The Regulation of Biological Products

Food and Drug Administration

Judy Ciaraldi
Linda Mattingly
Armando Zamora
Sharon O'Callaghan
Laura St. Martin, MD

Introduction to FDA

Judy Ellen Ciaraldi

BS, MT(ASCP)SBB, CQA(ASQ)

Division of Blood Applications, OBRR, CBER

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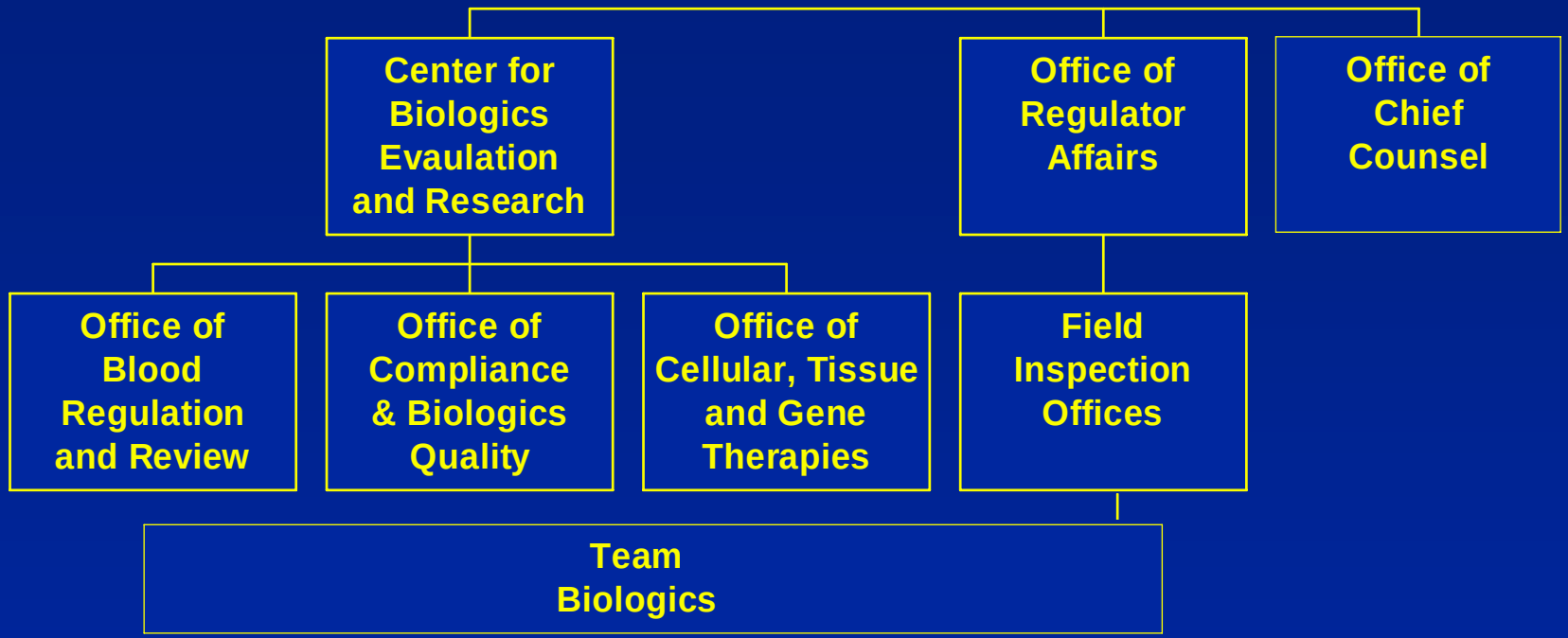
- Office of Regulatory Affairs

FDA Blood & Tissue Oversight



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The Mission of the *Center for Biologics Evaluation and Research* is to *protect* and *enhance* the *public health* through the regulation of biological products including blood, vaccines, therapeutics, and related drugs and devices, according to statutory authorities. The regulation of these products is founded on science and law to ensure their purity, potency, safety, efficacy and availability.

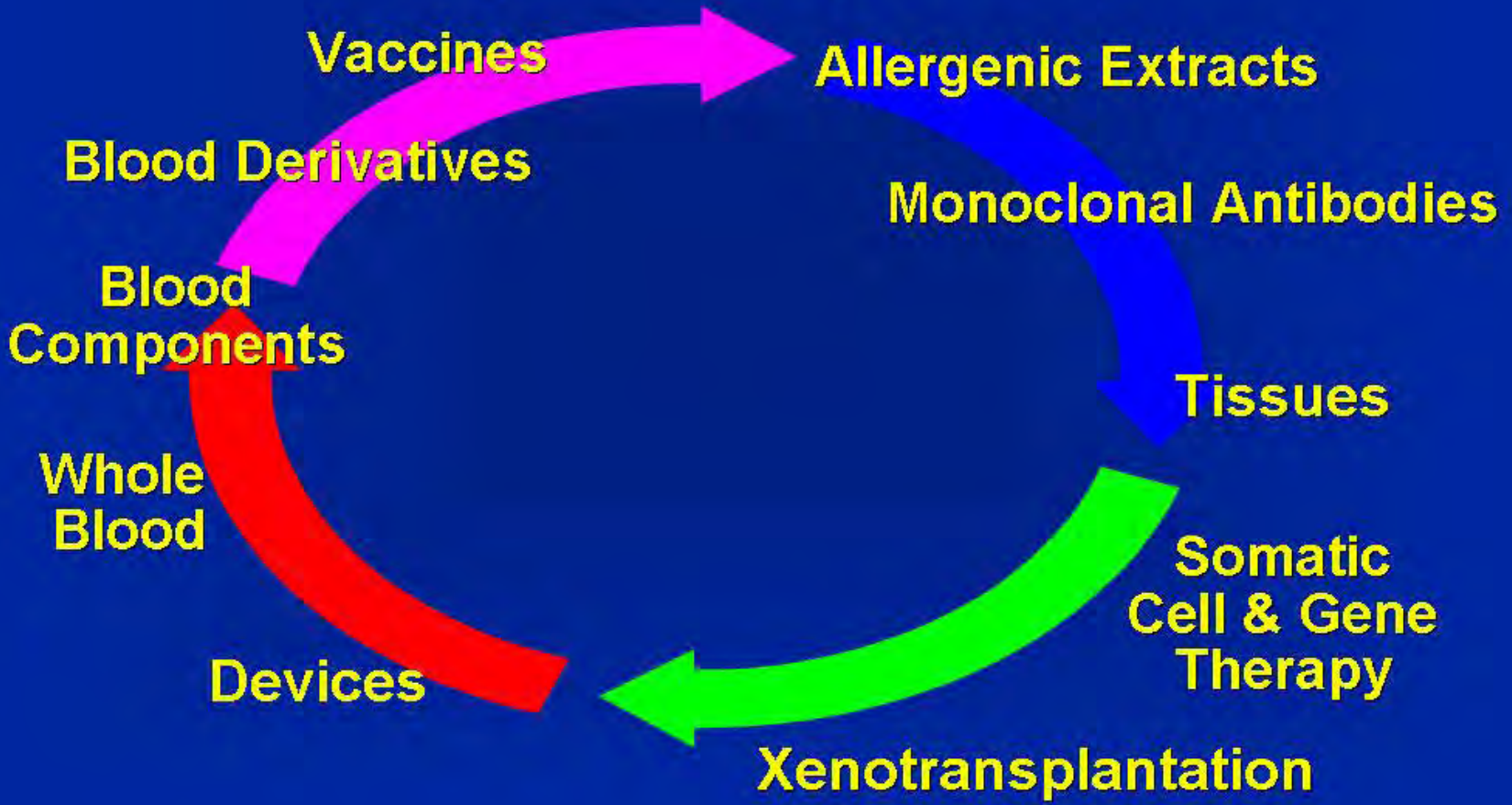
What is a Biological Product?

21 CFR 600.3(h), (h)(5) & (h)(5)(ii)

"Biological product means any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man:"

"A product is analogous…" "To a therapeutic serum, if composed of whole blood or plasma or containing some organic constituent or product other than a hormone or an amino acid, derived from whole blood, plasma, or serum."

Biological Products Regulated by CBER



What does OBRR review?

- Facilities that manufacture blood products and devices for injection, transfusion or for further manufacture that wish to engage in interstate commerce of that product
- Products for injection (vaccines), transfusion or for further manufacture that enter into interstate commerce
- Devices used in the collection, manufacture or testing blood products or donors (ex. BECS, blood bags, apheresis equipment, blood warmer, test kits, anticoagulants, etc.)

Regulated Blood Components

- **Blood components for transfusion**
  - **Whole Blood, Red Blood Cells**
  - **Platelets, Platelets Pheresis**
  - **Fresh Frozen Plasma, Plasma Cryoprecipitate Reduced**
  - **Cryoprecipitated AHF**
  - **Irradiated, leukocyte reduced, divided, washed, frozen, deglycerolized, rejuvenated**
- **Blood components for further manufacturing**
  - **Source Plasma**
  - **Source Leukocytes**
  - **Recovered plasma**

History of Regulation

Regulatory Tools

- **Statutes - laws, acts**
- **Regulations**
  - **Federal Register**
  - **Code of Federal Regulations (CFR)**
- **Recommendations**
  - **Memorandums**
  - **Guidance documents**
  - **Information sheets**

How Blood Regulation Began

- **1902 Biologics Control Act**
  - **Statutory authority to regulate biological products**
  - **Annual license, labeling, inspections, penalties**
- **1906 Food and Drug Act**
  - **Prohibited interstate commerce of misbranded & adulterated drugs and foods**

Laws and Regulations Governing Biological Products

- Food, Drug, and Cosmetic Act (FD&C Act)
- Public Health Service Act (PHS Act)
  - Sections 351 and 361
- Title 21 Code of Federal Regulations (CFR)
  - Drugs – Parts 210 and 211
  - Blood, Blood Components, and Blood Derivatives – Parts 606-660
  - Devices – Part 820
  - Human Tissues Intended for Transplantation – Parts 1270 and 1271

FDA Regulations

- Agency rules announced in the Federal Register and codified in the Code of Federal Regulations (CFR)
- Described in 21 CFR 10.90(a)
  - Interpretation of the laws
  - 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 CFR

Title 21 CFR Subchapter F

(Biological Product Regulations)

- **600 - General**
- **601 - Licensing**
- **606 - Current Good Manufacturing Practices**
- **607 - Registration**
- **610 - General biological product standards**
- **630 - General requirements for blood**
- **640 - Additional standards for blood and blood products (Whole Blood, RBCs, Platelets, Plasma, Cryoprecipitate, Source Plasma)**

Additional Resources for Blood Regulation

- **Guidance documents**
  - **FDA's recommendations (current thinking) on how to comply with statutes and regulations**
  - **Describe new policies and procedures**
  - **Developed under Good Guidance Practices (21 CFR 10.115)**
  - **Level 1 or Level 2 document**
  - **Not binding on FDA or regulated industry**
  - **Found on CBER website - http://www.fda.gov/cber/blood/bldguid.htm**
- **CBER SOPPs and specific SOPs**

Registration

Outline - Registration

- Why must I register with FDA?
- How do I register with FDA?
- What does being registered mean?
- What will I be required to do?
- What are the FDA activities with registered facilities?
- Are there any exemptions to being registered?
- What are unregistered facilities required to do?

Federal Food, Drug and Cosmetic Act (1938)

- Supercedes the 1906 Food and Drug Act
- Adds control of cosmetics and therapeutic devices
- Manufacturers must prove drug is safe before marketing
- Penalties for violations now include court injunction
- Requires facility registration
- Authorizes manufacturing facility inspections (1953 amendment)

Registration

- Required under the FD&C Act
- Described in 21 CFR 607.7
- All owners or operators of establishments that engage in the manufacture of blood products must register with FDA
- Does *not* permit shipping of blood product in interstate commerce
  - May engage in intrastate shipment

Product Manufacture

- Defined in 21 CFR 607.3(d)
- Collection, preparation, processing, compatibility testing and other procedures of any blood product that meets the definition of a drug
- Includes testing, control procedures, labeling and repackaging of the blood products
- Manufacturing steps can be performed by entity that owns product or by a contractor

Manufacturer

- Defined in 21 CFR 600.3(t)
- Legal person or entity engaged in the manufacture of products subject to licensure under PHS Act
- Manufacturer (licensed or unlicensed) assumes responsibility for compliance with applicable product and establishment standards, even if manufacturing is performed by contractor

Who Must Register?

- **Major Facilities**
  - Collection facility
  - Community blood bank
  - Component preparation facility
  - Hospital blood bank
  - Plasmapheresis center
  - Product testing laboratory
- **Auxiliary Facilities**
  - Distribution center
  - Donor center (Manual collection of Whole Blood)
- **Brokers**
  - who take possession and manipulate and/or relabel product

How do I register?

- **Submit registration form to CBER within 5 days after beginning manufacturing operations (21 CFR 607.21 & 607.22)**
- **FDA Form 2830: Blood Establishment Registration and Product Listing**
- **Complete a form for each facility and list all products in commercial distribution.**
  - **Include both licensed and unlicensed products**
- **Electronic registration (eBER)**
  - **http://www.fda.gov/cber/blood/bldreg.htm**
  - **Electronic registration will be required**

What's New

Allergenics
Blood
Cellular & Gene Therapy
Devices
Tissues
Vaccines
Xenotransplantation

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Blood Establishment Registration and Product Listing

BER

All owners or operators of establishments that manufacture blood products are required to register with the FDA, pursuant to section 510 of the Federal Food, Drug, and Cosmetic Act, unless they are exempt under 21 CFR 607.65. A list of every blood product manufactured, prepared, or processed for commercial distribution must also be submitted. Products must be registered and listed within 5 days of beginning operation, and annually between November 15 and December 31. Blood product listings must be updated every June and December.

The Electronic Blood Establishment Registration (eBER) Public Query Application is where you may search for information on registered blood establishments.

Blood establishments located outside of the United States that import or offer for import blood products into the U.S. are required to register with FDA. The name of the United States agent, the name of each importer, and each person who imports or offers for import these blood products must also be provided.

Form FDA-2830, Blood Establishment Registration and Product Listing, is used for submission of registration and product listing information to the FDA. The form (and accompanying instructions) may be downloaded to complete and submit by mail. Alternatively, the information may be submitted electronically. Instructions for completing the electronic form are available below.

- Electronic Submission of Blood Establishment Registration and Product Listing

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- USA.gov

Registered-Only Blood Establishments

- 10-15% of transfused blood is prepared in unlicensed, registered-only blood banks
- CBER does not review product manufacturing submissions from registered-only facilities unless:
  - Request a “variance” (21 CFR 640.120)
  - Apply for a licensure (21 CFR 601.2)
  - Contract manufacturer of licensed products (61 FR 24227, 5/14/96)
- Manufacturing activities observed during FDA inspections conducted by field investigators

Responsibilities of Registration

- Each year manufacturer must update the registration by June 30 or December 31 (21 CFR 607.30)
- Send updates to FDA or enter into eBER
- Manufacturer is responsible for complying with FDA regulations and cGMPs (including labeling, BPD, and fatality reporting)
- Facility will be FDA inspected every 2 years

Exempt from Registration

- Described in 21 CFR 607.65
- Facilities that do not manufacture products
- Transfusion services that:
  - Only perform compatibility testing and transfusion
  - Do not routinely collect or process products
  - Only prepare recovered plasma for further manufacture or RBCs for transfusion from Whole Blood
  - Pool platelets & cryoprecipitate or do bedside filtration
  - Are approved for Medicare reimbursement
- Brokers who do not take possession or do not manipulate or relabel product

Exempt from Registration

- **Exemption written to omit duplication of inspections by Federal government health agencies (FDA & CMS)**
- **Responsibilities of unregistered facility**
  - **Must comply with FDA regulations and cGMPs (including labeling, BPD and fatality reporting)**
- **Inspections**
  - **Done under the authority of CMS (or other deemed status organization)**
  - **FDA can inspect “for cause” (e.g., fatality investigation)**

Licensure

Outline - Licensure

- Why must I be FDA licensed?
- How do I obtain an US License from FDA?
- What does licensure mean?
- What will I be required to do once I am licensed?
- What are the FDA activities with licensed facilities?

Public Health Service Act (1944)

- Expanded from 1902 Biologics Control Act
- Regulation of biological products and control of communicable diseases
- Defines biological product to include blood, blood components and derivatives
  - Regulates blood and blood components like drugs
- Section 351 – stipulates requirements for licensure
- Section 361 – requires control of communicable diseases

Section 351- PHS Act

- **No person shall introduce or deliver for introduction into interstate commerce any biological product unless:**
  - **A biologics license is in effect**
  - **Each package of biological product is plainly marked**
  - **Biological product is safe, pure, potent and effective**
  - **Facility where product is manufactured meets standards**
  - **Applicant consents to inspection**
- **Secretary establishes requirements for approval, suspension and revocation of biologics license**

Significance of Licensure

- Manufacturers who manufacture biological products for distribution into interstate commerce must be registered and licensed
- Signifies FDA approval of product and facility
- License number appears on label of products approved in application
- Allows shipment of product in interstate commerce
- 85 – 90% of blood products transfused in US are prepared in licensed blood establishments

Definitions

- BLA – Biologic License Application
- Application - Original submission requesting a U.S. license
- Supplement - Submission to request change to an existing approved license application
- Amendment - Information submitted to an unapproved application or supplement to revise or modify the submission
- Submission – Application, supplement, amendment, labeling, product correspondence

How do I get licensed?

- **Submit BLA form - Form FDA 356h: Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use**
  - **Must accompany every submission and correspondence sent to FDA**
- **Complete the chemistry, manufacturing and controls (CMC) section**
  - **Contains information pertinent to the review and approval of submission**

Contents of the Submission

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" (May 1999)

http://www.fda.gov/cber/gdlnes/cmcblood.htm

General Submission Content

- **Cover Letter**
  - Products requested for licensure, including anticoagulants, additional processing (leukocyte reduction, irradiation, etc.)
  - Collection, processing and testing instruments (model, version no.)
  - Infectious disease testing (list agents, test kits used)
  - Blood centers preparing products (address, registration number)
  - Description of personnel training
  - Contractors used (name, address, registration number, license number (if appropriate), services provided)

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, irradiation, storage, shipping, equipment calibration, etc.**
  - **Adverse event and failure investigation**
  - **Quarantine and disposition of unsuitable products**
  - **Quality assurance program**

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
    - Apheresis Red Blood Cells (including leukocyte reduction)
    - Leukocyte reduced Red Blood Cells
    - Platelets and Platelets, Pheresis (including leukocyte reduction)
    - Each type of device at each center
  - Validation summary, including failure investigation

General Submission Content

- **Labeling**
  - **FDA form 2567**
  - **Circular of Information (606.122)**
  - **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)**

Which Products Must Comply with Bar Code Requirements?

- **Any blood component that can be transfused to a patient and blood components used to make the final transfusible blood component. Also includes:**
  - **Aliquots**
  - **Split or divided units**
  - **Syringes**
  - **Pooled units**
- **Intraoperatively collected autologous blood that is stored in and dispensed from the blood bank**
- **Fibrin/platelet sealant manufactured for allogeneic use**

Which Products are Exempt?

- Products for further manufacturing use – recovered plasma, Source Plasma, Source Leukocytes
- Devices – e.g., filters, apheresis instruments, blood collection sets
- Intraoperative autologous blood collected and transfused in OR or RR; includes salvaged autologous blood that stays with patient
- Autologous fibrin/platelet sealant manufactured and used intra-operatively
- Drainage collected in OR or ER as part of trauma care

Bar Code Information Requirements

- Must be on container label
- Must be unique to the blood component
- Must be surrounded by sufficient blank space so information can be scanned correctly
- Must remain intact under normal conditions of use

Information and Guidance

- **Final Rule: Bar Code Label Requirements for Human Drug Products and Biological Products (2/26/04)**

  http://www.fda.gov/cber/rules/barcodelabel.htm
- **Frequently Asked Questions: Bar Code Label Requirements for Blood and Blood Components (9/29/06)**

  http://www.fda.gov/cber/faq/barcodefaq.htm
- **Guidance for Industry: Bar Code Label Requirements: Questions and Answers (10/06)**

  http://www.fda.gov/cber/gdlns/barcode.htm

Information and Guidance

- **Guideline for the Uniform Labeling of Blood and Blood Components (8/85)**

  http://www.fda.gov/cber/guidelines.htm#95
- **Guidance for Industry: Recognition and Use of a Standard for the Uniform Labeling of Blood and Blood Components (9/22/06)**

  http://www.fda.gov/cber/gdlns/unilabbld.htm
- **Manufacturers Assistance and Technical Training Branch of Office of Communication, Training and Manufacturers Assistance, CBER**

  Email - matt@cber.fda.gov

Labeling

- False or misleading labeling could result in misbranding of product
- Misbranded products may be unsafe or ineffective
- Misbranding described in FD&C and PHS Acts
- FDA can seize misbranded products and use in criminal cases against manufacturer
- CBER does not regulate commercial label manufacturers

Shipping Products to CBER

- **What products are shipped**
  - **Platelets**
  - **Platelets, Pheresis**
- **When to ship products**
  - **After validation has been completed**
  - **After 2 months of QC has been completed**
  - **After all labeling and testing has been completed**
- **Scheduling shipment**
  - **Call CBER (Division of Hematology, Laboratory of Cellular Hematology (LCH)) at 301- 827- 3413**

BLA Application Review

- Desk Review of Documents
- Review for completeness and accuracy
  - Product manufacturing consistent with regulations and product standards
  - Donor safety issues
- Assign submission tracking number (reference number) and notify applicant
- Applicant can prepare product but cannot distribute product in interstate commerce
- Communicate with applicant if need additional information or revisions (via telecon, letter)
- Conduct a pre-license inspection

Resources for FDA Review

- 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
- Some checklists available at: http://www.fda.gov/cber/blood/checklist.htm

BLA Application Review

Pre-License Facility Inspection

- Continuation of desk review
- FDA notifies applicant of inspection dates
- FDA observes product manufacturing consistent with regulations, commitments in application, product specifications and cGMPs
- FDA-483 (Inspectional Observations) is issued if we observe deficiencies
- Applicant must acceptably respond to all cited observations

FDA Inspection

- **Observe Operations**
  - SOPs - procedures, personnel
  - Product manufacturing, labeling, storage
  - Equipment, computer systems
  - Physical facility – privacy, sufficient space
- **Review Records**
  - QA activities, training
  - Donor records, reactions, deferrals
  - Testing – infectious disease, QC, validation, donor screening
  - Product manufacturing
  - Contractor responsibilities

Which B&P submissions need inspections?

- New License
  - Hospital/Community Blood Bank
  - Source Plasma Center
- Amend Current License
  - Additional Blood or Plasma Centers
  - Blood Product Irradiation
  - RBC Immunization (in Source Plasma centers)
  - Product Testing Laboratory
  - Contract Manufacturer

License Approvals

- U.S. license number issued when all review and inspectional issues are addressed
- FDA approvals are very specific
  - Product (and apheresis instrument) specific
  - Facility specific
- Conditions for approval specified in approval letter
  - FDA no longer issues license certificates
- License number must appear on approved product labels

Responsibilities of Licensure

- Maintain current and correct registration
- Comply with FDA regulations and cGMPs (including BPD and fatality reporting)
- Notify CBER of any changes to the approved license, including contractor changes (21 CFR 601.12)
- Facility will be FDA inspected every 2 years
- License may be suspended or revoked for failing to comply with regulations or applicable standards

Reporting Changes to BLA

21 CFR 601.12

Changes to an approved application:

"…an applicant shall inform … (FDA) about each change … established in the approved license application(s). Before distributing a product made using a change, applicant shall demonstrate … the lack of adverse effect of change … as they may relate to the safety or effectiveness of the product."

Three Reporting Categories

- Prior Approval Supplement [PAS] – 21 CFR 601.12(b)
  - 12 month review timeline
- Changes Being Effected in 30 Days Supplement [CBE30] – 21 CFR 601.12(c)
  - Changes Being Effected Supplement [CBE] – 21 CFR 601.12(c)(5)
  - 6 month review timeline
- Annual Report [AR] – 21 CFR 601.12(d)
- Reporting category depends on how the change will affect the product and FDA's experience with the change

Comparability Protocol [CP]

- Described in 21 CFR 601.12(e)
- Plan for implementing specific change
- Change results in comparable product that:
  - Has defined product characteristics
  - Meets established standards
- Submitted as PAS
- Submission option. If approved, may allow for a more expedient distribution of product

Reporting Changes

Guidance for Industry

“Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture” (July 2001)

http://www.fda.gov/cber/gdlns/bldchanges.htm

Additional Manufacturing Requirements

Outline – Additional Requirements

- Contract manufacturing
  - Short Supply Agreement
- “Variances”
- Device Reviews
- Current Good Manufacturing Practices
  - Quality regulations

Cooperative Manufacturing Agreements

- Shared manufacturing – both parties licensed to perform some manufacturing steps
- Divided manufacturing – both parties licensed to perform all manufacturing steps
- Short supply – unlicensed product (recovered plasma) to be manufactured into licensed product (21 CFR 601.22)
- Contract manufacturing – need not be licensed but performs manufacturing steps

Contract Manufacturing

- **Manufacturer - need not perform all manufacturing steps or own facilities where steps are performed; may contract with others to perform manufacturing steps**
- **Contractor – manufacturer not under direct control of product owner, but who performs part or all of manufacturing steps as a service**
- **Cooperative manufacturing agreement – agreement between 2 or more manufacturers; describes responsibilities of each party**

Contracting Responsibilities

- Product manufacturer is responsible for compliance of all manufacturing steps of their product, even if not performed in own facility
- Licensed manufacturers must notify CBER if using contractor or changing contractor (21 CFR 601.12)
- Contractor must manufacture product according to regulations, cGMPs and product standards
- Contractor must inform product manufacturer of any changes in manufacturing
- Contractors performing manufacturing steps must be registered with FDA

Short Supply Agreement

- Described in 21 CFR 601.22
- Allows for unlicensed product to be shipped in interstate commerce and made into licensed final product
- Product is in short supply due to scarcity of the “animal” (human donor) required to manufacture product
- SS product is manufactured at facility other than licensed manufacturer’s facility making licensed final product
- Licensed final product manufacturer must apply for short supply agreement

Short Supply Agreement

- Collection of SS products considered initial or partial manufacturing of licensed final product
- SS agreement must be in effect before collection of SS products can begin
- SS product manufacturer (those who relabel, repack or pool) does not need to be licensed, but must be registered
- SS product manufacturer has established procedures to ensure compliance with regulations
- SS product shipped only to licensed final product manufacturer (may be shipped through a broker)

“Variances”

- Alternative procedure or exemption (21 CFR 640.120)
- Submitted by both licensed and unlicensed manufacturers
- Request for procedure that is not consistent with regulation in the 600s
- Approved on case-by-case basis
- Must have approval before implement procedure or distribute products
- Examples on CBER website

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

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Allergenics
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Cellular & Gene Therapy
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Tissues
Vaccines
Xenotransplantation

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Industry
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Product Information
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Exceptions and Alternative Procedures Approved Under 21 CFR 640.120

Title 21 Code of Federal Regulations 640.120(a) - The Director, Center for Biologics Evaluation and Research, may approve an exception or alternative procedures to any requirement in subchapter F (Biologics) of Chapter I (Parts 600 - 680) of title 21 of the Code of Federal Regulations regarding blood, blood components or blood products.

Both licensed and unlicensed blood establishments must submit requests for an exception or alternative procedure to the requirements in Parts 600-680. Licensed establishments should submit the request in accordance with 21 CFR 601.12 and may reference our guidance document entitled: Guidance for Industry: Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture (July 2001).

Requests for such exceptions or alternative procedures should ordinarily be made in writing, however, in limited circumstances, such requests may be made orally and permission may be given orally by the Director. Oral requests and approvals must be promptly followed by written requests and written approvals.

It should be noted that requests for exceptions or alternate procedures includes specific circumstances and may require submission of supporting data unique to the circumstance. Publication of these approvals for a specific exception or alternative procedure does not necessarily mean that they can be generally applied to other manufacturers.

FEDERAL REGISTER: Cumulative List of Exceptions and Alternative Procedures Approved by the Director of the Center for Biologics Evaluation and Research - 9/28/2004 - *(PDF - 61 KB)*

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Device Reviews

- **What is a biological device?**
  - One in which the active ingredient is a biological product
  - One that is associated with blood collection and processing
- **How are biological devices regulated?**
  - Licensed devices – Section 351 of PHS Act
  - Cleared devices – Section 510(k) of FD&C Act
- **Licensed vs. Cleared Devices**
  - Licensed devices – active ingredient is biological product and it gives a result
  - Cleared devices – involved in blood collection/processing

Licensed vs. Cleared Devices

- **Licensed devices are reviewed and approved in the same manner as other licensed products**
  - **Reagents used for donor testing**
  - **Infectious disease test kits used for donor and tissue testing**
- **Cleared devices are substantially equivalent to an existing (predicate) device**
  - **Apheresis collection instruments**
  - **Irradiators, filters, mixers, blood warmers, ba-con tests**
  - **Blood establishment computer systems**

Device Reviews

- Devices must be approved or cleared in order to be in interstate commerce
- Review timelines for device reviews
  - Licensed devices – 6 to 12 months
  - Cleared devices – 90 days
- Device manufacturers must register with FDA and list their products (21 CFR 807)
- Medical Device Reporting (21 CFR 803)
  - Incidents in which device caused or contributed to death or serious injury must be reported to FDA

Device Review Information

- CBER devices – www.fda.gov/cber/devices.htm
- Cleared 510(k) devices – www.fda.gov/cber/efoi/510k.htm
- Cleared blood establishment software – www.fda.gov/cber/products/510ksoft.htm
- Cleared/Approved donor screening tests for infectious agents – www.fda.gov/cber/products/testkits.htm
- Cleared/Approved donor screening tests for testing HCT/P donors – www.fda.gov/cber/tissue/prod.htm
- Device Guidances and Rules – www.fda.gov/cber/dap/devpubs.htm

cGMP Regulations

- Manufacturers must control manufacturing process to ensure product quality (61 FR 20105)
- cGMP regulations provide direction for control and include concepts of:
  - Quality assurance
  - Quality control
  - Process validation
- Flexible to allow manufacturer to select most suitable methods

cGMP Regulations

- 21 CFR 210 and 211s - Finished Pharmaceuticals
  - First published in FR in 1963 (26 FR 6385)
- 21 CFR 606s – Blood and Blood Components
  - Final Rule published in 1975 (40 FR 53532)
- 21 CFR 820s - Medical Devices
- 21 CFR 1271s – Tissues (includes cGTP)
- Blood establishments must follow 210, 211s and 606s

Why follow Drug cGMPs?

- 43 FR 18614 (May 28, 1974)
- Blood and blood components are used in diagnosis, prevention, treatment and cure of diseases in man
- Therefore blood meets definition of drug in section 201(g) of Federal Food, Drug and Cosmetic Act
- Blood products must meet all statutory requirements of FD&C Act

Quality Control Unit

- **21 CFR 211.22 - describes responsibilities and authority of QC unit**
  - **Approve/reject supplies, product, etc.**
  - **Review records**
  - **Investigate errors**
  - **Review and approve SOPs, validation protocols**
  - **Review changes in product, process, equipment, personnel, determine need for revalidation**
  - **Activities described in writing**

QC Unit
Additional Considerations

- Can be individual person or organizational element
- Does not need to perform all tasks, must ensure controls are implemented
- Review records for trending/corrective action; evaluate effectiveness of corrective action
- Accept/reject product produced by contractor
- Report results to organizational unit responsible for implementing change (e.g., management)

Who Must Follow FDA cGMPs?

- **Manufacturers who manufacture biological products for distribution into interstate commerce**
  - **Must be registered and licensed**
- **Manufacturers who engage in intrastate commerce only**
  - **Must be registered**
- **Transfusion service facilities**
  - **Unregistered, unlicensed**

FDA Quality Guidance Documents

- **Guideline for Quality Assurance in Blood Establishments (July 11, 1995)**
  http://www.fda.gov/cber/guidelines.htm
- **Guideline of General Principles of Process Validation (May 1987)**
  http://www.fda.gov/cder/guidance.htm
- **Guide to Inspections of Quality Systems (QSIT) (August 1999)**
  http://www.fda.gov/ora/inspect_ref/igs/qsit/default.htm