Blood products are considered an essential part of medical therapy worldwide. National systems are seen in much of the developed world (e.g., Europe, Canada, Australia, and New Zealand), with the United States as an exception. (In Canada, there is one national system and a second one for the province of Quebec.) Less developed countries often have hospital-based systems (in some cases with a small national system, as in Mexico). Many are run by the International Red Cross and are government subsidized.

In the United States, a majority of the blood is collected and distributed by community blood centers that generally are part of a trade organization called America’s Blood Centers (ABC). Consolidation among the members has been a recent development. The American Red Cross, which is separate from ABC, collects and distributes about 40% of the blood. The AABB (formerly the American Association of Blood Banks) is a professional society of individuals in the field, community blood centers, and hospital transfusion services. It publishes AABB Technical Manual and Standards for Blood Bank and Transfusion Services (as well as several publications containing standards for various specialized services) that both serve as voluntary guides to procedures and quality requirements and tend to establish a standard of care. A small percentage of blood is collected and processed by hospital-based blood banks. Testing has been centralized in large laboratories run by the American Red Cross and independent blood centers (e.g., Creative Testing Solutions and Qualtex). Blood centers have also become more active in recent years in offering transfusion services to hospitals.

Plasma collection and manufacturing organizations belong to a trade association known as the PPTA (Plasma Protein Therapeutics Association, or PPTA Source for collections), which is global and operates in the United States, Europe, and the rest of the world but embrace similar principles related to the efficacy and safety of blood products.

US perspective on ensuring blood and blood product safety and availability

History of safety and efficacy requirements for drugs and biologics in the United States

Regulatory approval of drugs and biologics in the United States is subject to federal law. Safety and efficacy requirements related to drug and biologics approval have evolved through the 20th and 21st centuries. In 1906, President Theodore Roosevelt included a recommendation for food and drug legislation in his annual message to Congress, which resulted in passage of the Pure Food and Drug Act (Public Law 59-384; 34 Stat. 768). The intent of the law was to prevent the manufacture, sale, and transportation of misbranded and adulterated foods and drugs. The passage of subsequent public health laws often followed several therapeutic tragedies. In 1937, the S.E. Massengill Co. introduced sulfanilamide dissolved in diethylene glycol. No drug safety testing was required by law at the time. The drug was promoted to treat streptococcal infections and caused deaths of more than 100 people in 15 states. This and similar incidents led to the enactment of the 1938 Food, Drug, and Cosmetic Act (FDCA) (Public Law 75-717; 52 Stat. 1040). The intent of the law was to prevent the manufacture, sale, and transportation of misbranded and adulterated foods and drugs. The passage of subsequent public health laws often followed several therapeutic tragedies. In 1937, the S.E. Massengill Co. introduced sulfanilamide dissolved in diethylene glycol. No drug safety testing was required by law at the time. The drug was promoted to treat streptococcal infections and caused deaths of more than 100 people in 15 states. This and similar incidents led to the enactment of the 1938 Food, Drug, and Cosmetic Act (FDCA) (Public Law 75-717; 52 Stat. 1040).

The law, which became effective in June 1939, differed substantially from the 1906 Act that it replaced. It extended coverage to include cosmetics and therapeutic devices. It required the predistribution clearance of new drugs for safety and provided authority to establish tolerances for potentially poisonous substances in foods and drugs. It added the sanctions of injunction and emergency permit control to the seizure and prosecution authority in the previous act. As the main purpose of the law was to prohibit the movement of mislabeled and adulterated food and drugs, it was extended to include cosmetics and therapeutic devices. It required the predistribution clearance of new drugs for safety and provided authority to establish tolerances for potentially poisonous substances in foods and drugs. It added the sanctions of injunction and emergency permit control to the seizure and prosecution authority in the previous act. As the main purpose of the law was to prohibit the movement of mislabeled and adulterated food and drugs, it was extended to include cosmetics and therapeutic devices. It required the predistribution clearance of new drugs for safety and provided authority to establish tolerances for potentially poisonous substances in foods and drugs. It added the sanctions of injunction and emergency permit control to the seizure and prosecution authority in the previous act. As the main purpose of the law was to prohibit the movement of mislabeled and adulterated food and drugs, it was extended to include cosmetics and therapeutic devices. It required the predistribution clearance of new drugs for safety and provided authority to establish tolerances for potentially poisonous substances in foods and drugs. It added the sanctions of injunction and emergency permit control to the seizure and prosecution authority in the previous act. As the main purpose of the law was to prohibit the movement of mislabeled and adulterated food and drugs, it was extended to include cosmetics and therapeutic devices. It required the predistribution clearance of new drugs for safety and provided authority to establish tolerances for potentially poisonous substances in foods and drugs. It added the sanctions of injunction and emergency permit control to the seizure and prosecution authority in the previous act. As the main purpose of the law was to prohibit the movement of mislabeled and adulterated food and drugs, it was extended to include cosmetics and therapeutic devices. It required the predistribution clearance of new drugs for safety and provided author...
section: Contemporary issues in donation and transfusion

The term “biological product” means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings. (PHSA Sec. 351(i))

As noted, regulatory approval of drugs and biologics in the United States is subject to federal law. Drugs are approved under Section 505 of the Food, Drug, and Cosmetic Act (21 U.S.C. 355), as amended. An order to approve an application is issued if none of the following applies: The investigations are found to be inadequate; the results either do not prove product safety or prove its unsafety; the data submitted as part of the application and other available information do not provide sufficient evidence of product safety and effectiveness; the methods, facilities, and controls used in manufacturing, processing, and packing are found to be inadequate to preserve the product’s identity, strength, purity, and quality; and the application lacks the required patent information. Although biologics are also considered to be drugs, because most of them meet the definition of the term drug in FDCA Section 201(g)(1) (21 U.S. C. 321), they are usually licensed under authority of Section 351 of the PHSA (42 U.S.C. 262), as amended. Under Section 351, which has been in effect since 1944, biologics license applications are approved following the applicants’ consent to the inspection of the facilities and on the basis of a demonstration that the products are safe, pure, and potent, and the facilities in which the biologics are manufactured pass an on-site inspection.

The FDCA of 1938 has been amended dozens of times. Major amendments include the FDA Modernization Act (FDAMA) of 1997, the Food and Drug Administration Amendments Act (FDAAA) of 2007, and the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012.

**FDA regulation of blood collection establishments**

**Overview**

Blood and blood components are used in the treatment of disease. Therefore, blood and blood components meet the definition of a drug in Section 201(g) of the FDCA; and blood products, including source plasma, must meet all statutory requirements of the FDCA. FDCA sections applicable to blood include Sections 201, Definitions; 301, Prohibited Acts; 501, Adulteration; 502, Misbranding; 510, Registration; and 704, Factory Inspection (see Ref. 26).

The fundamental principles of the regulation of blood collection establishments are to ensure the safety, effectiveness, and availability of blood and blood products; protect the health of the donors and recipients; and ensure that the blood collected is safe for transfusion or further manufacture (see Ref. 26). One of the means for assuring this is through the requirements for current good manufacturing practices (cGMPs). Applicable cGMP regulations are found in the US Code of Federal Regulations (CFR) within Title 21 Part 210, Manufacturing, Processing, Packing, or Holding of Drugs; Title 21 Part 211, Finished Pharmaceuticals; and 21 CFR 606a, Blood and Blood Components. Table 7.1 lists the subparts of 21 CFR Part 211 (cGMPs for finished pharmaceuticals), and Table 7.2 lists the applicable sections for blood and blood products in 21 CFR Parts 600–640.

The PHSA requires licensure for biological products in interstate commerce. In this regard, each package of a biological product is plainly marked; the biological product is required to be safe, pure, potent, and effective; the facility where the product is manufactured meets standards; and the applicant consents to inspection. Licensure
Table 7.1 21 CFR Part 211 cGMP for finished pharmaceuticals

- Subpart A: General Provisions
- Subpart B: Organization and Personnel
- Subpart C: Buildings and Facilities
- Subpart D: Equipment
- Subpart E: Control of Components and Drug Product Containers and Closures
- Subpart F: Production and Process Controls
- Subpart G: Packaging and Labeling Control
- Subpart H: Holding and Distribution
- Subpart I: Laboratory Controls
- Subpart J: Records and Reports
- Subpart K: Returned & Salvaged Drug Products

Table 7.2 21 CFR Parts 600–640: Applicable sections for blood and blood products

- 600: Biological products: general
- 601: Licensing
- 606: Current good manufacturing practice for blood and blood components
- 607: Establishment registration and product listing for manufacturers of human blood and blood products
- 610: General biological products standards
- 630: General requirements for blood, blood components, and blood derivatives
- 640: Additional standards for human blood and blood products

signifies FDA approval of product(s) and facility. It is intended to ensure the safety, effectiveness, and availability of blood and blood products, thereby allowing shipment of product(s) in interstate commerce. It also protects the health of the donor and recipients.

In applying the requirements of cGMP to a firm, the distinction between licensure and registration is more technical than real. Licensure is required to ship products in interstate commerce or internationally. Registration is required for all blood and tissue establishments, including those located in hospitals, that manufacture (collect, store, process, or distribute) blood components for transfusion or further manufacture. Registration requirements for manufacturers of human blood and blood products are outlined in 21 CFR Part 607; license requirements are in 21 CFR Part 601. Tissue for transplantation requirements are found in 21 CFR Part 1270. Elements of cGMP are listed in Table 7.3. The division into elements is arbitrary but is based on an analysis of commonality of the requirements of Title 21 as they apply to all aspects of blood center and hospital blood bank operations. Thus, it is irrelevant whether they are applied to blood collection or to infectious disease testing; each element is applicable for each discrete blood center operation. Because blood and plasma centers are required to follow their own standard operating procedures (SOPs), each SOP creates unique regulatory requirements for that center. From a regulatory standpoint, this concept is significant in that compliance standards and regulatory requirements are created by individual center SOPs. cGMP describes both the production methods used by blood centers to manufacture components and the manufacturing process controls in place. Each provision of a center’s SOPs must reflect the manufacturers’ instructions for licensed or approved systems used in the center.

Meticulous records of compliance with cGMP elements are required to assure both executive management and the FDA that a blood establishment’s manufacturing process is under control. Control, in this context, can be defined as compliance in every respect with the entire establishment’s manufacturing SOPs and FDA requirements. It is worth emphasizing that if a firm’s SOPs are more stringent than FDA requirements, it is not acceptable to deviate from the SOP, even if the FDA requirement is met, unless appropriate change control and reporting to FDA are carried out before the deviation. During inspections of blood centers, whether by the private sector or regulatory bodies such as the FDA, the overriding investigational concern is whether an establishment has control. Records should be designed to document control of manufacturing systems.

Management of SOPs lies at the heart of quality manufacturing and cGMP compliance. Although not required by the CFR, it is generally held that the Quality Assurance (QA) unit should organizationally be distinct from manufacturing to ensure its independence, and this de facto requirement appears in FDA guidances.10,11 In many blood centers, the director of the QA unit reports to the chief executive officer. All matters that relate to quality should funnel to a single person or group with broad knowledge of the entire blood center operation and access to the information necessary to assess the impact of proposed changes. These principles emphasize the importance with which the FDA views both the quality unit and SOPs. However, case law holds that upper management cannot avoid adverse consequences of noncompliance with regulatory requirements because a lower ranking employee is designated the authorized official.12 QA units can be deployed to enhance the quality of blood center operations in a variety of ways. They can assume responsibility for personnel training, especially in cGMP; maintain calibration and validation records; design validation protocols; and identify trends through statistical analysis. A well-directed QA unit can be of enormous value to both the authorized officials and the staff of the facilities in which it is established. However, QA unit staff are not the ideal staff to write SOPs, because they need to be the final approval authority, and their objectivity cannot be ensured when reviewing their own work.

Although internal audits are also not specifically required by regulations, procedures to detect problems are required and internal audits are an important means of ensuring that processes remain in control. Internal audits are considered confidential by the FDA and are not available to FDA investigators unless fraud is suspected or there appears to be an imminent threat to public health. The reason for this policy is to encourage audits that are complete and detailed with no information withheld. The FDA also respects supplier audits as confidential internal audit information. However, it is critical that the center have readily available SOPs for audits, schedules demonstrating that all elements of operations are reviewed regularly (at least annually), processes for ensuring and documenting corrective and preventive action and follow-up, and formal closure notices to complete the records. It is also essential...
that any deviations discovered in the course of audits be properly documented in records that are available to FDA investigators. The QA system must be assessed for effectiveness by management at regular intervals. Rigorous application of cGMP principles to the production processes of blood and blood components has greatly reduced, but not completely eliminated, risks associated with the transfusion of blood components. Fortunately, the availability of industrial models broadly applicable to blood centers has facilitated cGMP implementation.

Table 7.4 lists selected QA unit responsibilities.

**Inspections**

Facility inspectors are instructed that the facility must have knowledgeable staff, appropriate equipment, and adequate procedures to ensure that donors are screened and units are collected, stored, and shipped in accordance with FDA regulations. The establishment’s procedures must address donor screening; blood collection; unit identification; operation of all screening and collection equipment; handling of donor reactions; management of postdonation information reports; storage of product and supplies; quality control of reagents, supplies, and equipment; transport of collected units; and documentation and follow-up of any unexpected incidents. Inspections should include observations of the actual screening process and an examination of the physical layout of the facility to insure that there is limited public access to biohazardous areas, proper disposal of biohazardous materials, accessible restrooms and hand-washing equipment, and clean and organized storage areas. Supplies should be examined to make certain they are used within their expiration date.

As noted, biological products are regulated under the authority of Section 351 of the PHSA and under the FDCA as drugs or devices, with the exception of certain human cells, tissues, and cellular and tissue-based products (HCT/Ps) that are regulated solely under Section 361 of the PHSA (see 21 CFR 1271.10). Blood and blood products for transfusion are prescription drugs under the FDCA.


Apart from the requirement to report and investigate adverse reactions, as stipulated in 21 CFR 606.170, an organized error management process is not specifically required by the provisions of Title 21, although 21 CFR 606.171(c) mandates the reporting within 45 days of all biologic product deviations on released products. Table 7.5 provides a summary of the reporting criteria and examples of reportable and nonreportable events. Traditionally, 21 CFR 600.14 has always been interpreted to require licensed facilities to report promptly any error that may affect the safety, purity, or potency of the product, and it was understood that a system was needed for capturing these events consistently. The FDA has recognized the importance of this cGMP element in regulations finalized in 2000 (21 CFR 606.171). The rules are more broadly applicable to blood establishments than any preceding policies, although they are narrowly directed.13-14

The investigation and follow-up of deviations are critical to the successful improvement of blood center quality. Appropriate management of errors and deviations (accidents) forms the centerpiece of continuous improvement. Each blood center deviation should be treated as an opportunity to be used to improve center processes. All facilities must develop SOPs for reporting, managing, and correcting errors and deviations. These SOPs should form the centerpiece

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<th>Attributes of the Required Quality Unit</th>
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<tr>
<td>Responsibilities are described in writing.</td>
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<tr>
<td>Is independent of production.</td>
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<tr>
<td>Is involved in all quality-related matters.</td>
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<tr>
<td>Reviews and approves all quality-related issues.</td>
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<td>Has adequate analytic control facilities at its disposal.</td>
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**Quality Unit Responsibilities Should Include, but Not Be Limited to, the Following**

- Approve specifications.
- Approve test procedures, including process controls.
- Approve validation plans, protocols, or equipment.
- Review changes in product, process, or equipment, and determine if revalidation is required.
- Appropes specification changes, sampling plans, and test procedures.
- Approve sampling procedures.
- Approve reference standards.
- Conduct analytic investigations and evaluate results.
- Approve testing materials.
- Provide analytical reports.
- Approve or reject intermediates and active pharmaceutical ingredients manufactured, processed, packed, or held under contract by another establishment.
- Gather data to support retest dates (stability testing).
- Evaluate and approve contractors.
- Review batch records.
- Review complaints.
- Dispose of materials not meeting specifications.
- Dispose of materials returned to the establishment.
- Perform internal and external audits.
- Perform periodic assessments of procedures, policies, and responsibilities within the establishment’s manufacturing and control operations.

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<th>Examples of Nonreportable Biologic Product Deviations</th>
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<td>Transfusion errors occurred outside the blood facility.</td>
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<td>An error was corrected before distribution, and safety was not affected.</td>
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<td>Lookback, retrieval, or notification procedures were not followed.</td>
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<td>Donor protective measures were not met (age, colds, flu, etc.).</td>
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<tr>
<td>Previous donation records were not checked.</td>
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<tr>
<td>Labeling errors occurred that did not affect safety (short expiration, etc.).</td>
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<tr>
<td>Shipping paperwork contained errors.</td>
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<tr>
<td>Units were returned because of temperature deviations.</td>
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of both blood center staff training and continuous improvement. Error management efforts and results should be documented in the records of the quality unit. Monitoring corrective action outcomes to ensure effectiveness is an essential part of the system for addressing corrections.

Although error management systems are not defined in Title 21, some attributes of good systems have emerged both in blood centers and in industrial manufacturing establishments. They include:

1. Employees at all levels in the organization are encouraged to report errors. Punitive policies discourage reporting, and hence opportunities for systems improvements may be lost.
2. Employees involved in the process in which an error was made should be involved with the investigation and resolution of the error and process change. It is essential that the investigation be sufficient to determine the underlying root cause for the error rather than identifying mere “symptoms” of the root cause. The FDA also requires that staff be educated concerning the effect their errors have or potentially have on product quality; that is, it is required that they understand how their responsibilities have an effect on ensuring that only safe products are released.
3. Confirmation of the effectiveness of the corrective action is vital to ensure that the improved process continues to yield the expected results. Postchange monitoring is essential, and long-term evaluation should be performed at appropriate intervals (e.g., 3–6 months after a process improvement is completed).

CBER conducts a wide range of compliance and surveillance activities during the “life cycle” of biological products. These include:

- Conducting prelicense and preapproval inspections as well as postlicensure and postapproval 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 HCT/P deviation reports;
  - Investigations into transfusion- and donation-related fatalities and other adverse events; and
  - Product recalls.
- Monitoring reports of biological product shortages.
- Initiating regulatory action to address noncompliance with FDA laws and regulations.
- Monitoring of research conducted on biological products and assessing the protection of the rights, safety, and welfare of human research subjects and the quality and integrity of research data.
- Monitoring import and export activities.
- Reviewing product advertising and promotional labeling.

Device regulatory controls

All classes of medical devices are subject to what are known as general controls. General controls are the basic provisions of the May 28, 1976, Medical Device Amendments to the FDCA. They provide the FDA with the means of regulating devices to ensure their safety and effectiveness. General controls in the FDCA apply to all medical devices. They include provisions that relate to adulteration; misbranding; device registration and listing; premarket notification; banned devices, including repair, replacement, or refund; records and reports; restricted devices; and good manufacturing practices.

Class I devices are subject to general controls and are typically exempt from submission of a premarket 510(k) notification. They are viewed as posing the lowest risk to the patient and/or user. Class II devices are subject to what are known as special controls in addition to the general controls provision of the FDCA. Special controls may include compliance with a recognized standard, warning statements in the instructions for use, specific performance requirements, and/or other controls necessary to ensure a reasonable assurance of safety and effectiveness. Class II devices typically require FDA clearance of a premarket 510(k) notification to permit the device to be marketed and sold in the United States.

Class III devices are viewed as presenting a higher level of risk. They may be first-of-a-kind devices for which general and special controls are not adequate to ensure safety and effectiveness. Class III devices require FDA approval in the form of a premarket approval application prior to marketing, as well as compliance with device general controls.

The 510(k) premarket notification is a submission made to the FDA to demonstrate that the device to be marketed is at least as safe and effective as (i.e., is substantially equivalent to) a legally marketed Class I or II device of that same generic type. When determined to be substantially equivalent, the subject device may be legally marketed and sold in the United States.

The legally marketed device to which substantial equivalence is determined is known as the predicate device. A predicate device can be a preamendments device (legally marketed prior to the May 28, 1976, Medical Device Amendments to the FDCA) or a postamendments device that is, or was, legally marketed in the United States following the device amendments. A claim of substantial equivalence does not mean the new device must be identical to the predicate device. Substantial equivalence is based on a comparative assessment with respect to intended use, design, energy used or delivered, materials, performance, safety, effectiveness, labeling, biocompatibility, standards, and other applicable characteristics that would demonstrate the device is as safe and effective as the predicate device.

Blood establishment computer software

On December 3, 2014, the Blood Products Advisory Committee was seated as a device classification panel. In open session, the panel discussed the appropriate device classification of blood establishment computer software (BECS) and accessories to BECS. BECS is currently subject to the 510(k) premarket notification provisions of the FDCA. FDCA Section 513 established the risk-based device classification system for medical devices. BECS and BECS accessories have not been classified under this statutory provision. Currently, these devices are regulated as unclassified devices, subject to 510(k) premarket notification requirements. At this Blood Products Advisory Committee meeting, the committee also voted to recommend that BECS be designated as Class II devices.

Since the device amendments of May 28, 1976, BECS and BECS accessories have been found substantially equivalent to a device that was legally marketed prior to May 28, 1976 (i.e., a preamendments device). The preamendments devices include Advanced Medical Systems, a computer-based Blood Bank Management System used to perform compatibility testing, and the American National Red Cross (ANRC) computer-based Donor Deferral Register, which is used to determine temporary or permanent disqualification of donors.

Medical device data systems, regulated under Section 880.6310, are Class I medical devices exempt from 510(k) premarket notification, and were not included for consideration under the BECS and BECS accessories classification.
FDA Structure: Office of Blood Research and Review (OBRR)

FDA regulatory review of devices, drugs, and biologics is conducted by the Center for Drug Evaluation and Research (CDER), the Center for Devices and Radiologic Health (CDRH), and the Center for Biologics Evaluation and Research (CBER). All submissions and applications (including combination products) are assigned to one center for review. The OBRR within CBER is typically assigned biologics review (other than vaccines and cell, tissue, and gene therapies). Within OBRR, four divisions manage the review process: the Division of Hematology Clinical Review (e.g., clinical biologics and certain recombinant and transgenic analogs), the Division of Hematology Research and Review (e.g., chemistry, manufacturing, and controls), the Division of Emerging and Transfusion Transmitted Diseases (e.g., donor infectious disease testing), and the Division of Blood Components and Devices (e.g., licensing of blood establishments, immunohematology devices, and donor qualification). Policy (e.g., guidances) is developed by all four divisions along with the OBRR leadership. Numerous guidance documents (some previously titled as guidelines but now referred to as guidance) have been issued by OBRR and may be found at: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/default.htm

Guidances represent the FDA’s current thinking on a topic. They do not bind the FDA or manufacturers to any course of action. Alternative approaches are acceptable, if they satisfy the requirements of the applicable statutes and regulations.

Regulation and accreditation of hospital transfusion services

Overview

The Clinical Laboratory Improvement Act and Amendments (CLIA) stipulate requirements for the qualifications of staff who perform or supervise the testing conducted within a transfusion service. AABB standards and FDA cGMP regulations also require that the transfusion service have a process for personnel training and competency evaluation.

Written SOPs are required by the FDA in 21 CFR 606.100. A system must be in place to ensure process control for the validation of processes and procedures, introduction and change of processes and procedures, proficiency testing, quality control, and the use of materials and other aspects of performance of procedures. A defined system of documentation and record retention is required by 21 CFR 606.140 and 21 CFR 606.160 and also by AABB standards.

AABB standards state that the blood bank or transfusion service shall have a medical director who is a licensed physician and qualified by education, training, and/or experience. The medical director shall have responsibility and authority for all medical and technical policies, processes, and procedures—including those that pertain to laboratory personnel and test performance—and for the consultative and support services that relate to the care and safety of donors and/or transfusion recipients. The medical director may delegate these responsibilities to another qualified physician; however, the medical director shall retain ultimate responsibility for the medical director duties. However, the standards do not require that overall executive management be under the control of the medical director. The Joint Commission also does not require that the overall direction of the laboratory be performed by a physician but does state that “a pathologist or physician qualified in immunohematology, hemotherapy, and blood banking directs blood transfusion services” (HR 1.15). This often excludes the medical director from authority in personnel (other than policies and procedures), purchasing, budgeting, and other administrative matters. The regulation states that the laboratory director must be a doctor of medicine or doctor of osteopathy licensed in the state where the laboratory is located (42 CFR 493.1443).

The FDA, AABB, and the College of American Pathologists (CAP) all have requirements regarding the evaluation and reporting of adverse effects of blood transfusion. The FDA requires that records be maintained of any reports of adverse reactions to blood transfusion and that a thorough investigation of each reported reaction be conducted. All transfusion services must report deaths confirmed as being caused by a transfusion. The applicable regulation (21 CFR 606.170(b)) reads,

When a complication of blood collection or transfusion is confirmed to be fatal, the Director, Office of Compliance and Biologics Quality, CBER, must be notified by telephone, facsimile, express mail, or electronically transmitted mail as soon as possible. A written report of the investigation must be submitted to the Director, Office of Compliance and Biologics Quality, CBER, by mail, facsimile, or electronically transmitted mail (for mailing addresses, see 600.2 of this chapter), within 7 days after the fatality by the collecting facility in the event of a donor reaction, or by the facility that performed the compatibility tests in the event of a transfusion reaction. (http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/default.htm)

The AABB requires that a transfusion service have a process for the detection, reporting, and evaluation of suspected complications of transfusion and that all suspected transfusion complications are evaluated and reviewed by the medical director. The CAP requires that all transfusion reactions or incidents be reported immediately to the laboratory (TRM.41750), that documented procedures exist for actions to be taken in the event of a transfusion reaction (TRM.41700), and that the results of the investigation be recorded in the patient’s chart (TRM.42050).

Further aspects of FDA regulations and accreditation requirements of AABB, the Joint Commission, CAP, and other accrediting organizations are described in the “FDA Regulation of Hospital Transfusion Services” section.

FDA regulation of hospital transfusion services

Total quality systems have been required for blood banks and transfusion services since 1975 when the FDA incorporated cGMP into the Code of Federal Regulations. Although the regulations were aimed primarily at blood centers, many of the provisions apply to transfusion services as well. In 1995, the Center for Biologics Evaluation and Research produced a Guidance to assist establishments in developing quality programs in accord with applicable regulations.

In laboratories where clinical samples are tested, Clinical Laboratory Improvement Amendments (CLIA) requirements for quality control (QC), listed at 42 CFR Part 493, must also be followed. All personnel shall be trained in its application. The quality system shall be under the supervision of a designated person who reports to executive management. For reagents for which there are no QC requirements in Title 21, the QC testing described in the manufacturer’s package insert must be followed. It is mandated that “each laboratory establish and follow written policies and procedures for a comprehensive quality assurance program. . . . The laboratory’s quality assurance program must evaluate the effectiveness of its policies and procedures; identify and correct problems. . . . All quality assurance activities must be documented.”

For any hospital QA program to work successfully, physicians must give priority to the process, and hospital administration must
make the necessary resources available to ensure its development, implementation, refinement, and continuation.

The FDA requires that errors or accidents affecting the safety, quality, integrity, purity, or potency of a blood product be reported, and this requirement extends to both licensed blood establishments and transfusion services (21 CFR 606.171). However, this statutory authority extends only to the blood product itself, and does not permit FDA oversight of the actual transfusion episode. Although FDA MedWatch provides a voluntary venue for reporting adverse events, most hospitals do not voluntarily report errors to MedWatch (http://www.fda.gov/Safety/MedWatch/default.htm). Therefore, the FDA’s purview extends only as far as the laboratory door, and there is no requirement to report a patient misidentification error unless it results in a death. (A transfusion-related death, however, must be reported to CBER within 24 hours.) To give an example of this regulatory lacuna, the following example suffices: Failure to irradiate a unit of RBCs that was so ordered results in an FDA reportable error. Transfusion of the same unit to the wrong patient does not result in a reportable error unless the patient dies. When a death occurs that may be related to a blood transfusion, 21 CFR 606.170 applies as described above.

The FDA considers establishments that perform certain activities that it defines as manufacturing steps to be hospital blood banks, which are required to register annually using Form FDA 2830. A hospital blood bank is an entity that routinely collects or processes whole blood or blood components. These components may be collected by means of apheresis or prepared from whole blood. Processing includes freezing, deglycerolizing, washing, irradiating, rejuvenating, or removing leukocytes from components. However, the collection and processing of blood and blood components in an emergency situation, therapeutic collection of blood or plasma, preparation of recovered plasma for further manufacture, or preparation of red blood cells for transfusion do not require registration [21 CFR 607.65(f)].

Because blood and blood components are drugs under the Federal FDCA, the FDA cGMP regulations (21 CFR Parts 210 and 211) apply to the manufacture of these products. In addition, cGMP regulations for blood and blood components exist in 21 CFR Part 606. All of these regulations apply to FDA-defined hospital blood banks. FDA registration allows the agency to plan and perform routine cGMP inspections.

Although the FDA does not routinely inspect hospital transfusion services, these services also engage in manufacturing in the view of the FDA, because compatibility testing, blood storage, labeling, and recordkeeping are considered steps in the manufacturing process. Thus, transfusion services are also subject to cGMP regulations. Inspection of hospital transfusion services is overseen by the Centers for Medicare and Medicaid Services (CMS) through a 1980 memorandum of understanding with the FDA that addresses inspection of these establishments. In an effort to reduce duplication of inspections, it was agreed that inspection of hospital transfusion services that are approved for Medicare reimbursement and that engage in compatibility testing but that neither routinely collect nor process blood components would be subject to inspection by the CMS. This agreement pertains to responsibility for inspection only. No statutory authority transferred between the agencies. As part of the agreement, the CMS adopted FDA regulations in 21 CFR Part 606 titled "Current Good Manufacturing Practice for Blood and Blood Components" and 21 CFR Part 640 titled "Additional Standards for Human Blood and Blood Products." These are the FDA requirements that have been incorporated into the CLIA regulations. Observations made by the CMS may be communicated to the FDA, which has the authority to directly inspect a hospital transfusion service.

All transfusion services, registered or unregistered and regardless of FDA nomenclature, must also comply with the regulations in 42 CFR Part 493 in accord with CLIA 1988. For the purposes of CLIA certification, CMS retains responsibility for inspection of all transfusion services.

Many transfusion services may not be surveyed directly by the CMS. Some are in an exempt state or have been accredited by an organization that has been granted deemed status (discussed in the subsections below on AABB, the Joint Commission, and CAP).

**FDA and transfusion service error reporting**

Both registered and unregistered blood establishments, including transfusion services, must report errors and accidents in manufacturing to the FDA. Manufacture means “the collection, preparation, processing or compatibility testing by chemical, physical, biological, or other procedures of any blood product” and includes “manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term includes packaging, labeling, repackaging or otherwise changing the container, wrapper, or labeling of any blood product package in furtherance of the distribution of the blood product from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer” [21 CFR 607.3(d)]. Errors and accidents (termed biologic product deviations) and unexpected events in manufacturing that can affect the safety, purity, and potency of a product are deemed reportable (21 CFR 606.171 and 21 CFR 600.14). Form FDA 3486 is used for reporting these deviations. The requirement to report applies only to manufacturing errors and not to transfusion errors occurring in clinical areas outside of the transfusion service. Table 7.5 provides a summary of the reporting criteria and examples of reportable and nonreportable events.

Deviations must be reported only if the product was distributed. This is defined as having left the control of the establishment. If the product was not distributed, the incident still must be recorded in internal records [21 CFR 606.160(b)(7)(iii)]. If the product was distributed, a report must be submitted to CBER within 45 calendar days from the date information is acquired that reasonably suggests a reportable event occurred. The incident must also be recorded [21 CFR 606.160(b)(7)(iii) and 21 CFR 211.198] and investigated [21 CFR 606.100(c) and 21 CFR 211.192]. The FDA has stated that the purpose of this reporting system is to provide early warning of faulty processes as an indicator for potentially immediate problems that may be related to recalls and as surveillance for improving training and establishing guidance.

The deviation or unexpected event must occur in the facility or another facility under contract with the controlling facility. If a facility under contract to the hospital blood bank or transfusion service is responsible for a deviation, the hospital blood bank or transfusion service is responsible for reporting the problem if the product is distributed. The contract facility must perform an investigation but is not required to report. For example, if a test laboratory under contract to a hospital blood bank fails to provide viral marker testing and the unit is subsequently distributed, the blood bank must report this. If a transfusion service discovers that a unit is mislabeled with an extended outdate, the transfusion service must notify the blood center responsible for reporting to the FDA. The transfusion service would report this incident only if it further distributed the unit without correcting the label.
Deviations and unexpected events occurring within the facility or a facility under contract must be reported if they may affect the safety, purity, or potency of either licensed or unlicensed products that have been distributed. However, as noted, an error occurring after a product has left the facility need not be reported. Examples of events that would not require a report include a unit not being held at the appropriate temperature before transfusion after release from the blood bank, transfusion of a unit to the wrong patient, or failure by hospital staff to use a filter issued by the transfusion service. Reportable, unexpected events may occur even if all established procedures are followed within the transfusion service itself. An example of this would be a patient sample used for compatibility testing that was collected from the wrong patient.

The failure to report an event to the FDA within 45 days is not a reportable deviation, although a failure to report could be cited by an inspector as violative of an establishment’s procedure.

A recordkeeping deviation, such as failure to include the signature of the person preparing the unit in component preparation, would not be reportable, because it would not affect the safety, purity, or potency of the product. A unit labeled with a shortened expiration date would also not be reportable, nor would a unit drawn too soon after the last donation. In addition, it would not be a reportable event if an allogeneic unit were issued when autologous blood was available. However, a unit labeled with an extended expiration date would be a reportable deviation. In summary, a deviation or unexpected event is reportable if all of the following criteria are met:

- It was associated with manufacturing.
- It occurred in the facility or at a contract facility.
- It may have affected the safety, purity, or potency of the product.
- The facility had control over the product.
- The product was distributed.

Table 7.6 presents a synopsis of the final rule on the reporting of biological product deviations.

### FDA and defective product reporting

If the transfusion service determines that the transfused blood or blood component was at fault in causing the adverse event, a summary of the transfusion services’ investigation and conclusions must be sent to the manufacturer or blood collection establishment, who must then maintain such copies [21 CFR 606.170(a)].

### AABB

The AABB assessment incorporates evaluation of the quality system at an institution and of each operational system.15 The quality system assessment is based on the same criteria for every facility. The operational systems, however, are identified by the activities performed within an individual facility. This voluntary assessment is conducted every two years. AABB Standards for Blood Banks and Transfusion Services apply equally to member blood centers and transfusion services.15 AABB policy includes the provision that although some requirements are based on the FDA’s regulations, a committee with international expertise can review requests for variance from facilities outside the United States that involve a departure from US regulations.

In addition to standards and accreditation programs for blood banks and transfusion services, AABB has standards and accreditation programs for Cellular Therapy Services; Immunohematology Reference Laboratories; Molecular Testing for Red Cell, Platelet, and Neutrophil Antigens; Relationship Testing Laboratories; Perioperative Autologous Blood Collection and Administration; and a Patient Blood Management Program.

As noted above, AABB standards state that the blood bank or transfusion service shall have a medical director who is a licensed physician and qualified by education, training, and/or experience.15

In May 2014, AABB was granted deemed status for CLIA to meet CMS requirements. This status means that the CMS has determined that the AABB accreditation process provides assurance that facilities meet or exceed conditions required by federal law and regulations. A laboratory accredited by the AABB that designated AABB as its CLIA provider does not need to be inspected routinely by the CMS. However, these facilities are subject to validation surveys and surveys performed in response to complaints to the CMS or state agencies on behalf of the CMS. This deemed status applies to the following AABB Standards: Blood Banks and Transfusion Services; Cellular Therapy Services; Immunohematology Reference Laboratories; and Molecular Testing for Red Cell, Platelet, and Neutrophil Antigens.

The AABB works with CAP to coordinate the AABB assessment and CAP inspection at the same time if the institution falls under both AABB and CAP, but the activities are still separate and each organization makes their own determination of accreditation. AABB does not work with the Joint Commission in the area of accreditation. Many hospital transfusion services, especially if they are in smaller hospitals, are not members of AABB, but nearly all fall under the Joint Commission.

### The Joint Commission

Since 1961, review of blood use has been an element of the accreditation process of the Joint Commission.21 By 1970, the Joint Commission required review not only of blood utilization but also of transfusion reactions. The 1986 Standards were more comprehensive, mandating review of transfusion policies and procedures, ordering practices, and adequacy of the transfusion service generally. The standards also required evaluation of all transfusions.22 After repeated blood utilization reviews consistently documented appropriate blood use, sampling became acceptable. Although only a minority of hospitals complied with this requirement for 100% evaluation, this standard was nevertheless the driving force behind blood utilization review in the United States.

Since 1991, the Joint Commission has made a series of modifications to this standard, and 100% review is no longer required. The actual number of transfusions to be reviewed is not mandated, although recommendations are provided. Additionally, as part of an effort to reduce medical errors, the Joint Commission has developed National Patient Safety Goals; the number one goal is to "improve

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<tr>
<th>Table 7.6 Synopsis of final rule on reporting biological product deviations</th>
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<td>• The rule applies to all establishments: donor centers, blood banks, transfusion services.</td>
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<td>• Reporting time is not to exceed 45 days.</td>
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<td>• Report by mail: Director, Office of Compliance and Biologics Quality, Food and Drug Administration, 10993 New Hampshire Avenue, Silver Spring, MD 20993; or electronically via CBER’s website: <a href="http://www.fda.gov/cber/biodev.htm">www.fda.gov/cber/biodev.htm</a>.</td>
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<tr>
<td>• If the answers to the questions below are affirmative, the event is reportable:</td>
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<tr>
<td>• Was the event associated with manufacturing?</td>
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<td>• Did the deviation affect safety, purity, or potency?</td>
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<td>• Did it occur in a licensee’s or a contract facility?</td>
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<tr>
<td>• Did the facility have control over the product when the deviation occurred?</td>
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<td>• Was the product distributed?</td>
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the accuracy of patient identification.” Although this safety goal was implemented because of the recognition that patient misidentification affects all aspects of medical care, its relevance to transfusion therapy was clearly recognized by the Joint Commission. One of the implementation expectations for the goal clearly states that “Two patient identifiers are used when administering medications or blood products” and “when collecting blood samples . . . for clinical testing.” There are also explicit statements that specimens collected from a patient must be labeled at the bedside and that the patient’s location may not be used as an identifier. The patient safety goal is reiterated in the body of the standards themselves.

The Joint Commission views transfusion services from a dual perspective. Standards are devoted both to the entire process of blood transfusion from blood ordering through infusion and to the laboratory procedures and practices. Two accreditation manuals have standards regarding blood transfusion. The Comprehensive Accreditation Manual for Hospitals 23 provides specific standards for hospitals that transfuse and monitor blood components. The Comprehensive Accreditation Manual for Pathology and Clinical Laboratory Services 24 contains technical standards that are patterned after the CLIA 1988 requirements and AABB standards. This dual approach provides the Joint Commission with the opportunity to assess the entire spectrum of clinical and laboratory blood transfusion practices. The Joint Commission Laboratory Accreditation Program has deemed status for CLIA to meet CMS requirements.

Standards related to blood transfusion are included in the Comprehensive Accreditation Manual for Hospitals in those sections addressing the medical staff, provision of care, treatment and services, management of information, improvement of organization performance, environment of care, and sentinel event review.23 Among the salient standards, MS 3.10 states that the medical staff must have “a leadership role in hospital performance improvement activities to improve quality of care.” One of the specific elements of performance for MS 3.10 requires that the medical staff be “actively involved in measurement, assessment and improvement in the use of blood and blood components.” A similar provision, PI 1.10 in the section on performance improvement, states that the hospital must “collect data to monitor its performance,” and this requirement includes collecting data on blood and blood product use. PI 2.20 requires that “undesirable patterns and trends in performance are analyzed,” including all confirmed transfusion reactions. In addition, hemolytic transfusion reactions involving the administration of blood having major blood group incompatibilities are identified as reviewable sentinel events subject to specific review by the Joint Commission.

The Comprehensive Manual for Laboratory and Point of Care Testing 16 contains more specific provisions governing transfusion services. HR 1.15 requires that the director of the blood bank must be a physician, either a pathologist or other physician qualified in immunohematology and hemotherapy. Sections QC 5.10 through QC 5.260 provide guidance on what the Joint Commission regards as critical elements comprising an acceptable transfusion service. Section QC 5.10 requires that the transfusion service have written policies and procedures that “are acceptable in format, content, review process and availability.” These policies and procedures must be consistent with AABB standards, and must be reviewed annually. There must also be policies and procedures governing transfusion reactions and adverse events. Every adverse event must be evaluated by the medical director and documented in the patient’s medical record.

Accreditation by the Joint Commission is voluntary.

College of American Pathologists
CAP has an established accreditation program for transfusion services.18,25,26 This program examines pre-analytical, analytical, and post-analytical aspects of quality management in the laboratory. These include the performance and monitoring of general quality control, test methodologies and specifications, reagents, controls and media, equipment, specimen handling, test reporting and internal performance assessment, and external proficiency testing. In addition, personnel requirements, safety, document management, and other administrative practices are included in the inspection process. The CAP laboratory accreditation program expects a participant laboratory to demonstrate that it is in compliance with the CAP standards for laboratory accreditation. These standards relate to requirements for laboratory direction, physical facilities and safety, quality control and performance improvement, and inspection. Assessment of whether a laboratory meets the standards is accomplished through a series of checklists. Any applicable question that cannot be answered “yes” is considered a deficiency and must be corrected within 30 days with the submission of supporting documentation for accreditation to be achieved. The inspector does not grant or deny accreditation, but makes a recommendation. The accreditation decision is made by the CAP Accreditation Committee. In addition to the on-site inspection program, the CAP laboratory accreditation program monitors the proficiency testing performance of its participant laboratories. The CAP has deemed status with the Joint Commission and for CLIA to meet CMS requirements. As requested, CAP assesses hospital blood banks and transfusion services as well as blood collection establishments every two years.

Inspection of transfusion services is not limited to the contents of the Transfusion Medicine Checklist, but includes the All Common Checklist (COM) and all applicable portions of the Laboratory General Checklist (GEN). All sections of the laboratory must be familiar with and in compliance with the requirements of the COM and GEN Checklists. The Transfusion Medicine checklist contains the following: "Note: Many of the requirements in this Checklist reflect United States regulatory requirements, particularly those of the US Food and Drug Administration (FDA). These requirements may not be applicable in other countries for purposes of CAP accreditation."18

Transfusion Medicine Committee
A clinical staff committee concerned exclusively with practices and policies related to transfusion and the transfusion service is not mandated by federal regulation, the Joint Commission, or other accreditation entities. However, it has become routine to have such committees in most hospitals because a standing transfusion committee is an efficient way of meeting QA and peer review requirements.27 In fact, one of this committee’s principal activities in many institutions has been the utilization review of transfusion: both overtransfusion and undertransfusion. Assessment of transfusion practices has the potential to enhance the knowledge and judgment of healthcare professionals; provide significant information about patient care; reduce the risk of litigation; decrease costs; ensure compliance with regulatory and accreditation requirements; conserve the blood supply; provide an opportunity to demonstrate quality and value to the public; and help create, sustain, and document excellence in patient care. Many committees have also been engaged in developing informed consent practices for
transfusion as well as policies related to “lookback” to find patients who may have previously been infected by a blood transfusion at the committee’s institution.

This committee typically reports to the healthcare evaluation office or committee, or directly to the medical policy committee of the institution.

Conclusion: US structure and regulations

FDA and the voluntary accrediting agencies seek to advance and protect public health. Federal regulations that carry the force of law, federal guidelines that contain nonbinding recommendations, and voluntary accreditation standards issued by the organizations addressed in this chapter are the instruments used to achieve these goals. Blood donor qualification and the collection of blood and blood components as well as their processing, storage, transport, and subsequent manufacturing at hospital transfusion services are FDA-regulated activities to which certain biologic and drug laws apply.

Although blood components typically represent only approximately 1% of a large hospital’s budget and less in smaller hospitals, transfusion is at once a life-saving and potentially life-threatening procedure. The regulations, guidelines, and standards are crafted so that compliance by the affected institutions is feasible while providing the greatest protection possible to blood donors and patients.

International perspective on ensuring blood and blood product safety and availability

From a global perspective, WHO, the European Union (EU), the Council of Europe (CoE), and the FDA are the most prominent organizations that develop guidance documents, regulations, directives, and standards, used nationally or internationally to ensure the quality, safety, efficacy, and availability of blood and blood products. Although these organizations do not co-develop their regulations, they do collaborate on common initiatives, comment on each other’s public documents, and exchange ideas, all of which promotes a general convergence of their regulatory and advisory activities. The information and standards that these organizations provide are employed by many developed and developing countries to establish their own national blood programs. International trade associations, patient and professional organizations, and professional societies also contribute to global blood and blood product safety. In this section, we describe the programs and the organizational structures related to blood products of WHO, the EU, the CoE, and the FDA; and cite other major international organizations that advance global blood and blood product safety and availability.

WHO programs for blood and blood component transfusion safety

WHO is the authority within the UN system that is responsible for the coordination of health policy. It has a mandate for “providing leadership on global health matters, shaping the health research agenda, setting norms and standards, articulating evidence-based policy options, providing technical support to countries and monitoring and assessing health trends.” WHO is in the forefront of providing guidance for safe blood collection and transfusion. “The objective of the WHO program on Blood Transfusion Safety is to ensure provision of universal access to safe, quality and efficacious blood and blood products for transfusion, their safe and appropriate use, and also ensuring blood donor and patient safety.” WHO has a 50-year history of involvement in improving blood safety and availability. In 1975, a World Health Assembly resolution urged member states to promote the development of national blood transfusion services based on voluntary non-remunerated blood donations and to take other actions to promote and protect the health of blood donors and recipients of blood and blood products. These objectives are further elaborated in WHO’s strategic directions for 2008–2015 to: build a conducive political, social, and economic environment for the effective integration of sustainable national blood programs in health systems; respond to country needs to enhance national blood programs and improve clinical transfusion practice; build effective collaboration and partnerships for coordinated action; and strengthen systems for assessing, surveillance, vigilance, alerting, monitoring, and evaluating.

WHO has developed an extensive program to promote access to safe blood transfusion products, particularly to address the needs of less developed and transitional countries. This includes giving advice on improving blood systems by establishing a national blood system recognized through a national blood policy. Functions of the national blood system should include “policy formulation and standard setting, strategic and operational planning, provision of sufficient resources and national coordination and management to ensure an adequate supply of blood and blood products and safe clinical transfusion.”

WHO recommends the implementation of a quality system that “provides a framework within which activities are established, performed in a quality-focused way and continuously monitored to improve outcomes.” The risk associated with blood transfusion can be significantly reduced through the introduction of quality systems, external quality assessment, and education and training for staff.

Other programs supported by WHO include voluntary blood donation, donation testing, blood processing, proper clinical use of blood transfusion products, and hemovigilance.

Implementation of WHO programs for access to safe blood transfusion

WHO has established a number of collaborations and partnerships to share knowledge, coordinate technical support to increase blood donations, support blood system strengthening, and promote universal access to blood transfusion. One means that WHO uses to coordinate activities related to blood is through the work of WHO Collaborating Centers (WCCs) on Blood Transfusion Safety and Blood Products, whose members currently (2014) include Iran, Thailand, the United Kingdom, China, Slovenia, Brazil, Tunisia, and Germany.

Another WHO partnership is through the WHO Global Safety Network comprised of members of the WHO Expert Advisory Panel on Blood Transfusion Medicine, the WCCs on Blood Transfusion, nongovernmental officials in official relations, key developmental and implementing partners for blood safety, WHO regional focal points for blood safety, and WHO Blood Transfusion Safety staff. This group shares information from the WCCs and develops mechanisms of working together to enhance WHO strategies and objectives in the area of blood transfusion safety.

In 1998, WHO established a Global Data Base on Blood Safety to address global concerns about the availability, safety, and accessibility of blood for transfusion. The database reports the number of blood transfusions and donations in countries throughout the world, and provides information that can be used to assess where deficiencies lay and identify where progress is being made. A fact
In low-income countries, up to 65% of blood transfusions are given to children under five years of age; whereas in high-income countries, the most frequently transfused patient group is over 65 years of age, accounting for up to 76% of all transfusions.

Blood donation rate per 1000 population in high-income countries is 36.8 donations; it is 11.7 donations in middle-income countries, and 3.9 donations in low-income countries.

An increase of 8.6 million blood donations from voluntary unpaid donors has been reported from 2004 to 2012. In total, 73 countries collect over 90% of their blood supply from voluntary unpaid blood donors; however, 72 countries collect more than 50% of their blood supply from family/replacement or paid donors.

Only 43 of 156 reporting countries produce plasma-derived medicinal products (PDMPs) through the fractionation of plasma collected in the country, whereas the majority of the other 113 countries import PDMPs from abroad.

WHO QA and safety programs for blood products and related biologicals

In addition to programs focused on ensuring safe blood components for transfusion, WHO has an interest in providing technical guidance and QA tools to regulatory authorities, national control laboratories, and manufacturers to support implementation of quality and safety systems for the production and control of blood products and related in vitro diagnostic devices worldwide.

Input for the development of these tools is provided by technical experts from academia, industry, national regulatory authorities, professional societies, and WHO’s Collaborating Centers for Biological Standards and Standardization (i.e., the National Institute of Biological Standards and Control [NIBSC], United Kingdom; the Paul Ehrlich Institute [PEI], Germany; and the Center for Biologics Evaluation and Research [CBER], Food and Drug Administration [FDA], United States).

As an example of these resources, WHO has issued a document entitled Assessment Criteria for National Blood Regulatory Systems to assist “capacity building of national regulatory authorities for the regulation of blood and blood products. The document is intended to help Member States identify gaps and priorities when developing capacity building programs, and to support the introduction of regulation of blood products.” This document outlines “elements and functions which may support the creation of an appropriate blood regulatory system where none exists so far, and which may also be used as a tool to assess strengths and gaps of established systems.” It “identifies the essential elements and core regulatory functions that should be present in an effective national regulatory authority to assure the quality, safety and efficacy of blood and blood products, as well as associated substances and medical devices including in vitro diagnostics.”

In addition to this document, WHO has produced a series of technical reports that give guidance on topics such as GMPs for blood establishments; recommendations for the production, control, and regulation of human plasma for fractionation; and guidelines on viral inactivation and removal procedures intended to assure the viral safety of human blood plasma products.

Major WHO advisory groups relevant to blood product safety, quality, and standardization

The Expert Committee on Biological Standardization (ECBS) and the WHO Blood Regulators Network (BRN) are two advisory groups associated with WHO whose work directly promotes blood product safety and quality.

ECBS was established in 1947 to provide detailed recommendations and guidelines for the manufacturing, licensing, and control of blood products and related in vitro diagnostic tests, biotechnology products, and vaccines along with the establishment of WHO Biological Reference Materials. The ECBS meets annually and reports directly to the Executive Board, the executive arm of the World Health Assembly.

Members of the ECBS are scientists from National Regulatory Agencies, academia, research institutes, and public health bodies. The decisions and recommendation of the committee are based entirely on scientific principles and considerations of public health.

Written guidelines and recommendations submitted to the ECBS are drafted through a consultative process during which WHO brings together experts from around the world on a given topic.

Written guidelines and recommendations describe procedures for the manufacture and quality control testing of biological medicinal products to ensure safe and effective products. Guidelines provide more general information on a range of topics of interest to National Regulatory Authorities (NRAs) and manufacturers, whereas recommendations establish the technical specifications for manufacturing and quality control of specific products. By adopting these guidance documents in their pharmacopoeias or equivalent legislation, national governments ensure that the products produced and used in their country conform to current international standards. Regulatory guidance documents also advise NRAs and manufacturers on the control of biological products, with the aim of establishing a harmonized regulatory framework for products moving in international markets.

In addition to guidelines and recommendations, WHO has played a key role for over 50 years in establishing the WHO Biological Reference Materials necessary to standardize biological materials. Reference materials are required to standardize potency, purity, and identity measurements for complex biological materials. “The WHO Biological Reference Materials provide a global standard against which experimental values can be compared and expressed, thereby allowing direct comparisons between products and measurements across different methodologies and assays in use around the world.” Reference materials are established through scientific studies involving the establishment, discontinuation and replacement of the WHO Biological Reference Materials as well as on the adoption of Guidelines and Recommendations. The TRS are available electronically as well as publications, and relevant topics can be searched either by the TRS number or by topic.

The WHO BRN is a group whose work helps to ensure blood product safety in a timely manner. BRN was established in 2006 and is composed of leading international regulatory authorities that have responsibility for the regulation of blood, blood products, and related in vitro diagnostic (IVD) devices.

Members of the BRN exchange information and opinion on blood-related issues. The BRN focuses on scientific assessment of current and emerging threats to the safety and availability of blood...
and blood products, assesses the impact of new blood-related technologies, and also explores opportunities for regulatory cooperation and collaboration, where possible.

Member organizations have legal standing and well-established, demonstrated institutional capacity to regulate blood and blood products, and the necessary expertise to address emerging global public health challenges. The WHO acts as Secretariat to the BRN and coordinates network activities under the conditions of the Terms of Reference. BRN recommendations and considerations are communicated to the ECBS, through WHO. Documents published by the BRN contain the collective views of members and do not necessarily represent the decisions or the stated policy of WHO or of the participating regulatory authorities.42

Examples of the work of BRN are the publications Position Paper on Collection and Use of Convalescent Plasma or Serum as an Element in Filovirus Outbreak Response and Potential for Use of Convalescent Plasma in Management of Ebola. These documents were published in August and September 2014, respectively, and demonstrate BRN’s ability to respond quickly to emerging threats to the blood supply.

**Regulation of and guidance on blood products in Europe**

The regulation of blood components for transfusion, and blood plasma derivatives and analogous recombinant analogs, in Europe is complex because of historical considerations and the balance that is needed between the role of a centralized authority and the involvement of the many independent member states that have their own medicines regulatory authorities. The functionality of the system depends on the exchange of information among the member states and their acceptance of common standards and practices. The standards, guidance documents, and authorized medicines produced within the European framework stretch beyond its borders and have been adopted in many other parts of the world.

Organizations involved in European regulatory processes include the following (see Figure 7.1).

**The European Union and associated organizations**

**European Union:** The European Union was founded in 1948 to promote stability and economic cooperation among member states. It consists of 28 member states and “operates through a system of supranational independent institutions and intergovernmental negotiated decisions by EU Member States. The European Union has developed a single market through a standardized system of laws and the same rules and harmonized procedures apply to all the 28 Member States regarding the authorization of medicines and the supervision of the safety of medicines.”

**European Commission:** This executive arm of the European Union proposes legislation, sets objectives and priorities, and grants centralized marketing authorization.

**European Economic Area (EEA):** This includes the European Union plus Norway, Iceland, and Liechtenstein.

**European Medicines Agency (EMA):** The agency within the European Union responsible for the scientific evaluation of applications for marketing authorizations for human and veterinary medicines in the centralized procedure. Its main responsibility is...
Authorization in Europe of plasma derivative and analogous recombinant products

The regulation and authorization of manufactured blood products in Europe involve an interplay among the EMA, national competent authorities (NCAs), CHMP working parties, and the EDQM that includes the PhEur and OMCLs. There are three pathways for authorizing medicines in Europe. In the “centralized” procedure, pharmaceutical companies submit a single marketing-authorization application to the EMA. For blood products, the EMA’s CHMP carries out a scientific assessment of the application and gives a recommendation on whether or not to grant a marketing authorization. Once granted by the European Commission, the centralized marketing authorization is valid in all EU member states. Most innovative medicines go through this procedure.43

Most medicines are not authorized through the centralized procedure. Instead, they are authorized by NCAs in member states. When a company wants to authorize a medicine in several member states, it can use one of the following procedures:

- The decentralized procedure, through which companies can apply for the simultaneous authorization of a medicine in more than one EU member state if it has not yet been authorized in any EU country and it does not fall within the mandatory scope of the centralized procedure; or
- The mutual-recognition procedure, through which companies that have a medicine authorized in one EU member state can apply for this authorization to be recognized in other EU countries.

This process allows member states to rely on each other’s scientific assessments. Rules and requirements applicable to pharmaceuticals in the European Union are the same, irrespective of the authorization route for a medicine.43

Safety monitoring of medicines in Europe

EudraVigilance is an EU web-based information system within the EMA that collects, manages, and analyzes reports of suspected side effects of medicines. Information is obtained from EEA members, and these data are continuously monitored in order to identify any new safety information.

The EMA has a committee dedicated to the safety of medicines for human use—the Pharmacovigilance Risk Assessment Committee (PRAC). If there is a safety issue with a medicine that is authorized in more than one member state, patients and healthcare professionals in all member states are given the same guidance by the committee, and the same regulatory action is taken across the European Union.

The PRAC has a broad remit covering all aspects of pharmacovigilance. In addition to its role in risk assessment, the committee provides advice and recommendations to the European medicines regulatory network on risk management planning and postmarketing benefit–risk assessment for medicines.45

International cooperation

The EMA and the European Commission work with member states and other organizations around the world to foster international cooperation and timely exchange of information on regulatory and scientific matters. One such interaction related to blood products is the so-called Blood Cluster meeting with the FDA and Health Canada where pharmacovigilance information and other blood product–related matters are exchanged on a regular basis.

EMA works with WHO on issues such as medicines intended for markets outside of the European Union, and the quality of medicines. EMA also cooperates with the International Conference on
Harmonization of Technical Requirements (ICH) on matters related to harmonizing requirements to assure the safety, quality and efficacy of drugs.

Activities to promote blood component safety in Europe

The CoE has been actively contributing since the 1950s to the implementation of standards for blood transfusion. In 2007, the secretariat responsible for blood transfusion activities was transferred to the EDQM. Within the EDQM, the European Committee on Blood Transfusion (CD-P-TS) is in charge of steering and coordinating the actions of the CoE in this area. The membership of CD-P-TS includes the CoE member states, and parties to the Convention on the Elaboration of a European Pharmacopoeia. The European Commission, WHO, and other CoE Committees (European Public Health and Bioethics Committees) are special observers to the CD-P-TS.49

Activities of the CD-P-TS include, among others, addressing issues about quality and safety standards for blood transfusion, including collection, storage, distribution, and use of blood components; improving blood transfusion services; promoting the principle of voluntary non-remunerated donations; and establishing good practices in transfusion medicine and monitoring their use in Europe. These objectives are attained by setting standards and preparing guidance on professional practices (e.g., Guide to the Preparation, Use and Quality Assurance of Blood Components); organizing and evaluating surveys on blood components; and using resolutions to promote continuous improvement of an ethical, organizational, and regulatory approach to blood transfusion.49

Other major international organizations involved in the regulation or standardization of blood, blood products, and their biotechnology analogs

International Conference on Harmonization: Regulatory authorities and pharmaceutical industry experts from Europe, Japan, and the United States discuss scientific and technical aspects of product registration. The work of this organization is especially relevant to biotechnology products. Although ICH does not include the blood industry, ICH activities address blood secondarily by use of the Common Technical Document. A significant output of ICH has been guidance on informed consent for and ethical conduct of clinical trials.50

Pharmaceutical Inspection Co-operation Scheme and Pharmaceutical Inspection Convention (PIC/S): A collective of pharmaceutical inspectorates involved in information exchanges, training, and guideline development related to good manufacturing, device, clinical, and laboratory practices.51

International Working Group on the Standardization of Genomic Amplification Techniques for the Virological Safety Testing of Blood and Blood Products (SoGAT): A WHO technical discussion group that works on issues of international standardization and quality of genomic amplification techniques for the testing of products.52

National Institute of Biological Standards and Control (NIBSC): They prepare reference materials, for WHO among others, and organize international collaborative studies on reference preparations.53

Paul Ehrlich Institute (PEI): German regulatory authority that has a major influence on the development of blood products in Europe and is a WCC.54

Trade, professional societies, and patient-sponsored international forums

International Society on Thrombosis and Hemostasis (ISTH), Scientific and Standardization Subcommittee (SSC): This society works on the understanding, prevention, diagnosis, and treatment of thrombotic and bleeding disorders. ISTH focuses on issues about blood coagulation, hemorrhagic disorders, platelet function and regulation; the mechanisms of thrombosis, fibrinolysis and thrombolysis; and problems of thromboembolic disorders. SSC-ISTH also helps to evaluate candidate reference standards for consideration by ECBS.55

America’s Blood Centers/European Blood Alliance (ABC/EBA): Works to harmonize requirements and decision-making processes to promote safe and high-quality blood products in North America and Europe.56

World Federation of Hemophilia (WFH): Works on issues involving hemophilia and other bleeding disorders, including supply, affordability, safety, and regulatory harmonization.57

European Hemophilia Safety Surveillance (EUHASS): This is a pharmacovigilance program to monitor the safety of treatments for people with inherited bleeding disorders in Europe.58

Plasma Protein Therapeutics Association (PPTA): This is the international trade association and standards-setting organization for the world’s major producers of plasma-derived and recombinant analog therapies, collectively referred to as plasma protein therapies.59

International Plasma Fractionation Association (IPFA): This is an international association for nonprofit organizations involved in the manufacture of blood products made from blood collected from non-remunerated donors.60

International Society of Blood Transfusion (ISBT): The ISBT promotes research, new developments, and changing concepts in blood transfusion medicine.53

FDA role in the global regulation of blood and blood products

The activities of the FDA have a large impact on the global regulation of blood and blood products. FDA’s international standing is bolstered by the substantial medical and scientific resources that it devotes to ensuring the safety, efficacy, and availability of blood and blood products. Within the FDA, the Office of Blood Research and Review (OBRR), in CBER, has the responsibility of regulating blood and blood components; plasma derivatives and analogous products; blood donor screening tests; retroviral diagnostic tests; and other medical devices, including software used to test, collect, process, or store donated blood.

FDA is strongly supportive of harmonization efforts that will maximize national and global health. A convergence of thinking on regulatory and guidance issues is important for trade as well; because many of the companies involved in blood product manufacture are international in scope; the US market for these products is extensive; and a large amount of plasma, intermediates, and manufactured products are distributed abroad.

FDA influences global regulatory and guidance norms for blood and blood product safety, through its interactions with all of the organizations cited in this chapter. For example, FDA representatives are members of the WHO’s ECBS and the BRN, have Observer status with EDQM’s Expert Group 6B, and routinely communicate with the EMA and Health Canada through Blood Cluster meetings. In addition to interacting with organizations that are composed of multiple international partners, FDA has bilateral memoranda of
understanding and confidentiality arrangements with a number of individual countries. All of these relationships facilitate cooperative activities and the sharing of information, which support the common goal of enhancing the global safety and availability of blood and blood products.

Key references

A full reference list for this chapter is available at: http://www.wiley.com/go/simon/transfusion


