

# Blood Regulation and Safety

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CBER | US FDA

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# Learning Objectives

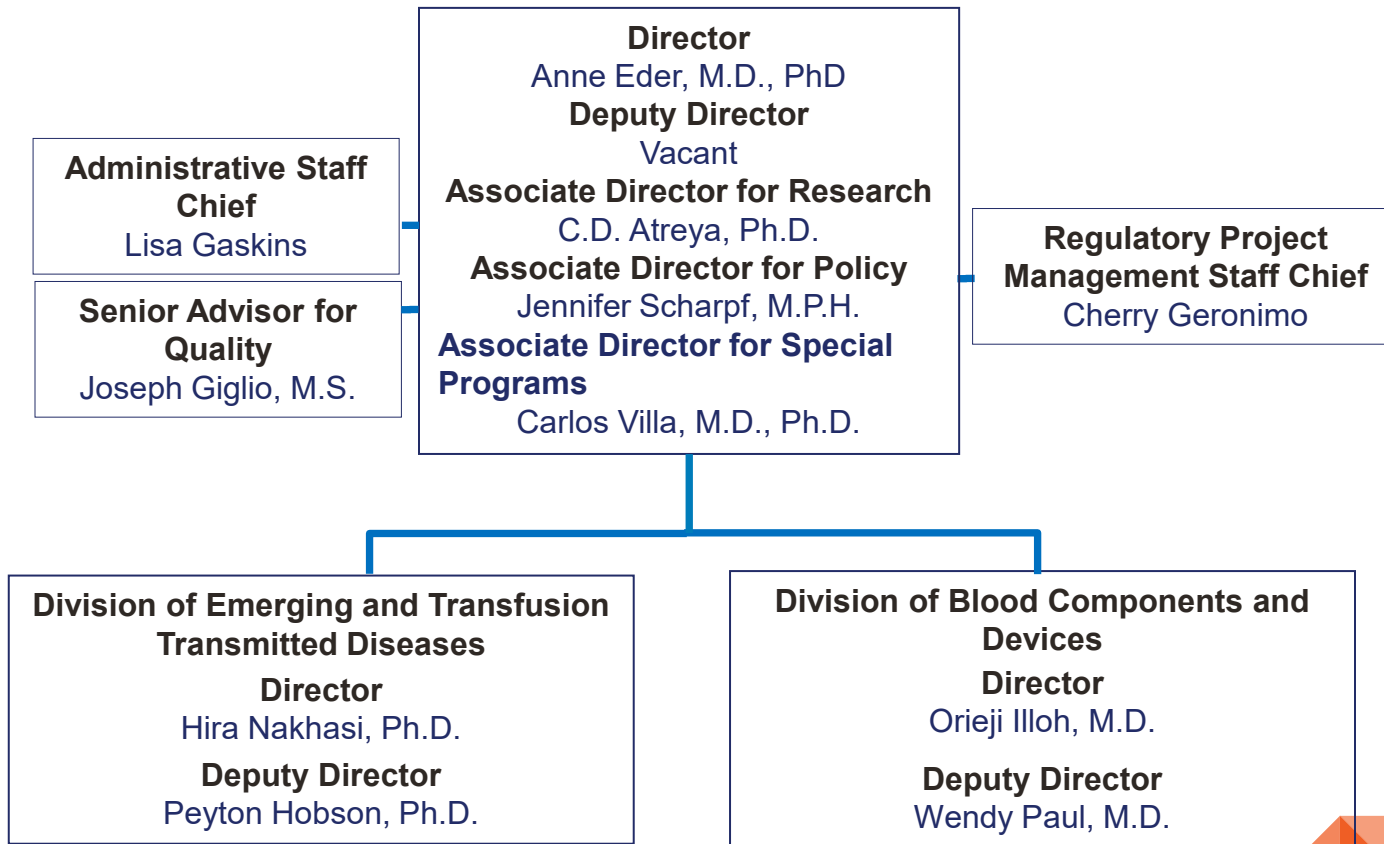


- Describe the functions of OBRR and products reviewed
- Understand OBRR's approach to the regulation of blood and blood components and donor safety
- Describe the process for blood licensure



# OBRR Functions and Products

# Office of Blood Research and Review



# OBRR Functions



## Regulatory Review

- Blood and blood components
- Biological products e.g., Albumin, Hemoglobin based oxygen carriers
- Devices and drugs related to blood manufacturing

## Mission-related research



# OBRR Functions (cont'd)



## Policy

- Regulations, Guidance documents
- Safety communications

## Inspections & Compliance

- Serious adverse reaction and fatality reports and investigations
- Inspections of blood establishments

# OBRR Products (examples)



- Blood and blood components for transfusion or further manufacture
- Devices used in manufacture of blood components
- Blood collection containers and additive solutions
- Pathogen reduction devices
- Blood donor screening and supplemental tests for RTTIs (e.g., HIV, HBV, HCV)
- Immunohematology reagents and compatibility tests

# Blood Products Regulated by OBRR



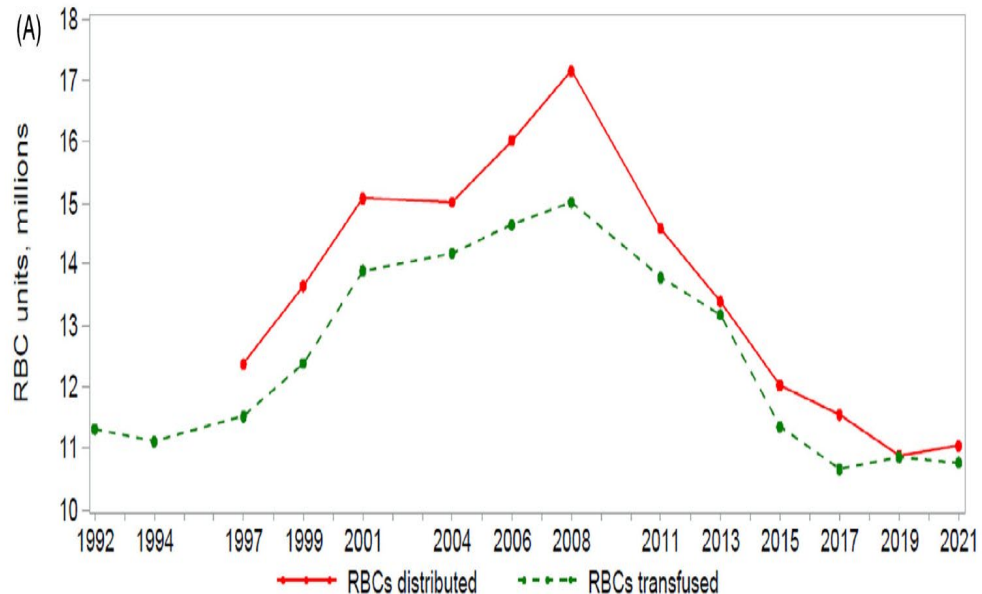
- Blood and blood components for transfusion
- Source Plasma (SP) for further manufacturing
  - normal SP, disease associated or disease state SP, SP from immunized donors





# U.S. Blood Collection and Transfusion (2019)

- ~14 million blood donations for transfusion
- ~15 million blood components distributed and transfused



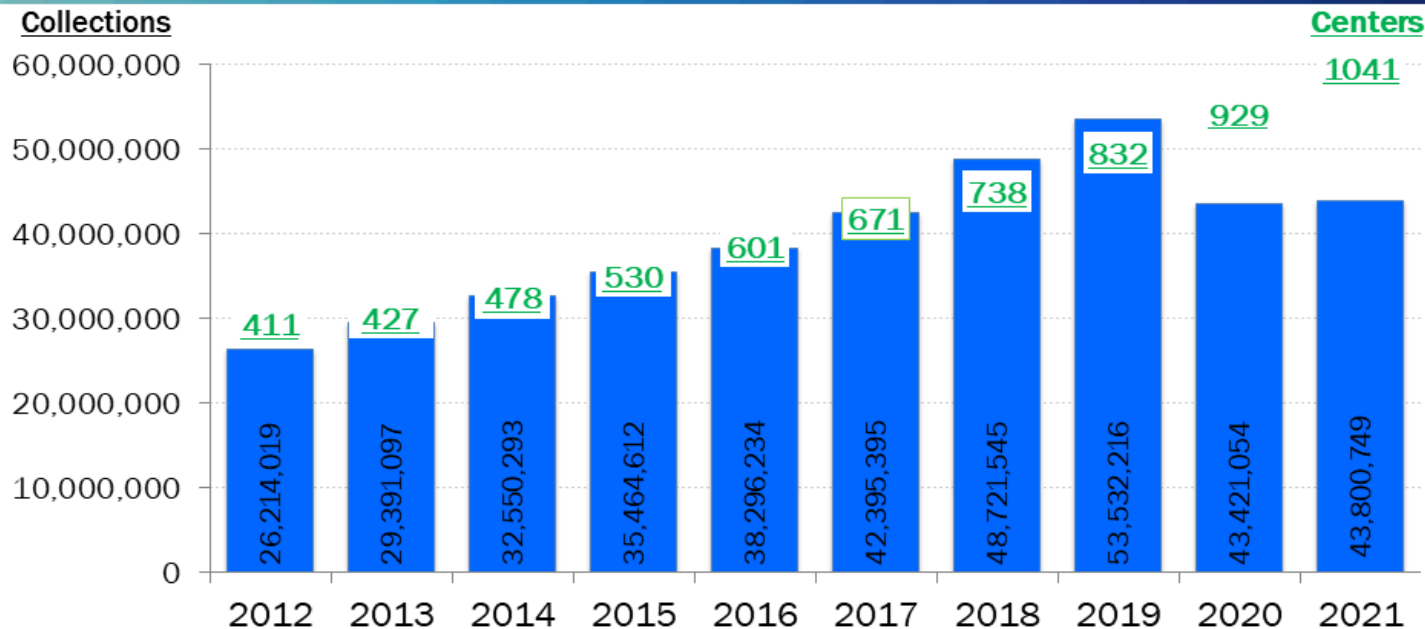
Free RJ, et al. Continued stabilization of blood collections and transfusions in the United States: Findings from the 2021 National Blood Collection and Utilization

[fda.gov/cdersbia](https://www.fda.gov/cdersbia) Survey. Transfusion. 2023; 63(S4): S8–S18. <https://doi.org/10.1111/trf.17360>

# Source Plasma Collections



## NA Collections & # Centers (providing data)



Source: <https://www.pptaglobal.org/resources/plasma-collection-and-manufacturing>

# Challenge Question #1



**OBRR regulates all the following products except:**

- A. Devices for HIV testing
- B. Blood components and Source Plasma
- C. Intravenous Immunoglobulin Preparations
- D. Immunohematology testing devices



# FDA's Approach to the Regulation of Blood and Blood Components for Transfusion and Further Manufacture

# Public Health Service (PHS) Act



- Blood is a Biologic (Section 351)
  - License required for distribution in interstate commerce
  - Biological products must be manufactured in a manner to ensure the safety, purity, and potency
- Blood is subject to regulations to prevent communicable diseases (Section 361)

# Federal Food, Drug, and Cosmetic (FD&C) Act



- Blood is a drug
  - Blood components are intended to cure, mitigate, treat, or prevent disease in humans
- Blood manufacturers are subject to:
  - Current Good Manufacturing Practice (cGMP) regulations
  - Prohibitions on adulteration and misbranding of products
  - Inspection of manufacturing facilities

# Regulations for Blood and Blood Components



- Part 600- General
- Part 601 – Licensing, reporting manufacturing changes
- Part 606 – Current good manufacturing practice (labeling, bacterial risk control, fatality reporting)
- Part 607 – Blood establishment registration and listing

# Regulations for Blood and Blood Components (cont'd)



- Part 610 – General biological product standards (blood testing, dating period)
- Part 630 – Requirements for donor eligibility, donation suitability
- Part 640 – Additional standards (red blood cells, platelets, plasma, source plasma)



# Regulations to Protect Donor Health



21 CFR 630.10, 21 CFR 630.15

Examples include:

- Donor questioning for medical conditions and medications
- Physical examination
- Hemoglobin measurement, donation frequency
- Total protein measurement and serum protein electrophoresis



# FDA Guidance for Blood Establishments

- Blood Guidances | FDA
- Guidance documents generally explain FDA's current thinking on a regulatory issue
  - May clarify or explain how manufacturers may comply with the statute or regulations
  - May establish good manufacturing standards for blood products



# Blood Licensure Requirements and Review Process

# OBRR Blood and Plasma Branch (BPB)



- Oversee blood establishment registration
- Review applications for the manufacture of blood components intended for transfusion or further manufacturing
- Conduct inspections
- Develop blood policy
- Advise blood establishments on regulatory issues

# Registered and Licensed Blood Establishments (April 2024)



Registered only (e.g., hospital blood banks, transfusion services)	765
Licensed blood collection establishments	948
Licensed Source Plasma establishments	1152

# Biologic License Application Process



- Submit Biologic License Application (BLA)- 21 CFR 601
  - Cover letter, Form FDA 356h
  - List of the blood components that will be manufactured
  - Description of the manufacturing process including the submission of written SOPs
  - Validation data summary, quality control data
  - Blood component labels

# BLA Supplements



- Submit changes to manufacturing process in an approved BLA (21 CFR 601.12)
  - Major Change: Prior Approval Supplement (PAS)
  - Moderate Change: Changes Being Effected in 30 Days Supplement (CBE30) or Changes Being Effected Supplement (CBE)
  - Minor Change: Annual Report (AR)

(FDA Guidance: [Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture | FDA](#))

# BLA Regulatory Decisions



- Filing letter (on receipt of application)
  - If incomplete, will send a refuse- to- file letter
- Approval letter
- Complete response letter
  - Deficiencies identified in submission
  - Failure to address the deficiencies may lead to withdrawal of the application



# Timelines for Common Submissions



- Original BLA – 12 months
- BLA supplements (including submissions with inspections)
  - PAS: 12 months (target 6-9 months)
    - Review of major changes
  - CBE-30, CBE: 6 months
    - Review of moderate changes

# BLA Applications Reviewed by BPB in 2023

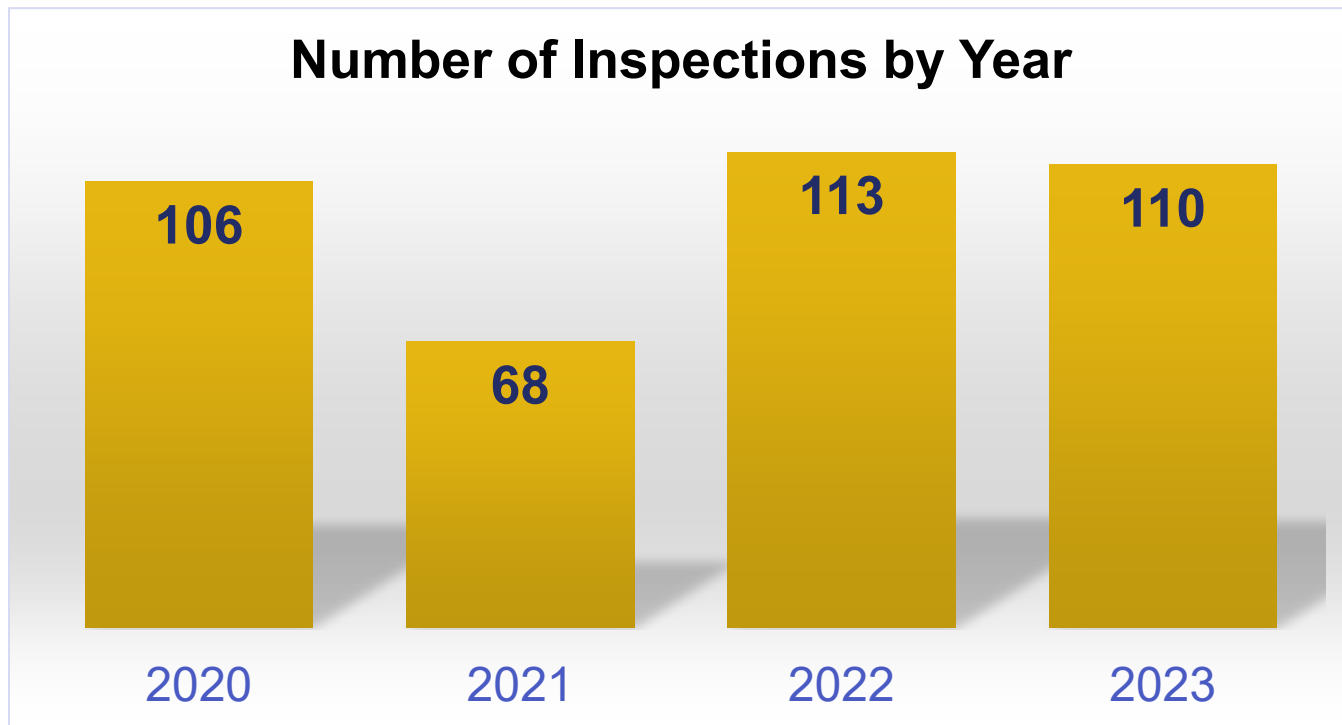


Submission Type	Number
Original BLA	5
Prior Approval Supplement	146
Changes Being Effected in 30 Days Supplement	67
Changes Being Effected Supplement (CBE)	24
Annual Reports	87
Product Correspondence	126

# Inspections

- Goal: To determine that products are manufactured in compliance with regulations
  - Original BLA (pre-license inspection)
  - BLA supplements and new facility (pre-approval inspection)
- Blood establishment pre-approval and pre-license inspections are conducted by BPB staff
  - Mainly domestic and takes 2-3 days

# Inspections Conducted by BPB (2020 to 2023)



# Inspection Decisions

- Issue Form 483: *Inspectional Observations*, if objectionable conditions are identified
- Final inspection actions
  - No action indicated (NAI)
  - Voluntary action indicated (VAI)
  - Official action indicated (OAI)
- Inspection findings are considered when making regulatory decisions on applications

# Summary



- OBRR functions include efforts to maintain the safety and availability of blood products for transfusion and for further manufacturing
- Blood and Blood components including Source Plasma are subject to the PHS and FD&C Act
- Manufacturers must obtain a biologics license before placing a product in interstate commerce.
- BLA application review includes the review of SOPs and related material, QC data and inspections

# Contact Information

- For OBRR regulatory submissions
  - Contact Regulatory Project Management Staff  
[Cherry.Geronimo@fda.hhs.gov](mailto:Cherry.Geronimo@fda.hhs.gov)
- For inquiries related to blood manufacturing
  - BPB Inquiries mailbox:  
[CBEROBRRInquires@fda.hhs.gov](mailto:CBEROBRRInquires@fda.hhs.gov)
- CBER contact:
  - Consumers: [ocod@fda.hhs.gov](mailto:ocod@fda.hhs.gov)
  - Manufacturers: [Industry.Biologics@fda.hhs.gov](mailto:Industry.Biologics@fda.hhs.gov)

# Challenge Question #2



Which of the following statements is **NOT** true?

- A. Applicants found to have submitted incomplete applications are issued refuse-to-file letters identifying the reasons preventing full reviews
- B. The licensure process for blood establishments may include inspections to ensure compliance with the regulations
- C. Licensed blood establishments do not need to report changes in manufacturing to FDA
- D. Failure to address the deficiencies in a complete response letter may lead to withdrawal of the application