

## **FDA Regulation of Blood and Blood Components in the United States**

### **SLIDE 1**

This presentation will review the FDA Regulation of Blood and Blood Components in the U.S.

### **SLIDE 2**

Within the Center for Biologics Evaluation and Research, the Office of Blood Research and Review, or OBRR, is responsible for ensuring the safety, efficacy, and availability of blood components intended for transfusion and further manufacture; plasma volume expanders and oxygen carrying solutions; blood donor screening tests; and other medical devices, including software used to test, collect, process, or store donated blood.

The office is also responsible for the regulation of retroviral diagnostic tests.

OBRR not only conducts regulatory review, but also develops many of the policies related to the use of products that it regulates.

### **SLIDE 3**

The Public Health Service Act and the Food, Drug and Cosmetics Act, or FD&C Act, are the two major statutes that empower FDA to regulate blood. Both Acts apply to the regulation of blood, because blood components are regulated both as licensed biologics and as drugs.

The FD&C Act is frequently amended by Congress. Some of the recent amendments that have taken place include the Prescription Drug User Fee Act, or PDUFA, the Medical Device User Fee Act, or MDUFA, and, more recently, the Food and Drug Administration Amendments Act, or FDAAA, which increased the authority for FDA to conduct post-marketing safety surveillance. Most recently the 21st Century Cures Act amended the FD&C Act to help accelerate medical product development and bring new innovations and advances to patients.

Regulations are written by FDA and are published in the Code of Federal Regulations or CFR. They are issued as proposed rules for public comment. FDA considers the comments in developing the final regulation.

### **SLIDE 4**

Licensure is a requirement of the Public Health Services Act as it applies to the regulation of biologics. The law states that no person can introduce or deliver for introduction into interstate commerce a biologic product, unless a biologic license is in effect, and each package is plainly marked with the proper name of the product; the name, address and license number of the manufacturer; and the expiration date of the product. The law provides the Secretary of Health and Human Services with the ability

to promulgate requirements for the approval, suspension, and revocation of specific licenses. These functions have been delegated to the FDA.

To be approved, the manufacturer of a biologic product must demonstrate that it is safe, pure and potent, which FDA has interpreted to mean effective. In addition, the facility where the product is manufactured must meet CGMP standards, and is subject to inspection.

Eighty-five to 90 percent of blood products for transfusion are prepared in licensed facilities. Licensure is significant, particularly in the blood community, because it signifies FDA approval of the product. The product label provides the license number permitting interstate shipment, and helps to assure that blood components shipped around the country meet a suitable safety and cGMP standards.

### **SLIDE 5**

These are some of the regulations that apply to blood collection.

The biologics-related CFR regulations related to blood include:

- Part 600 covering General considerations.
  
- Part 601 - Licensing requirements.
  
- Part 606 - Current Good Manufacturing Practices specific for blood. Additional cGMPs are found in Parts 210 and 211.
  
- Part 607 - Registration.
  
- Part 610 - General Biological Product Standards including testing of blood donations.
- Part 630 - Requirements for Blood and blood components intended for transfusion or for further manufacturing use, which includes donor eligibility requirements,
- And, Part 640, which addresses Additional Standards for Blood and Blood Products.

### **SLIDE 6**

Guidance documents are the primary means by which FDA provides information to manufacturers of blood products on how to comply with the regulations. Guidance documents represent FDA's current thinking on a topic. They do not create or confer any rights for or on any person and do not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations.

Guidance related to blood can be found at the website indicated in the slide.

### **SLIDE 7**

Within the Office of Blood Research and Review there are about 142 full-time staff, and 20 to 30 contract staff, who serve as research fellows or temporary employees. The organizational structure includes the Immediate Office of the Director and two divisions. The Division of Blood Components and Devices is responsible for regulating blood

collection establishments, reviewing applications for in-vitro tests used for blood typing, pathogen reduction devices, and blood volume expanders. The Division of Emerging and Transfusion-Transmitted Diseases reviews submissions for donor screening tests for infectious diseases and retroviral diagnostics.

OBRR interacts with other FDA offices including the Office of the Center Director, Office of Tissues and Advanced Therapies, Office of Biostatistics and Epidemiology, Office of Compliance and Biologics Quality, as well as the Center for Devices and Radiological Health.

OBRR also interacts frequently with the other Public Health Service agencies including the National Institutes of Health, the Centers for Disease Control and Prevention, and the Office of the Assistant Secretary of Health and Human Services.

### **SLIDE 8**

There are a wide range of regulatory functions conducted by OBRR. These include establishing regulatory policies and standards and reviewing regulatory applications. For instance, if the Office reviews a new blood screening test, not only is the performance of that test reviewed, but also, CBER defines policies as to whether blood collectors should use that test.

The Office also reviews lot release protocols for products that it regulates and establishes panels used for lot release testing for certain products.

OBRR staff participate in inspections of OBRR regulated products, including both pre-market and post-market inspections. If a product is found to have a problem that might threaten public health, OBRR works with our Compliance office and field investigators to conduct product investigations. OBRR medical officers also frequently provide health hazard evaluations of any unexpected product-related observation.

OBRR has a very active program of mission-related research and proactive planning for emergencies, such as terrorism, flu pandemics, and natural or manmade disasters.

OBRR has world-class research scientists working in our laboratories. These scientists present their findings at scientific meetings and pursue collaborations around the world.

### **SLIDE 9**

OBRR primarily focuses on blood and blood products used in transfusion medicine.

The office reviews several different types of regulatory applications with respect to blood and blood components. This includes biologics license applications, called BLAs, which represent the regulatory pathway for approving blood components. OBRR's focus on transfusion includes review of applications for Albumin and hemoglobin-based oxygen carriers. OBRR regulates devices used to prepare or process blood components such as Apheresis machines.

OBRR also regulates in vitro devices used to screen donors for transfusion-transmitted infectious diseases or to determine their blood type using the BLA regulatory pathway. Review of these devices as biologic licenses allows CBER to apply a higher level of manufacturing oversight, including lot release testing and pre-licensure inspection.

### **SLIDE 10**

The regulatory pathway for New Drug Applications, or NDAs, is most commonly used within the Center for Drug Evaluation and Research, or CDER.

Within OBRR, several NDA applications are reviewed each year, mostly involving solutions used for the collection of blood, such as anticoagulants and red cell nutritive solutions. If a collection bag contains an anticoagulant solution, then it is regulated as a drug. OBRR also regulates blood volume expanders as NDAs.

### **SLIDE 11**

Most devices are reviewed by the Center for Devices and Radiological Health or CDRH. However, OBRR reviews both Class Two and Class Three devices used in the manufacture of blood. For example, devices used to reduce pathogens found in blood for transfusion are regulated as Class III devices in OBRR. In addition, by agreement with CDRH, diagnostic tests for HIV are regulated in OBRR.

At the time HIV diagnostics tests were first developed, much of the expertise for HIV testing was located within OBRR, so these tests are regulated in this office.

### **SLIDE 12**

Class Two devices are referred to as "510(k)s" reflecting the applicable section of the Food, Drug and Cosmetic Act.

These devices include Blood Establishment Computer Software which is used in the manufacture of blood components to identify ineligible donors, prevent release of unsuitable blood components, and perform positive identification between patients and blood components. Other 510(k) devices regulated in OBRR include apheresis machines, blood warmers and human leukocyte antigen, or HLA test kits.

### **SLIDE 13**

OBRR reviews several types of pre-market investigational studies. The investigational new drug application, or IND, is used to authorize the administration to humans of an unapproved drug or biologic in support of a biologics license application or new drug application. Such products can only be shipped from state to state or outside the country if they are part of an IND study.

Investigational Device Exemption, or IDE, is the equivalent investigational pathway to support use of investigational devices in humans that provides data to support a future Class Two or Class Three device application.

#### **SLIDE 14**

Blood transfusion in the United States has been decreasing for the last few years because of changes in transfusion practices. Currently, there are approximately 6.2 million volunteer blood donors who provide about 13.8 million Whole Blood, Red Blood Cells, Platelets and Plasma donations that result in about 17.2 million transfused units.

In general, the U.S. collects just what is needed to maintain adequacy in the blood supply. Although blood shortages may be seen in the summer months and winter holidays in certain states, they generally do not reach serious proportions, and the public generally responds very generously to appeals for additional blood donors.

For many decades, blood collected for transfusion has come from voluntary non-remunerated donors because of concern about higher risk from paid donors. Although it is legal to pay donors, the practice is very rare and the unit must be labeled as being collected from a paid donor.

#### **SLIDE 15**

Currently, within the U.S., the American Red Cross, holds a single license for blood collection and collects about 46 percent of the U.S. blood supply. America's Blood Centers, whose members comprise individually licensed blood centers, collects an additional 47 percent of the nation's blood supply. The remaining 7 percent is collected in military facilities and in hospitals.

Hospitals typically do not ship blood. So, they're often registered with the FDA for blood collection, but are generally not licensed for interstate shipment of blood products.

#### **SLIDE 16**

Whole Blood is processed into several blood components including Red Blood Cells, Platelets, and Fresh Frozen Plasma. Plasma from a Whole Blood unit that is not used for transfusion can be converted to recovered plasma and used for further manufacturing into plasma derivative products. Automated blood collection by apheresis produces Red Blood Cells, Platelets, and Plasma products.

#### **SLIDE 17**

Source Plasma is also a major blood component collected in the United States. Source Plasma is primarily used in the manufacture of plasma derivatives such as clotting factors, immune globulins and albumin. Almost all Source Plasma in the U.S. is collected from paid donors. These units, are not required to be labeled as collected from paid donors. The manufacturing process for plasma derivative products includes steps to remove or inactivate most pathogens.

#### **SLIDE 18**

There's been an increasing demand for Source Plasma for the past several years primarily because of the demand for immune globulin products. In 2016, there were about 38 million donations of Source Plasma collected.

## **SLIDE 19**

OBRR has established a multi-layered approach to blood safety.

The Five Layers of Blood Safety include overlapping safeguards, so that if any one layer happened to fail, then there would still be protections in place to help keep the blood supply safe.

These five layers include: one, donor screening to select eligible donors.

Donors are provided educational material to inform them about potential risks to blood safety and to assure the donor is healthy. They are asked questions about factors that may have a bearing on the safety of their blood. For example, donors with a history of non-prescription injection drug use are routinely deferred. A limited physical assessment is performed to determine if it is safe for the donor to donate.

Donor deferral registries: Blood establishments must keep current a list of deferred donors and use it to make sure that they do not collect blood from anyone on the deferral list.

Infectious disease testing is performed on the donated blood. This testing involves both antibody and nucleic acid tests for HIV, HCV, and HBV, testing for Hepatitis B virus surface antigen, testing for antibodies to Human T-cell lymphotropic virus, testing for syphilis and for West Nile virus. More recently testing for T. cruzee, and Zika virus has been performed

Quarantine: Donated blood must be quarantined until it's tested and shown to be free of infectious agents.

The final step is for blood establishments to monitor, investigate, and take corrective actions to address any problems or deficiencies in the manufacturing process and notify the FDA when product deviations occur in distributed products.

## **SLIDE 20**

OBRR establishes product standards which it publishes both in regulations and in guidance documents. CGMP, or Current Good Manufacturing Practices, are an important mechanism to ensure the control of manufacturing throughout the manufacturing process. cGMP includes having employees with the background and training to perform their jobs; the equipment used in collection and manufacturing is maintained, standardized, and calibrated; the process for manufacturing blood has been validated and there are standard operating procedures for each step of the process; labeling controls; quality control testing; records for each step in the manufacturing process; and periodic audits.

Lot release testing of blood screening tests takes place to make sure that the products that are actually produced for public distribution meet the same standards as the products that were approved originally.

## **SLIDE 21**

Manufacturers may decide to modify their existing licenses. 21 CFR Part 601.12 describes the types of submissions that are required when a change is made to an approved application. There are three categories through which changes can be reported. The category depends on the potential of the change to have an adverse effect on the product.

The categories are:

- the Prior Approval Supplement, or PAS;
  
- Changes Being Effected in 30 Days Supplement, known as the CBE-30.
  
- Changes-Being-Effected Supplement, or CBE;
- and
- Annual Report, or AR.

An annual report is filed by all license holders annually if changes in this category are made. The relevant sections in the regulations for each type of change are noted in the slide.

## **SLIDE 22**

Blood establishments and biologics manufacturers are inspected by FDA at regular intervals. During an inspection, the FDA observes the operations at the site. This includes observing actual operations, personnel roles and compliance with standard operating procedures; product labeling; operation of equipment, instruments, and computer systems; and the general physical facility, including donor privacy and sufficient space considerations. During inspections, prior records are also reviewed, including quality assurance-related documentation, records concerning training, donor reactions, immunization, testing for infectious disease, quality control, validation, and product manufacturing.

## **SLIDE 23**

OBRR has a large role in the development of science-based policy related to blood oversight and regulation. The policy development process generally goes through a public deliberation process involving an external scientific review committee.

One of the committees used by FDA is the Blood Products Advisory Committee, or BPAC. The BPAC is made up of scientists, physicians, consumer representatives and other experts who may advise the FDA on the scientific aspects of a donor policy or product approval.

An additional committee was established to advise the Assistant Secretary for Health on blood issues. It's called the Advisory Committee on Blood and Tissue Safety and Availability, or ACBTSA. The ACBTSA also considers scientific issues, but has a broader scope, in that it can consider the economics and ethics of a particular policy

decision. The ACBTSA recommendations are provided to the Assistant Secretary for Health for his or her consideration.

There's substantial discussion within the Public Health Services agencies any time blood issues come to the forefront. These issues are frequently discussed on a monthly conference call, or through the deliberations of several working groups.

Policy decisions are frequently considered collectively by the heads of the relevant Public Health Service agencies or their designees before recommendations are made to the Assistant Secretary. This group, which is chaired by the Assistant Secretary, is known as the Blood, Organ and Tissue Senior Executive Committee, or BOTSEC.

#### **SLIDE 24**

Examples of active policy development areas include:

- pandemic and emergency preparedness
- donor behavioral screening in the era of nucleic acid testing or NAT
- donor screening and confirmatory tests for emerging agents
- bacterial contamination of Platelets
- pathogen reduction for blood components, and
- biovigilance.

#### **SLIDE 25**

There is a lot of information that can be learned from the CBER website.

#### **SLIDE 26**

Other useful websites related to blood regulation and science include:

- AABB (formerly the American Association of Blood Banks)
- Plasma Protein Therapeutics Association
- The Department of Health & Human Services, Blood Safety and Availability Committee.
- The Centers for Disease Control and Prevention.
- And, the National Heart, Lung and Blood Institute



**SLIDE 27**

This concludes the presentation,  
"FDA Regulation of Blood and Blood Components in the United States." We would like  
to acknowledge those who contributed to its development. Thank you.