FDA Regulation of Blood and Blood Components in the United States

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

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The FDA Center for Biologics Evaluation and Research, or CBER, Office of Blood Research and Review, called OBRR, 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 blood components. The BLA regulatory process also applies to biological drugs such as fractionated plasma products.

OBRR also regulates in-vitro diagnostic devices used for screening of collected blood, and does so also 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. This regulatory pathway applies to infectious disease tests for blood screening, as well as blood grouping and phenotyping reagents.

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

Within the Office of Blood, several NDA applications are reviewed each year, mostly involving solutions used for the collection of blood, such as anticoagulants and red cell nutritive solutions. Interestingly, a blood bag that does not have a solution inside is regulated as a device. If the bag has a solution, then it is a drug-device combination product, but is regulated as a drug.

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OBRR reviews both Class Two and Class Three devices. Class Three devices in OBRR include diagnostic tests for HIV regulated as pre-market approvals, called PMAs. These are reviewed by OBRR rather than by the Center for Devices and Radiologic Health, or CDRH, for historic reasons.

At the time HIV diagnostics tests were first developed, much of the expertise for HIV within the FDA was concentrated on protecting the blood supply.

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Class Two devices are referred to as "510(k)s" reflecting the applicable regulatory citation in the Code of Federal Regulations, or CFR.

These devices include Blood Establishment Computer Software, commonly known as BECS, which is used to run the manufacturing process within a blood center. Other 510(k) devices in OBRR include apheresis machines, blood warmers and HLA, or human leukocyte antigen, test kits.

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OBRR reviews several types of pre-marketing investigational studies. The investigational new drug process, or IND, is used to authorize the administration to humans of a drug or biologic in support of a license or new drug submission. Such products can only be shipped from state to state or outside the country if they carry a license number or an IND number.

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 submission.

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Within the United States, there are about eight million voluntary donors per year who contribute to our blood supply. It is legal to pay a donor for whole blood collection under FDA regulations.

However, that unit needs to be labeled as being from a paid donor. In practical terms, hospitals choose not to use products that are labeled from a paid donor for liability reasons. From these eight million donors, there are about fifteen million blood donations per year, virtually all of which are processed into individual blood components, such as red blood cells, platelets, and plasma. About 5 percent of the eligible public donates each year. An upward or downward trend of one to two tenths of a percent can greatly influence the blood supply.

In general, the U.S. collects just what is needed to maintain adequacy in the blood supply. Although blood shortages are still seen in the summertime and holidays, they generally they do not reach serious proportions, and the public generally responds very generously to appeals for additional blood donors.

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Whole blood is processed into red blood cells, random donor platelets, and fresh frozen plasma. Plasma from a whole blood unit that is not used for transfusion therapy can be converted to recovered plasma, and used for further manufacturing into plasma derivative products. Automated blood collection by apheresis produces red cells, platelets, and other cellular products in combinations designed to maximize the value of each donation.

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Currently, within the U.S., the American Red Cross -- which operates 36 Regions, but holds a single license for blood collection -- collects about 45 percent of the U.S. blood supply. America's Blood Centers, comprised of individually licensed blood centers, collects an additional 45 percent of the nation's blood supply. The remaining 10 percent is collected in military facilities and in hospitals.

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

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Source plasma is also a major blood component in the United States. Most source plasma in the U.S. is from paid donors. In contrast to whole blood collections, these units, under Federal Regulations, are not labeled as collected from paid donors. In part, this is because all source plasma is used to further manufacturing use only.

This manufacturing process includes several overlapping steps of manufacturing, which remove or inactivate most pathogens.

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The mission statement for the Office of Blood Research and Review is to ensure the safety, purity, potency, and effectiveness of blood and blood products used for the prevention, diagnosis, and treatment of human disease, conditions, or injury.

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

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 how blood manufacturers should use that test.

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This slide lists the wide range of regulatory functions conducted by OBRR. These include establishing regulatory policies and standards and review of regulatory applications under the user fee regulations.

The Office also reviews lot release protocols for any product that it regulates and, in some cases, actually conducts in the laboratory lot release testing for certain products.

OBRR staff participate in inspections related to the 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 conducts product

investigations. OBRR physicians also frequently provide health hazard assessments of any unexpected product-related observation.

All of this work is done in close collaboration with other FDA offices. These include: The Office of Regulatory Affairs, or ORA; the Office of Compliance and Biologics Quality, or OCBQ;and our Office of Chief Counsel, or OCC.

OBRR also 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 the laboratories. These scientists make scientific presentations and pursue collaborations around the world. OBRR also conducts site visits under a Center program to some of the regulated manufacturers on a non-inspectional basis, and as a mechanism to get a firsthand look at the manufacturing process in an informal setting.

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Within the Office at the time this presentation was prepared, there are about 192 full-time staff, and 20 to 30 contract staff, who serve as research fellows or temporary employees. The structure includes the Division of Blood applications, which manages much of the regulatory review process, and the Division of Emerging and Transfusion-Transmitted Diseases or DETTD, which reviews the products that are used for infectious disease screening, and conducts lot release on these products.The Division of Hematology regulates a wide range of hematologic products, and like DETTD, maintains a very active research program.

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The Five Layers of Blood Safety comprise the model used for maintaining blood safety. These layers are overlapping, like layers of an onion, 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, selection of suitable donors by donor education and risk factor screening; two, the use of deferral registries to identify unsuitable donations; and three, infectious disease testing on donated blood units. This testing involves both antibody and nucleic acid tests for HIV and HCV, tests for HBS Antigen, antibody testing for Human T-cell lymphotropic virus, tests for syphilis, and tests for West Nile virus. The fourth layer of blood safety is quarantine of blood until all the test results are available and known to be negative. The final step is monitoring, investigating, and taking corrective actions to address any errors or accidents in the manufacturing process, and the investigation of an adverse reaction in product recipients.

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The Office helps to define 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 through process validation, labeling, quality control testing, employee training, and audits.

Lot release testing of blood screening 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.

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The Public Health Service Act, or PHS Act, and the Food and Drug and Cosmetics Act, or FD&C Act, are major pieces of legislation passed by Congress that provide the authorities for FDA's work. Both of these 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, or PDUFA, the medical device user fee, or MDUFA, programs, and, more recently, the Food and Drug Amendments Act, or FDAAA, which increased the authority for FDA to conduct post-marketing safety surveillance.

Regulations are written by FDA and are published in the CFR. One regulation that is unique to blood recognizes the importance of blood availability, and allows variance from other regulations to sustain the blood supply.

For instance, if a certain process related to manufacture of a blood unit needs to be altered due to a natural disaster, such as the use of a different storage facility, a blood center can apply to FDA for an exception to the usual procedure. If determined to be a safe change, FDA will often provide flexibility to sustain the local supply of blood components.

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The biologics-related CFR chapters in FDA regulations include:
- Chapter 600 covering General considerations.

- Chapter 601 - Licensing issues.

- Chapter 606 - Current Good Manufacturing Practices.
Additional GMPs are found in Chapters 210 and 211.

- Chapter 607 - Registration.

- Chapter 610 - General biological product standards.

- And, Chapter 640, which addresses additional standards for blood and blood products.

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Guidance documents are the major means by which the Office of Blood regulates blood products. Standard operating policies and procedures are also maintained at the CBER and OBRR level.

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Licensure is a unique concept provided by the Public Health Services Act for the regulation of biologics. The regulation 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 packaged end shipment needs to be plainly marked. The law provides requirements for the approval, suspension, and revocation of specific licenses.

In essence, a license provides that a biologic product is safe, pure, potent and efficacious, and that the facility where the product is produced meets CGMP standards, and is subject to inspection.

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Licensure signifies several things. It signifies FDA approval of product and facility. It allows for interstate shipment of product for commerce - meaning the sale, barter, or exchange for introduction, or delivery for introduction into interstate commerce. The license number must appear on the label of approved products. And, the license certificate must be displayed at the licensed facility.

85 to 90 percent of blood products 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 effectiveness standard.

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Existing licenses can be modified. 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. The relevant sections in the regulations for each type are noted in the slide.

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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 concordance operationally, and, in terms of personnel roles with standard operating procedures; product labeling; operation of equipment, instruments, and computer systems; and the general physical facility, including privacy and sufficient space considerations. During inspections, 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.

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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 major committees is the Blood Products Advisory Committee, or BPAC. The BPAC is made up of scientists and physicians, who advise the FDA on the scientific aspects of a policy.

An additional committee advises the Assistant Secretary for Health. It is called the Advisory Committee on Blood Safety and Availability, or ACBSA. This meets approximately quarterly during the year. The ACBSA also considers scientific issues, but has a broader scope, in that it can consider the economics and ethics of a particular policy decision. The ACBSA advises the Assistant Secretary for Health.

There is 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.

Final policy decisions are frequently considered collectively by the heads of all relevant Public Health Service agencies. The group is known as the Blood, Organ and Tissue Safety Executive Committee, or BOTSEC.

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Examples of active policy areas include:
- Pandemic and emergency preparedness.

- Donor screening and confirmatory tests for emerging agents.

- Pathogen Reduction for Blood Components.

- Donor behavioral screening in the era of Nucleic acid testing or NAT.

- And, biovigilance.

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CBER has a very active web site, which covers the topics shown on this slide, and much more.

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Other useful web links related to blood regulation and science include:
- AABB, the major U.S. trade organization for blood.

- The Department of Health & Human Services, Blood Safety and Availability Committee.

- The Centers for Disease Control.

- And, the National Heart, Lung and Blood Institute.

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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.