and Research (CBER)

  Food and Drug Administration

  8800 Rockville Pike

  Building 29, Room 323

  Bethesda, MD 20892

- **If desired, enclose a pre-paid, self-addressed shipping label to facilitate return of shipping boxes and coolants**

Summary

- CBER reviews based on:
  - Regulations and Guidance Documents
  - Operator's Manuals and Package Inserts
- Submission should contain information for substantive review
  - Consult CBER review checklists
  - Consult operator's manuals and package inserts
- Some reviews may require:
  - Platelets sent to CBER for testing
  - Facility inspections

Summary

- **Comparability Protocol is a submission option**
  - **May allow implementation of CP in a reduced reporting category**
  - **CP must be implemented as approved**
  - **Report any changes in approved CP**
  - **CP not appropriate for all types of submissions**
- **Approvals are specific for:**
  - **Apheresis instrument**
  - **Product collected**
  - **Collection facility**

Contact Information

- **Mailing Address**

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  HFM-370

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