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Regulatory Knowledge Guide for Blood and Blood Products

NIH SEED Innovator Support Team

Introduction

Every two seconds in the U.S., someone receives a blood transfusion or blood product. Blood-based products include a wide range of medicines and devices that help treat diseases and support many medical procedures. In 2022, the global blood product market was estimated to be worth $37.49 billion. It is expected to grow 4.5% annually. In the U.S., the increasing geriatric population is fueling much of this growth. The U.S. **Food and Drug Administration** (FDA) is responsible for assuring the safety of patients who receive these life-saving products.

From a regulatory perspective, blood-based medicines are a type of biological product and are regulated by FDA's **Center for Biologics Evaluation and Research** (CBER). They oversee the development, testing, and review of blood-based products with input from FDA's Blood Products Advisory Committee that is responsible for assessing data on the safety, efficacy, and proper use of blood, blood-derived products, serum, and biotechnology intended for diagnosing, preventing, or treating human diseases. CBER works closely with the Center for Devices and Radiological Health (CDRH) in regulating blood-directed devices including blood collection and storage containers. CBER also works with parts of the Public Health Service (PHS) to establish blood standards, and to identify and respond to potential threats to blood safety or supply. In all cases, the collection, testing, formulation, shipping, and storage of blood and its components must conform with FDA regulations and guidance.

This knowledge guide focuses specifically on blood-based products made with or for use with whole blood, and whole blood components. These FDA-regulated products include devices associated with blood donor testing, devices used by blood banking, as well as blood donor screening and product testing. Other FDA-regulated products, such as solutions used in the collection of blood and plasma donations are omitted from this guide. Included in this guide is information on specific aspects of blood-based product development, process and manufacturing considerations, the product development lifecycle, and FDA's regulatory framework.

Blood Products Regulated by the FDA	Blood Products Not Regulated by the FDA
Whole Blood and Blood Components Source Plasma Plasma-Derived Products Bone Marrow and Cord Blood Stem Cell Products Tissue Transplants Recombinant Blood Products Establishments and Blood Banks Donor Eligibility Testing Labeling and Advertising	Blood Donations for Personal Use Some Cellular Therapies

Throughout this guide, there will be references to the Regulatory Knowledge Guide for Biological Products, the Regulatory Knowledge Guide for Cell and Gene Therapies, and the Regulatory Knowledge Guide for Therapeutic Devices as appropriate. These resources provide more detail about the regulatory information shared between these products and blood-based products.

Please use the navigation panel to jump to sections relevant to your specific needs. If you have additional questions about the blood-based product development process, contact the SEED Innovator Support Team or FDA.

After reading this Regulatory Knowledge Guide, you will have a better understanding of the blood and blood products development and regulatory lifecycle. Specific topics that will be described are listed below:

- The regulatory pathways and applications that are applicable to blood-based products.

- Key differences between developing and manufacturing blood-based products and other biologics.
- Process for obtaining the human raw material needed for developing and manufacturing blood products.
- Safety measures required for mitigating infection risks while manufacturing blood-based products.
- Special considerations and the regulatory pathways of blood-directed devices.

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1 Regulatory Overview

As noted in the introduction, blood-based medicines are biological products and therefore follow the regulatory processes described in the Regulatory Knowledge Guide for Biological Products and, when appropriate, the Regulatory Knowledge Guide for Cell and Gene Therapies. This more focused guide describes processes and considerations specific to blood-based products – including using human blood as a source material and the special considerations required for its testing, manufacturing, transportation, and storage.

Similarly, blood-directed devices follow the same regulatory pathways as other medical devices and diagnostics. Section 4 of this guide provides a high-level overview of blood-directed devices including blood collection and storage devices. For more comprehensive descriptions of the regulatory processes for medical devices and diagnostics, refer to the Regulatory Knowledge Guide for Therapeutic Devices and the Regulatory Knowledge Guide for In Vitro Diagnostics.

1.1 Applications and Pathways

An essential step in developing a blood-based product is to determine the appropriate regulatory pathway to bring it to market. CBER oversees the development, testing, and review of blood-based products. The regulatory pathway depends on the type of blood-based product you are developing. New blood-based product innovators will likely use one of the following applications and pathways.

Biologics License Application (BLA) is used with fractionated plasma products and blood donor screening tests for infectious diseases and blood grouping and phenotyping.
New Drug Application (NDA) is for solutions used in the collection of blood and plasma donations.
Premarket Approval (PMA) pathway applies to devices associated with blood donor testing and pathogen reduction devices.
510(k) pathway applies to devices used by the blood banking industry including blood establishment computer software, transfer devices, collection systems, separators, culture bottles, fluid warmers, etc.

Note that you must submit an Investigational New Drug Application (IND) to obtain authorization to administer an investigational blood-based product to humans. An IND is required prior to conducting any clinical studies to collect safety and effectiveness information in support of a marketing application for a blood-based product. Similarly, an Investigational Device Exemption (IDE) is required to conduct a clinical trial to demonstrate safety and effectiveness of a significant risk medical device used to collect, process, or store blood products.

In addition, FDA strongly advocates for early engagement through meetings while developing new products or devices. These meetings with FDA, which can be arranged before submitting review applications, offer innovators a chance to gain valuable feedback on their plans. FDA highly recommends this proactive approach, as it helps align expectations, reduces the possibility of

misunderstandings, and lessens the risk of delays in later development stages. Although these meetings are specifically highlighted in the context of blood-directed devices, their importance is applicable across all sectors.

More information about meetings with FDA is available in Section 7 of the Regulatory Knowledge Guide for Small Molecules, Section 9 of the Regulatory Knowledge Guide for Biological Products, and Section 4 of the Regulatory Knowledge Guide for Therapeutic Devices.

Resource:
FDA: Approved Blood Products
NIH SEED: Basics of Interactions with FDA (CDER/CBER)

1.2 Special Paths and Designations

Special paths, designations, or expedited approval pathways for blood, components, and products may be available under certain circumstances, especially when addressing unmet medical needs or public health emergencies. In addition, regulatory agencies such as FDA and the European Medicines Agency (EMA) provide frameworks that can facilitate the development and approval process for new therapies, including blood-based products. The FDA pathways include:

- **Breakthrough Therapy Designation** (FDA) can be granted to drugs or biologics that may demonstrate substantial improvement over existing therapies based on preliminary clinical evidence for treating serious or life-threatening conditions. FDA works closely with the innovator to provide guidance and expedite the development and review process.
- **Fast Track Designation** (FDA) aims to facilitate the development and expedite the review of drugs and biologics to treat serious conditions to fill unmet medical needs where no therapy is available or, if there are available therapies, provides an advantage over existing therapies. FDA may provide more frequent meetings and communication with the innovator and allow for a rolling review of the submitted data.
- **Priority Review** (FDA) shortens FDA's review period for a new drug or biologic application from the standard ten months to six months. It is granted to products that could significantly improve the safety or effectiveness of a serious condition's treatment, diagnosis, or prevention.
- **Accelerated Approval** (FDA) allows for the earlier approval of drugs or biologics that treat serious conditions based on surrogate endpoints that are reasonably likely to predict clinical benefit. Post-marketing studies are required to confirm the expected clinical benefit.

The European pathways include:

- **Conditional Marketing Authorization** (EMA) enables the EMA to grant temporary approval for a medicine that addresses an unmet medical need, even if comprehensive data on its efficacy and safety are unavailable. The approval is conditional upon the sponsor providing additional data from ongoing or new studies within a specified timeframe.

- **PRIME** (Priority Medicines, EMA) is a program designed to enhance support for developing medicines that target an unmet medical need. It provides early and enhanced dialogue with the EMA, which can result in a faster assessment and potentially early access for patients.

These expedited approval pathways aim to shorten the time it takes for lifesaving or life-improving therapies to reach patients in need. However, they do not compromise the stringent safety and efficacy requirements for ensuring the quality and effectiveness of blood, components, and blood-based products.

Resources:
FDA: Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review
EMA: Conditional Marketing Authorization
EMA: PRIME – Priority Medicines

2 Using Human Blood as a Source Material

Whole blood is comprised of red blood cells and white blood cells, platelets, and plasma. These components serve as the raw material for many blood-based products. Because human-source materials carry a risk of exposure to infectious agents, the blood product collection, testing, and distribution processes involve several steps to ensure the safety and quality of human-source material. These steps include:

- **Donor screening** – To determine eligibility, donors must undergo a screening process, which includes questions about medical history, travel history, and lifestyle habits, such as drug use or risky sexual behavior. The screening also includes a physical examination to check the donor's blood pressure, pulse, and hemoglobin levels.
- **Donation** – The blood collection process involves inserting a sterile needle into the donor's vein to withdraw between 450 and 500 milliliters (mL) of blood, depending on the donation type. Blood can also be collected using an apheresis device which allows for the selective removal or retention of specific blood components such as platelets or plasma.
- **Testing** – The donated blood is sent to a laboratory for testing to ensure it is safe for transfusion. The tests include screening for infectious diseases such as HIV, Hepatitis B and C, and West Nile virus. The blood is also tested for blood type and Rh factor.
- **Processing and Storage** – Once the blood has passed all the required tests, it is processed and stored until it is needed for transfusion. The blood can be separated into different components, such as red blood cells (RBCs), plasma, and platelets, to be used for different medical purposes.
- **Quality control** – Regular quality control checks are performed to ensure the safety and efficacy of the blood components.
- **Distribution** – The blood components are distributed to hospitals and clinics for transfusion to patients in need.

Because human-source materials carry a risk of exposure to infectious agents, the blood product collection, testing, and distribution processes involve several steps to ensure the safety of the blood.

As is the case with the development of all new drug products, innovators must submit and receive approval from an Institutional Review Board before starting biomedical research involving human subjects. This review and approval are in addition to any FDA required reviews or approvals.

2.1 Safety Considerations and Risk Mitigations

Many blood-based products are complex and carry an inherent risk for transmitting infectious diseases. Therefore, zero risk may be unattainable. The role of CBER is to drive that risk to the lowest level achievable without decreasing the efficacy and availability of these lifesaving raw material resources.

CBER compliance and surveillance activities for blood-based products
Pre-license and pre-approval inspections of manufacturing facilities and products under clinical study
Monitoring the safety, purity, and potency of biological products through review of: • Biological Product Deviation Reports and Human Cells, Tissues and Cellular and Tissue-based Products Deviation Reports) • Investigations into transfusion/donation-related fatalities and other adverse events (e.g., transfusion-transmitted infections) • Product recalls
Monitoring reports of blood-based biological product shortages
Initiating regulatory action to address non-compliance with FDA laws and regulations
Monitoring research conducted on blood-based biological products and assessing the protection of the rights, safety, and welfare of human research subjects and the quality and integrity of research data • IRB and medical device reporting for research documentation approval and medical device reports, respectively
Monitoring import and export activities
Reviewing product advertising and promotional labeling

One safety issue relevant to current transfusion products is contamination by pathogens, such as bacteria, during the collection process. The current approach to minimizing risk of transfusing contaminated products is to test them for the presence of pathogens. See 2.1.2 Pathogen Reduction Technologies for information on pathogen reduction technologies (PRTs), which is a process intended to reduce the risk of transmission of pathogens prior to blood product use.

2.1.1 Donor Screening and Testing

FDA has progressively strengthened the overlapping safeguards that protect patients from unsuitable blood and blood products. Blood donors are asked specific questions about risk factors that could impact the safety of the donation, and blood centers are required to maintain lists of unsuitable donors.

FDA has progressively strengthened the overlapping safeguards that protect patients from unsuitable blood and blood products.

Donated blood undergoes the following panel of infectious disease testing performed on samples taken at the time of donation:

- HBV (covers Hepatitis B Surface Antigen and Hepatitis Core Antigen)
- Human Immunodeficiency viruses, Types 1 and 2 (HIV 1,2)
- Human T-Lymphotropic viruses, Types 1 and 2 (HTLV 1,2)
- Antibody to Trypanosoma
- Babesia Antibody and Nucleic Acid Testing
- West Nile Virus – locations at risk during peak mosquito seasons
- Hepatitis C Virus (HCV)
- Zika Virus

FDA requires blood establishments to have a quality assurance program in place which includes a process to identify and report any adverse events or reactions (both donor and recipient) associated with blood donation, including allergic reactions, hematomas, and syncope. They must have a system in place to notify donors of any abnormal test results or adverse events associated with their blood donation while maintaining the confidentiality of donor information.

Resource:
CFR: Part 610.40 Test Requirements

2.1.2 Pathogen Reduction Technologies

In a continuous effort to address the risks inherent in using human-source materials in blood-based products, FDA encourages the development of tools designed to evaluate innovative technologies to reduce, inactivate, or eliminate pathogens from FDA-regulated products. Proactive methods for enhancing blood transfusion safety are commonly known as pathogen reduction technologies (PRTs).

There are FDA-approved PRTs (e.g., the INTERCEPT Blood System™) but no PRTs are required as of the writing of this document. Various PRTs have been developed, such as chemical treatment, solvent/detergent treatment, and a light treatment (with or without a photosensitizer). All techniques offer non-specific pathogen reduction, but each technology's mode of action influences the types of pathogens reduced, the specific blood components treated, and the effect on those components. The decision to use PRTs should consider multiple factors, including potential future epidemic risks. PRTs are vital in improving blood transfusion safety and reducing disease transmission risk, complementing existing blood screening and testing procedures.

Using PRTs for primary and secondary blood products (see Section 3.1) offers several benefits. By inactivating a wide range of clinically relevant viruses, bacteria, and protozoa, PRTs help reduce residual infection risks when donor screening tests cannot detect transfusion-relevant pathogens like HIV. Unlike screening tests for transfusion-borne pathogens, PRTs may proactively protect against emerging contagious agents entering the blood supply in each community.

PRTs are vital in improving blood transfusion safety and reducing disease transmission risk, complementing existing blood screening and testing procedures.

All PRT methods used to treat cellular blood products function by impairing the target pathogen's ability to replicate. Alone or combined, ultraviolet light and alkylating agents cause irreversible damage to the nucleic acids of pathogens. Consequently, they effectively reduce classical pathogens like viruses, bacteria, fungi, and protozoa but are ineffective against prions, protein-based pathogenic agents that can cause disease in humans (e.g., sporadic and variant Creutzfeldt–Jakob disease) and are only partially effective for non-enveloped viruses (e.g., Hepatitis e) and spore forming bacteria.

In some regions of Asia, Canada, Europe, and the U.S., PRTs for platelets and plasma are used. FDA recently recommended using approved PRTs as an alternative to bacterial detection methods to control the risk of bacterial contamination in platelets adequately. FDA suggests importing blood from unaffected areas unless donations are screened using a laboratory test or blood components are subjected to PRTs using an approved method. FDA has approved the INTERCEPT Blood System for pathogen reduction in apheresis platelets stored in plasma and platelets in additive solutions, as well as plasma. Additionally, FDA has approved another pathogen-reduced pooled plasma product, Octaplas® (Octapharma), which employs a solvent/detergent method. PRTs for whole blood have not yet received approval. The current focus is primarily on PRTs for blood components, such as plasma and platelets. However, some PRTs for RBCs are in development or undergoing clinical trials.

Significant concerns regarding PRTs implementation involve the impact on blood component integrity and the toxicity of chemicals used in these systems. Although only small quantities of photochemical compounds are used in PRTs and appear to provide sufficient safety margins, it cannot be ruled out that alkylating agents may be carcinogenic in the long term in a subset of transfused patients. PRTs

without photoactive substances have the significant advantage of eliminating the risk of photo-reagent-related adverse events but can also negatively impact the quality of the transfusion product.

2.1.3 Fresh Blood

Donated fresh blood is tested for infectious diseases, blood type, and Rh factor. Fresh whole blood and RBCs typically can last up to 42 days after collection (timing is dependent on the anticoagulants (whole blood) and additive solutions (RBCs)) after which the blood may begin to degrade and lose its effectiveness.

After separation, the primary and secondary blood components are stored based on their varying shelf lives (details provided in Section 3.1 Blood Components). Most plasma-based products can be frozen for extended periods of time.

Resource:
AABB: Regulatory for Blood and Blood Components (aabb.org)

2.1.4 Pooled Outdated Blood

Pooled outdated blood is generally no longer used to produce blood products, including human albumin, due to safety concerns and strict regulations. Blood products have expiration dates to ensure their quality and effectiveness. Using outdated blood can pose significant patient risks, including reduced efficacy and potential adverse reactions.

Regulatory agencies like FDA, the EMA, and other national organizations set guidelines and requirements for blood collection, processing, storage, and distribution. These agencies aim to minimize risks associated with blood transfusion and ensure that blood products are safe and effective for their intended use. Under some circumstances, FDA may issue an exception or alternative regarding blood, blood components, or blood products.

For example, human albumin is a blood product that serves various therapeutic purposes, such as volume expansion and maintenance of oncotic pressure. It is derived from human plasma, which undergoes a fractionation process to separate and purify its components. Donated plasma is typically pooled from multiple donors, but strict quality and safety requirements must be met. Outdated plasma would not meet these requirements or be used to produce human albumin or other blood products.

Resources:
FDA: Part 640 Additional Standards for Human Blood and Blood Products
FDA: Exceptions and Alternative Procedures Approved Under 21 CFR 640.120
EMA: Guideline on Plasma-Derived Medicinal Products
Article: Production of Human Albumin Solution: A Continually Developing Colloid
Article: Recommendations for the Use of Albumin and Immunoglobulins

2.2 Oversight Compliance and Surveillance

In addition to strengthening donor safeguards, FDA has significantly increased its oversight of the blood industry and inspects blood facilities at least every two years. Facilities with a history of non-compliance are inspected more often. These facilities are required to maintain the same level of quality standards as pharmaceutical manufacturers. All enterprises that manufacture blood products are required to register with FDA and submit a list of every blood product manufactured, prepared, or processed for commercial distribution.

FDA also works closely with other parts of the PHS to identify and respond to potential threats to blood safety, to develop safety and technical standards, to monitor blood supplies, and to help industry promote an adequate supply of blood and blood products by:

- Collaborating with Centers for Disease Control and Prevention and other public health agencies on surveillance, epidemiology, and research activities related to blood safety.
- Issuing guidance documents and recommendations based on the latest scientific evidence.
- Reviewing and approving new tests and technologies for blood screening and processing.
- Communicating with blood establishments, healthcare providers, and the public about emerging risks and safety measures.

2.2.1 CBER Compliance and Surveillance Programs

CBER oversees compliance programs for blood products to ensure their safety, efficacy, and quality. These compliance programs include:

Establishment Inspections: CBER conducts inspections of blood establishments to assess compliance with applicable regulations and standards related to the collection, processing, testing, and distribution of blood products.

Biological Product Deviation Reporting: Blood establishments are required to report any deviations from the applicable regulations and standards that could affect the safety, purity, or potency of blood products. CBER reviews and evaluates these reports to determine if additional regulatory action is necessary.

Recall Procedures: Blood establishments are required to have procedures in place to initiate a recall of blood products that may be unsafe or ineffective. CBER oversees and monitors these recalls to ensure that they are conducted in accordance with applicable regulations and standards.

Donor Eligibility: Blood establishments are responsible for ensuring that donors meet eligibility criteria for donating blood products. CBER provides guidance on donor eligibility criteria and monitors compliance through inspections and other oversight activities.

Labeling and Advertising: Blood establishments are required to ensure that the labeling and advertising of blood products are truthful, accurate, and not misleading. CBER reviews and approves labeling and advertising materials and monitors compliance with applicable regulations and standards.

CBER also oversees surveillance programs for blood-based products to monitor their safety and effectiveness after they have been approved for use. These surveillance programs include:

Adverse Event Reporting: Blood establishments, healthcare providers, and patients are required to report any adverse events or side effects associated with the use of blood products. CBER reviews and analyzes these reports to identify potential safety concerns and take appropriate regulatory action.
Blood Donor Hemovigilance: CBER conducts surveillance of blood donors to identify potential safety issues related to blood collection and donor eligibility. This includes monitoring trends in donor reactions and assessing the impact of changes in donor eligibility criteria.
Product Quality Monitoring: CBER conducts surveillance of blood products to monitor their quality and ensure that they meet applicable standards. This includes testing of blood products for infectious diseases and other quality indicators, as well as monitoring manufacturing and distribution practices.
Post-Marketing Studies: CBER may require post-marketing studies of blood products to address specific safety or effectiveness concerns that arise after approval. These studies may be conducted by the manufacturer or by independent researchers.
Risk Communication: CBER communicates with healthcare providers and patients to inform them of potential safety concerns related to blood products and provide guidance on safe and effective use.

Resources:
FDA: Compliance Programs
FDA: Compliance Actions (Biologics)

2.2.2 Blood Establishment Registration and Product Listing

All blood product manufacturers must register with the FDA within five days of starting to operate and provide a list of all blood products. Blood establishments register through the electronic blood establishment registration (eBER) system. All blood product listings must be updated biannually in June and December. To find a blood establishment, you can search the Blood Establishment Registration Database.

Resource:
FDA: Blood Establishment Registration and Product Listing

3 Blood-Based Medical Therapeutics

Blood and blood products are defined as medicinal substances derived from whole human blood, plasma, serum, or any derivative originating from a whole blood component. Whole blood and blood components, derived from whole blood, have different storage, processing, and temperature requirements for therapeutic efficacy. These requirements, and best practices, are noted below.

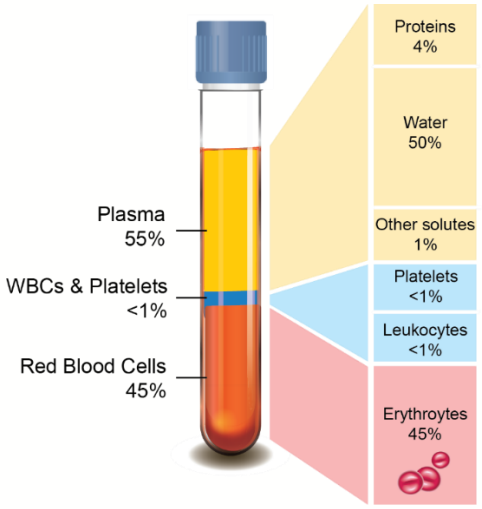

Figure 1. Blood Components

3.1 Blood Components

Each blood component must follow rigorous standards for isolation, use, and storage to ensure the safety and efficacy of the final blood products. The following is a brief overview of these standards. These and other standards can be found in links provided in Section 3.4 Chemistry, Manufacturing, and Controls.

Of note, leukocyte reduction (the removal of white blood cells from whole blood and blood components) can be performed by blood establishments. Benefits of leukocyte reduced blood and blood components include minimized adverse events, such as febrile reactions and alloimmunization. Guidance for leukocyte reduction of whole blood and blood components provides additional recommendations on leukocyte reduction parameters (i.e., $< 5.0 \times 10^6$ residual white blood cells per each whole blood, RBCs or platelets, and pheresis collection).

Whole blood is typically stored between 1°C and 6°C to preserve the unit's viability and prevent bacterial growth. Blood is tested for transfusion-transmitted infectious agents (see Section 2.1.1), antigens A, B, AB or O, and the Rh factor and then sent to a blood bank or processing center.

Red blood cells (RBC) are prepared from whole blood using centrifugation to separate them from the liquid plasma component. They are stored between 1°C and 6°C for up to 42 days depending on if they are stored in an additive solution. In addition to filtering RBC products to remove leukocytes for some patients, RBC products are washed with saline to remove plasma and additives that may cause allergic or anaphylactic reactions in some recipients (note that washing reduces the shelf life of RBC products to a maximum of 24 hours). Other specific RBC products are irradiated with gamma rays to prevent transfusion-associated graft-versus-host disease in certain recipients who are at risk of immune suppression or donor-recipient human leukocyte antigen (HLA) matching. Like whole blood, all RBC

products must be tested for infectious diseases and for ABO and Rh antigens. Some RBC products are also tested for other clinically significant antigens.

Platelets are isolated from whole blood by centrifugation or apheresis. Generally, platelets are stored at a temperature of 22°C ± 2°C with constant agitation to prevent clumping and preserve function. The shelf life of platelets is usually five days if the platelets are stored in bags approved for seven-day storage and tested for bacterial contamination. Storage of platelets in the cold is currently being investigated and may provide longer shelf life for platelets

Fresh Frozen Plasma (FFP) is prepared by separating plasma from whole blood through centrifugation at 4°C to separate the plasma from other blood components. The plasma is then rapidly frozen (-30°C) within six to eight hours of collection. It can be stored for up to 12 months at -25°C or below.

Platelet-Rich Plasma (PRP) is blood plasma enriched with platelets. PRP is autologous (from the patient), separated from the patient's blood via centrifugation, and injected at the treatment site. Note that devices such as centrifuges used in PRP preparation are regulated under the 510(k) statute (see Section
4 Blood-Directed Devices). FDA has, so far, only cleared the devices for preparation of PRP but not the PRP. Clinical use of PRP is at the discretion of the physician.

Cryoprecipitate is a cold-insoluble precipitate manufactured from whole blood or plasmapheresis and is enriched in clotting factors, such as fibrinogen, factor VIII, factor XIII, von Willebrand factor, and fibronectin. FDA quality control requirements mandate a minimum of 80 international units of factor VIII. Frozen cryoprecipitate can be stored at -18°C or colder for up to 12 months from the original collection date. Thawed cryoprecipitate can be stored at 20°C to 24°C for up to six hours if it is in a closed system (single unit or pooled using a sterile method). Thawed cryoprecipitate can be stored at 20°C to 24°C for up to four hours if it is in an open system (pooled using a non-sterile method). Human serum albumin is a sterile solution of albumin derived from plasma. It is separated from other blood proteins through cold ethanol fractionation, ultrafiltration, diafiltration, isoelectric precipitation, and pasteurization. The final product can be either a 4, 5, 20 or 25% solution of albumin protein.

Immunoglobulins are purified from other proteins in pooled and fractionated plasma using methods including chromatography. Potential viral pathogens are inactivated or removed using heat treatment, solvent-detergent treatment, nanofiltration, or other methods. Immunoglobulin products are formulated by adjusting the pH and osmolality, and by adding stabilizers and preservatives to ensure stability and safety. The final product should have ≥ 96% of the total protein as immunoglobulin G (IgG).

Coagulation factors are manufactured from human blood plasma. The manufacturing steps of coagulation factor products may vary depending on the source and type of product. Generally,

fractionated plasma is further processed to isolate specific coagulation factors, using various methods, such as filtration, chromatography, or heat treatment, to remove any remaining impurities and inactivate any potential viruses. Coagulation factor concentrates are stable for up to three months if frozen at -24°C or lower. If frozen at -74°C, coagulation factor concentrates are stable for at least 18 months, most for 24 months. Coagulation factors can also be manufactured with recombinant DNA technology.

Alpha-1 antitrypsin (AAT) is a protein found in plasma and alpha-1 antitrypsin deficiency is treated with AAT products. Several AATs, also known as alpha$_1$-proteinase inhibitors, are available as therapy for severe AATD deficiency. For all available therapies, the fraction of plasma containing AAT is isolated and purified by cold ethanol fractionation. To reduce the risk of viral transmission, AAT can be heat-treated solely, or exposed to a combination of heat inactivation with ultrafiltration, or solvent/detergent with nanofiltration. The purified AAT is formulated into a liquid or lyophilized (freeze-dried) product with appropriate stabilizers and preservatives. AAT should be stored at room temperatures not exceeding 25°C, with the liquid form of AAT also capable of storage at 2°C to 8°C.

Resource:
AABB: Blood Component Cards

3.2 Blood Substitutes

Currently, no FDA-approved oxygen-carrying blood substitute product exists commercially. However, artificial blood, a theoretical product currently under research, aspires to replicate the essential functions of natural blood, predominantly the transport of oxygen and carbon dioxide. Although it could have potential life-sustaining utility during significant blood loss events, current developments do not yet replicate secondary functions of blood, such as fighting infections.

Most research efforts are concentrated on developing substitute blood components, including red cells for oxygen/carbon dioxide exchange and platelets for clotting. There are two primary types of synthetic blood products under development that aim to facilitate oxygen and carbon dioxide transport, but further research is required to validate their safety and efficacy. A third type, known as platelet substitutes, is the most robust area of research and has existed for decades.

Hemoglobin-based oxygen carriers (HBOCs) are typically derived from human or bovine hemoglobin. This protein in red blood cells carries oxygen throughout the body. HBOCs utilize modified hemoglobin in a solution suitable for transfusions. They aim to mimic the oxygen-carrying functionality of red blood cells, especially vital during medical emergencies, surgeries, or low blood supply conditions.

Perfluorocarbons (PFCs) are synthetic compounds capable of carrying and delivering oxygen, like hemoglobin's function. They dissolve gases like oxygen and carbon dioxide, allowing transport within

the bloodstream. The critical advantage of PFCs is their non-biological nature, thus eliminating the risk of disease transmission associated with donated blood products.

Platelet substitutes are another area of research since they can assist with clotting and stopping bleeding and lessen reliance on blood donations. They can be derived from red cell derivatives, liposomal derivatives, or nanoparticles. Global platelet scarcity, particularly in less developed countries, is being addressed through nanotechnology. Artificial nanosystems resembling cells with controlled release mechanisms are also being developed as platelet substitutes.

3.3 Umbilical Cord Blood

The FDA has formulated guidelines to oversee the use of cord blood—the residual blood found in the placenta and umbilical cord following childbirth—and recommendations to meet the regulatory requirements for use of cord blood in BLAs and INDs. These regulations are implemented to ensure cord blood units' safety, purity, and potency. Cord blood banks must be registered with the FDA and comply with good tissue practice regulations. These regulations cover the methods, facilities, and controls used to manufacture HCT/Ps (human cells, tissues, and cellular and tissue-based products).

Umbilical cord blood is a crucial substitute for bone marrow transplants, given its natural abundance of blood components, particularly blood-forming stem cells akin to those in bone marrow. Compared to bone marrow transplants, umbilical cord blood transplantation necessitates less rigorous matching criteria between donor and recipient, offering a more flexible choice for transplantation.

The FDA provides guidance documents on aspects of cord blood regulation, such as donor screening and testing, and standards for cord blood collection, processing, testing, and storage. Cord blood units utilized in unrelated donor transplants are subject to additional requirements and must be licensed by the FDA. This process includes a comprehensive review of the manufacturing process and rigorous product testing to ensure safety and efficacy. Cord blood banks are mandated to report any adverse reactions to the FDA.

3.4 Chemistry, Manufacturing, and Controls

The **chemistry, manufacturing, and controls** (CMCs) are the specific activities and processes a manufacturer undertakes during the development/production lifecycle of a therapeutic agent. FDA requires blood-based product manufacturers to verify the suitability (identity, purity, potency, and safety) of every raw material as part of a quality management system. The **critical quality attributes** (CQA) of the blood components must be maintained throughout the manufacturing process and any in-process impurities must be identified and removed during manufacturing operations.

FDA requires blood-based product manufacturers to verify the suitability (identity, purity, potency, safety) of every raw material in their product.

The Code of Federal Regulations (CFR) provides CQAs for many primary and secondary blood products, as well as product specifications, such as dating period limitations. Examples of such CQAs are listed in Table 1. Of note, some blood products (i.e., coagulation factors) may not have CFR-provided CQAs but do have general reference standards.

Table 1: Select CQA Categories for Primary and Secondary Blood Products

Type of Blood Product	CFR CQAs
Whole Blood	CFR Subpart A: Whole blood (640.1), General requirements (640.2), Blood collection (640.4), Blood testing (640.5), and Modifications (640.6)
Red Blood Cells	CFR Subpart B: RBCs (640.10), General requirements (640.11), Donor eligibility (640.12), Blood collection (640.13), Blood testing (640.14), segments for testing (640.15), Processing (640.16), and Modifications (640.17)
Platelet	CFR Subpart C: Platelets (640.20), Donor eligibility (640.21), Collection of source material (640.22), Blood testing (640.23), Processing (640.24), and General requirements (640.25)
Plasma, including Fresh Frozen Plasma	CFR Subpart D: Plasma (640.30), Donor eligibility (640.31), Collection of source material (640.32), Blood testing (640.33), and Processing (640.34) CFR Subpart G (640.60-640.76)
Albumin	CFR Subpart H: Albumin (640.80), Processing (640.81), Final product testing (640.82), General requirements (640.25), and Labeling (640.84)
Immunoglobulin	CFR Subpart J: General requirements (640.101), Manufacture of Immune globulin (640.102), Final product (640.103), Potency (640.104)
Cryoprecipitate	CFR Subpart F: Donor eligibility (640.51), Collection of source material (640.52), Blood testing (640.53), Processing (640.54), U.S. Standard preparation (640.55), and Quality control test (640.56)

For additional CMC information generally applicable to all biological products, see Sections 5 and 6 in the Regulatory Knowledge Guide for Biological Products.

Resources:
NIH SEED: Quality Management Systems for Biological Products
FDA: CMC and GMP Guidances

3.4.1 Processing and Manufacturing

FDA guidance provides recommendations to manufacturers of human plasma derivatives and components, including plasma protein therapies and blood clotting factors, on the testing methods and procedures needed to ensure the safe manufacturing of these products.

In all cases, manufacturers of blood-based products should follow specific manufacturing controls, such as **current Good Manufacturing Practices** (cGMPs), to ensure the safety and quality of their products. One of the main components of viral safety for blood products is the implementation of dedicated virus reduction methods (virus inactivation and/or virus removal) during large-scale production processes. Ensuring the highest possible level of virus safety to human plasma products is enabled by the cumulative effect of multiple cGMP-compliant measures.

Ensuring the highest possible level of safety in human plasma products is enabled by the cumulative effect of multiple cGMP-compliant measures.

Manufacturers are also required to report any adverse events or reactions associated with their products and maintain accurate records of all testing, manufacturing, and distribution activities. The existence of a traceability system from donors to patients and vice versa is an additional cornerstone of the pathogen safety of blood products. This enables performing "look-back" procedures if suspicions of viral transmission to recipients, or viral risks from a donor are identified.

3.4.2 Testing

With blood-based biologics, testing is typically segregated into donor screening (see Section 2.1.1) and product testing phases to mitigate the risk of adventitious agents (including viruses, bacteria, fungi, mycoplasma, and prions).

While donor screening entails the examination of individual blood or plasma donations for a range of infectious agents, product testing is intended to identify any residual adventitious agents, and establish product purity, potency and identity standards with tests varying based on the product in question. For example, FDA's guidance on product testing for human plasma derivatives and components requires that they be tested for certain parameters, such as purity, potency, and identity, to ensure the product meets established standards and specifications. The specific testing requirements vary depending on the product and its intended use, as well as applicable regulations or guidelines.

Testing or verifying blood-based products during development will be a significant, but routine, step throughout manufacture. Using qualified/validated testing methods to measure the characteristics or critical attributes of blood-based products is essential. The methods chosen to prove the effectiveness of design and final product should be performed using "fit for purpose" qualified methods, when possible, versus new or experimental methods. Establishing a baseline of results using qualified or

validated methods, to measure and characterize your blood-based product, adds validity to the overall process.

Using qualified/validated testing methods to measure the characteristics or critical attributes of blood-based biologics is essential.

A laboratory must demonstrate it can obtain performance specifications comparable to a qualified method for accuracy, precision, reportable range, and normal or reference values. If a laboratory develops its own methods and introduces a test system not subject to FDA approval or clearance, or makes modifications to an FDA approved testing method, the laboratory must establish the specifications before reporting results. The laboratory must also establish calibration and control procedures and document all activities for test method validation. Refer to CFR 493.1253 Standard: Establishment and verification of performance specifications to learn about these requirements.

3.4.3 Contamination Risk Mitigation Strategies

Adventitious agents present a risk of inadvertent contamination in the production of biological products. This risk is particularly pertinent for biologics derived from human blood or blood components, given the potential for the donor population to harbor infectious agents and include clotting factors, albumin, immunoglobulins, and cellular therapeutic products. Therefore, these biological products have distinct isolation, storage, and testing protocols to ensure their safety and efficacy. Additionally, specific regulatory guidelines may be applicable depending on the intended use of the products.

CMC precautions and adventitious agent testing reduce the risk of biopharmaceutical contamination when utilizing materials derived from humans in biological manufacturing, including cell culture-based manufacturing processes. Three primary, complementary strategies for controlling contaminants include establishing barriers to entry, conducting tests to verify absence, and implementing procedures for inactivation/removal. Cells used in these processes may be autologous (from the patient) or allogeneic (from another individual). Therefore, the FDA requires comprehensive documentation detailing cell processing and gene modification procedures (if applicable). This documentation includes a description of the cell type, the source of cells, the collection procedure, compliance with donor eligibility requirements, and adventitious agent testing for allogeneic cells.

For more details on pilot production of biological products, see Section 5 of Regulatory Knowledge Guide for Biologics and Section 3 of the Regulatory Knowledge Guide for Small Molecules.

3.5 Cell and Gene Therapy Considerations

Cellular and gene therapy products derived from human whole blood are biological products that use blood cells or components to treat various diseases or conditions. They are classified into two broad categories: cellular therapy and gene therapy products.

Cellular therapy products use living cells that are isolated, modified, or cultured from blood or other sources to restore or enhance a specific function in the body. Some examples of cell therapy products are stem cells and stem cell derived products, (e.g., those from hematopoietic, mesenchymal, embryonic, umbilical cord blood), cancer vaccines and immunotherapies, (e.g., dendritic cell vaccines, activated T or B lymphocytes, monocytes), and modified or unmodified cancer cells, allogeneic pancreatic islet cells, chondrocytes for cartilage repair, keratinocytes, fibroblasts, and hepatocytes. Gene therapy products use genetic material, such as DNA or RNA, to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use. Some examples of gene therapy products include plasmid DNA, viral vectors, bacterial vectors, human gene editing technology, and patient-derived cellular gene therapy products.

The manufacturing process for blood components utilized in cellular and gene therapy can differ depending on the product's complexity and type. The cell therapy sector is especially diverse in product technology and manufacturing processes. This is particularly true for specific product categories such as RBCs, platelets, hematopoietic stem cells, and various immune cells, including tumor-infiltrating lymphocytes, viral reconstitution T cells, dendritic cells, gamma delta T cells (also known as γδ or gd T cells), regulatory T cells, macrophages, and genetically modified T cells. At present, the production techniques and strategies for these products are wide-ranging and lack uniformity, with no dependable platforms having emerged yet. Establishing a manufacturing "platform" is crucial for the swift development and commercialization of biologics, as it involves standardized systems designed for efficient production using streamlined, scalable, and reproducible methods.

The manufacturing process for cell and gene therapy products needs to conform to cGMP standards as well as FDA's specific guidelines for various cellular and gene therapy products, such as hematopoietic stem cells, CAR T cells, genome editing products, and viral vectors.

Resources:
NIH SEED: Regulatory Knowledge Guide for Cell and Gene Therapies
FDA: Cellular and Gene Therapy Guidance
FDA: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular/Tissue-Based Products
FDA: Cellular & Gene Therapy Products
FDA: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs)
Article: Cell-Based Therapy Technology Classifications and Translational Challenges

4 Blood-Directed Devices

As noted in the introduction, CBER is also responsible for regulating blood-directed devices. CBER, working closely with CDRH, oversees the regulation of medical devices related to licensed blood and cellular products by applying appropriate medical device regulations. These devices are closely associated with blood collection and processing procedures as well as other cellular therapies regulated by CBER. Note that blood-directed devices do not include all devices that encounter blood. For example, an artificial heart valve that promotes blood flow is not a blood-directed device but rather a cardiovascular therapeutic medical device. Whereas, a centrifuge used in platelet-rich plasma preparation is a blood-directed device (product code KSN). For more examples, see 21CFR864 hematology and pathology devices.

CBER authorized blood-directed devices follow the same regulatory pathways of CDRH devices and diagnostics.

Many innovative medical devices have been developed in recent years. These devices prepare blood components for pharmaceutical and vaccine innovations, reduce complications during blood transfusion administration, and protect blood cells through pathogen activation processes. In addition, new filtration techniques reduce adverse results during processing. If your research is for a regulated medical device, you must familiarize yourself with the regulatory requirements before bringing it to market. Refer to the Regulatory Knowledge Guide for Therapeutic Devices and the Regulatory Knowledge Guide for *In Vitro* Diagnostics as the regulatory processes described in these documents are applicable to blood-directed devices.

Generally, most blood-directed devices follow one of these three regulatory pathways:

- **510(k)s** are moderate-risk devices which have similar (predicate) devices already on the market and include devices used by the blood banking industry (e.g., blood establishment computer software, transfer devices, collection systems, separators, culture bottles, fluid warmers).
- **PMAs** are high-risk devices without comparable devices on the market and include devices associated with blood donor testing and pathogen reduction (e.g., pathogen reduction technologies, *in vitro* diagnostics). Clinical trials are usually required to demonstrate the safety and efficacy of these devices.
- **De Novos** are moderate-risk devices which are "new" to regulation with no predicate devices on the market. The risk from these devices can be controlled by general and special controls which assure safety and effectiveness of the device. This pathway may be used for novel blood devices to pave the way forward for future 510(k)s (e.g., a new type of point-of-care coagulation device).

Some blood product devices can be used as general-purpose devices intended for *in vitro* use in blood banking. This generic type of device includes products such as blood bank pipettes, blood grouping slides, blood typing tubes, blood typing racks, and cold packs for antisera reagents. These devices do not include articles that are licensed by CBER and are considered class I (low risk). Most class I devices fall under "enforcement discretion," meaning FDA does not intend to enforce regulatory requirements for these specific types of devices.

Researching previously approved blood-directed devices in the CBER databases is advisable. Summaries of cleared 510(k), PMA, and De Novo devices are available. You can also search for keywords (e.g., blood) in the Device Classification Database.

Resources:
NIH SEED: Quality Management Systems for Medical Devices
NIH SEED: CBER Small Business Support – Manufacturers Assistance and Technical Training Branch
NIH SEED: De Novo Pre-Submission Meetings
NIH SEED: 510(k) Pre-Submission Meetings
NIH SEED: Overview of CDER and CBER Interactions-FDA
FDA: Devices Regulated by the Center for Biologics Evaluation and Research
FDA: Currently Approved CBER Device Premarket Applications

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