**New at CBER - Regulatory and Organizational Updates**

**SLIDE 1**
Since the inception of the online foreign regulatory web training program in 2011, CBER has undergone some organizational changes and has updated its regulatory approaches to address the global availability of safe and effective medical products. This presentation will provide a high level overview of what's new at CBER since the 2011 Foreign Regulatory Webinar.

**SLIDE 2**
Included in this presentation is a historical review of this online regulatory web training program, CBER's current organization, an overview of CBER's regulatory framework, and programs intended to expedite the approval of biologics, and Office-specific updates. This presentation concludes with some helpful weblinks for CBER.

**SLIDE 3**
CBER's mission is to ensure the safety, purity, potency, and effectiveness of biological products.

Using sound science and regulatory expertise, CBER strives to protect and improve public and individual health in the U.S., and, where feasible, globally. However, a changing global reality has introduced new challenges, and opportunities, for CBER and our foreign regulatory counterparts. FDA and foreign counterparts work collaboratively to both enhance public health protection and to use human and financial resources efficiently.

**SLIDE 4**
Due to an overwhelming number of requests from our foreign regulatory counterparts for training on the regulation of biologics, CBER provided an online web training program in 2011 to help broaden CBER's reach in addressing the training requests in the most efficient manner. Over time, CBER's organization and regulatory mandates have changed, and some of those changes and updates are incorporated here in this presentation, as well as in other presentations in this online web series. Please be sure to view all the presentations to gain full benefit from this training program.

**SLIDE 5**
Shown here is the current CBER organizational chart. The most significant change is the restructuring of the Office of Cellular, Tissue, and Gene Therapies, now reorganized into the Office of Tissues and Advanced Therapies. This change will be described in later slides.

**SLIDE 6**
FDA's regulatory authority comes from statutes or laws passed by Congress and signed by the President, specifically the Federal Food, Drug and Cosmetic Act, or FD&C Act, and the Public Health Service, or PHS Act.

Regulations developed by FDA interpret statutes. FDA writes legally binding regulations based on authority received from Congress. FDA writes guidance documents to assist stakeholders with understanding FDA's current thinking on how to comply with statutes and regulations.

**SLIDE 7**

In recent years, there have been amendments to the FD&C Act and the PHS Act.

In 2007, Congress passed the Food and Drug Administration Amendments Act, referred to as FDAAA, which reauthorized a number of provisions, adding significantly to FDA authority.

In 2010, the Biologics Price Competition and Innovation Act, or BPCI Act, was enacted.

In 2012, another significant law was signed, known as the Food and Drug Administration Safety and Innovation Act, or FDASIA, which introduces the "breakthrough therapy" designation. We'll review FDASIA in upcoming slides.

In 2016, Congress enacted the 21st Century Cures Act, to help accelerate new advances in medical product development. Some of the features of this Act will be discussed later in these slides.

In 2017, the FDA Reauthorization Act was passed, known as FDARA.

For more information on each of these important amendments, please see the reference web links at the end of this presentation, as well as the presentation in this series called "FDA Laws, Regulations and Guidance Documents".

**SLIDE 8**

Expediting the regulatory approval process for drugs and biologics to treat serious or life-threatening conditions is a priority in CBER. FDA offers four mechanisms to facilitate development of products that have a HIGH public health impact: Accelerated Approval, Fast Track, Breakthrough Therapy Designation, and Priority Review.

Details on the expedited programs can be found in the guidance document, "Guidance for Industry: Expedited Programs for Serious Conditions - Drugs and Biologics".

**SLIDE 9**

In particular, FDA may grant Accelerated Approval to a product for a serious or life-threatening disease or condition upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit -- or on a clinical endpoint that can be measured earlier than irreversible- morbidity-or- mortality, or IMM, that is reasonably likely to predict an effect on IMM or other clinical benefit -- taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.

Surrogate endpoints are defined as a "laboratory or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, and survives and that is expected to predict the effect of therapy."

FDA also may consider an Intermediate endpoint, which is defined as a measure of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on IMM.

**SLIDE 10**
Fast track designation is given when a product is intended to treat a condition where there is an unmet medical need. Fast Track encourages close early communication between the FDA and sponsor to improve the efficiency of product development and allows for the possibility of a rolling submission for a marketing application.

**SLIDE 11**
A recently added process is the Breakthrough Therapy Designation.

Products are eligible for breakthrough therapy if the preliminary clinical evidence on effectiveness or safety may demonstrate substantial improvement over available therapies for a serious condition on one or more clinically significant endpoints.

Benefits include intensive guidance from FDA on product development, and commitment from the FDA to work together to expedite the development. Also, sponsors are permitted to submit applications using the same rolling review process as the fast track designation.

Note that if the designation is not supported by subsequent data, FDA may rescind the designation of Breakthrough Therapy.

**SLIDE 12**
Priority review is granted when a drug offers major advances in the treatment of a life-threatening condition or when no adequate therapy exists for the disease. The review time is shortened by 4 months.

**SLIDE 13**
Moving to specific CBER product offices and their Updates, this is the current organizational chart for the Office of Tissues and Advanced Therapies, or OTAT. OTAT was formed in October 2016 by merging the former Office of Cellular, Tissue and Gene Therapies, or OCTGT, and components of the Office of Blood Research and Review, Division of Hematology, Laboratories of Plasma Derivatives and Homeostasis.

**SLIDE 14**
The basis for the formation of OTAT was the overlap in regulatory expertise in the clinical divisions in OCTGT and the Division of Hematology in OBRR. Additionally, an

increase in the number of cell and gene therapy products to treat hemophilia and immune deficiencies submitted to OCTGT supported the merger.

**SLIDE 15**

Products regulated in OTAT include stem cell and stem cell-derived products. These include hematopoietic, mesenchymal, cord blood, embryonic, and iPSC-derived products.

Somatic cell therapies include pancreatic islets, chondrocytes, myoblasts, keratinocytes, and hepatocytes.

The therapeutic vaccines and other antigen-specific active immunotherapies include cancer vaccines and immunotherapies, such as dendritic cells, lymphocyte-based therapies, cancer cell-based therapies, peptides, proteins. Also, non-infectious disease therapeutic vaccines, such as peptides, proteins, and small molecules.

**SLIDE 16**

Other regulated products within OTAT include gene therapies. These involve genetically modified cells, as well as plasmids, viral vectors, and bacterial vectors.

Xenotransplantation products, purified and recombinant proteins for hematology (for example coagulation factors, thrombin, botulism antitoxin, diphtheria antitoxin, fibrin sealants), and antivenins.

OTAT also regulates some devices and combination products, like devices with a cellular component, and selection devices for the manufacture or delivery of cells.

**SLIDE 17**

The 21st Century Cures Act was signed into law on December 13, 2016 to accelerate medical product development and bring innovative medical products to patients. The law provides a framework for certain regenerative medicine therapy products to qualify for the regenerative advanced therapy designation program, which FDA generally refers to as "regenerative medicine advanced therapy" or "RMAT."

To qualify for RMAT designation, the regenerative medicine therapy must be intended to treat, modify, reverse, or cure a serious life-threatening condition, and preliminary clinical evidence must indicate that it has the potential to address unmet medical needs for a specific disease or condition.

**SLIDE 18**

Requests for RMAT designation can be made concurrently with an Investigational New Drug Application, or IND submission, or as an amendment to an existing IND. A request should contain a brief description of available therapies for the disease or condition, a description of the study design, identification of the study population and endpoint or endpoints used, and study results with the statistical analysis. For additional

information, see the web reference to the "Guidance for Industry: Expedited Programs for Serious Conditions - Drugs and Biologics".

**SLIDE 19**

One of the programs within the Oncology Center of Excellence, or OCE, is the Oncology Cell and Gene Therapy program, which emphasizes emerging oncology science to achieve excellence in medical product regulation.

The program leverages skills of the clinical oncology staff and regulatory scientists from other disciplines such as manufacturing experts, pharmacologists and toxicologists, and statisticians.

The Oncology Cell and Gene Therapy program collaborates with academia, industry, patient advocacy groups, professional societies and other countries' regulators to expedite the time to market for these products.

The OTAT update slides presented here incorporate new organizational changes, as well as recent regulatory updates. For more information, please view the OTAT training presentations shown in this series.

**SLIDE 20**

Let's transition to CBER's Office of Blood Research and Review, or OBRR.

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 products including Red Blood Cells, Platelets, Plasma and Source Plasma, 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.

**SLIDE 21**

The Office of Blood Research and Review is responsible for ensuring the safety and efficacy of blood and blood components. OBRR focuses primarily on products involved in transfusion medicine such as Red Blood Cells, Platelets and Plasma.

OBRR's regulatory oversight includes establishing regulatory policies and standards;
Reviewing regulatory applications;
Performing establishment inspections, product investigations, and health hazard evaluations, in collaboration with FDA's Office of Regulatory Affairs and CBER's Office of Compliance and Biologics Quality.

OBRR also conducts mission-related research; is involved in emergency preparedness, and engages in outreach to stakeholders, such as liaison interactions and workshops.

**SLIDE 22**

OBRR oversees the regulation of blood establishments that collect blood for transfusion or Source Plasma for further manufacture. In 2016, there were approximately 6.2 million volunteer blood donors who provided about 13.8 million Whole Blood, Red Blood Cell, Platelet and plasma donations, resulting in about 17.2 million transfused units. An additional 38 million donations of Source Plasma were collected for further manufacture into plasma derivatives such as clotting factors or immune globulins.

**SLIDE 23**

The Office of Blood Research and Review regulates devices used in the manufacture of blood components including blood bags, pathogen reduction devices, blood establishment computer software, and apheresis machines. OBRR approves or clears the devices used to collect and process blood, such as the apheresis machines, using the device authorities of the FD&C Act. Recently, FDA approved a device that can reduce or inactivate pathogens in platelets or plasma. In doing so, OBRR used the device authority under the FD&C Act.

OBRR approves infectious disease donor screening tests and blood typing tests using the Biologics License Application, or BLA, provisions of the PHS Act. OBRR also establishes requirements and provides recommendations for the use of these tests in blood establishments.

For example, OBRR has licensed both antibody and nucleic acid screening tests for HIV. Under FDA regulations, both tests must be used to screen blood donations. In response to emerging epidemics such as West Nile virus or Zika virus, FDA worked with blood establishments and device manufacturers to rapidly develop, license and implement tests to screen blood donations.

Under the BLA, CBER also regulates blood components and albumin. Note that other plasma-derived products are regulated in the Office of Tissues and Advanced Therapies.

And under NDAs, or New Drug Applications, FDA reviews blood bags containing solutions used for collection of blood and plasma donations.

For more detailed information on the regulation of blood and blood components, please view the OBRR training presentations shown in this series.

**SLIDE 24**

Moving to CBER's Office of Vaccines Research and Review, or OVRR, the Office has three divisions: the Division of Bacterial, Parasitic and Allergenic Products; the Division of Viral Products, and the Division of Vaccines and Related Products Applications.

Note that OVRR regulates preventive vaccines. Therapeutic vaccines are regulated by CBER's Office of Tissues and Advanced Therapies.

The next few slides give CBER's "current thinking" on particular issues discussed in the OVRR training presentations shown in this series.

**SLIDE 25**
As of April 2017, FDA has licensed 95 vaccines.

The FDA continually develops guidance documents to assist sponsors and the developers of new biologics. For recent guidance documents related to the development of vaccines and related products, please see the website referenced on this slide.

**SLIDE 26**
With regards to assay validation, FDA expects that all clinical assays that support licensure will be validated by the Phase 3 efficacy studies. Chemistry manufacturing and controls, or CMC assays that support licensure should, at a minimum, be qualified by Phase 3. All assays supporting licensure should be validated by the time the Biologics License Application, known as the BLA, is submitted.

**SLIDE 27**
As stated, OVRR regulates preventive vaccines for infectious disease indications. Within OVRR, an adjuvant is defined as an agent that is added to or used in conjunction with a vaccine antigen to augment or potentiate and possibly target the specific immune response to an antigen. In the U.S., licensed vaccines still contain primarily aluminum-containing compounds as adjuvants. Also, in the U.S., vaccine adjuvants are not licensed on their own. Instead, each specific antigen plus adjuvant combination or formulation is licensed.

**SLIDE 28**
FDA continues to evaluate and approve adjuvanted vaccines. Examples of approved vaccines with novel adjuvants include Cervarix (AS04),
Q-Pan (AS03), and Fluad (MF59).

Vaccine sponsors should refer to the current FDA guidance concerning the nonclinical evaluation of products with novel adjuvants.

Also review the additional guidance: WHO Guidelines on the Nonclinical Evaluation of Vaccine Adjuvants and Adjuvanted Vaccines, published in 2013.

When toxicology study reports are available, they should be included in the new IND application, or in a Master File to be cross referenced to the new IND.

**SLIDE 29**
Broader information on toxicology studies can be found in the training presentation, "Regulatory Considerations
in the Safety Assessment of Adjuvants and Adjuvanted Preventive Vaccines".

FDA has updated this information by recommending that the vaccine dose used in repeat toxicology studies be administered as a single dose and not split if possible.

In the case of a novel adjuvant, it may be advisable to include additional lower and higher doses of the adjuvanted vaccine formulation or adjuvant alone, in order to identify a safe dose that could be used in a first-in-human clinical trial.

Another consideration is to include an adjuvant only group, especially if a novel adjuvant is being evaluated.

**SLIDE 30**

FDA has updated recommendations concerning the numbers of animals per sex and group that are needed for non-clinical toxicology studies. When using mice and rats, treatment phase studies should use 20 animals per experimental group. Recovery phase studies should use 10 animals per experimental group.

When using rabbits, treatment and recovery phase studies should use at least 10 animals per experimental group.

Regardless of the animal model, experimental groups should include equal numbers of male and female animals.

**SLIDE 31**

FDA has clarified that body weights should be monitored daily for the first week after vaccination. Later, 2-3 times per week is sufficient.

With regard to body temperature, if there is an increase in temperature, additional measurements should be taken every 24 hours until the values return to baseline.

In addition to the previously provided recommendations for parameters to be monitored, FDA recommends that species-appropriate acute phase reactants, for example, C-reactive protein be measured prior to immunization 24-48 hours and 7 days after vaccination.

**SLIDE 32**

New to these recommendations, FDA has updated information concerning the parameters to be monitored when there is local reactogenicity. Studies include a daily assessment of local reactogenicity, limb use impairment after each injection, until resolved.

The injection site reaction after inoculation should be scored using a prospectively defined system, for example the modified Draize test.

The site of administration and any other site that comes in contact with the adjuvant or adjuvanted vaccine such as eye exposure during aerosol administration, or digestive tract after oral administration, should also be evaluated histopathologically.

And, a description of cellular infiltrates based on routine histological staining, if present, should be reported in the postmortem evaluation, as well as any manifestation of tissue damage at the site of injection and surrounding anatomic structures, for example sciatic nerves, nasal cavities, or olfactory bulb.

**SLIDE 33**
FDA has updated information concerning the timing of toxicology studies.

As a reminder, the repeated dose toxicity study report should be submitted prior to initiating Phase 1 clinical trials. Sponsors should obtain CBER's agreement prior to or during pre-IND meetings and need to provide adequate information on their clinical plan.

Additionally, reproductive developmental toxicology studies should be conducted prior to initiating clinical trials in pregnant women of vaccines developed for use in pregnancy. For vaccines indicated for females of childbearing potential and where pregnancy precautions are recommended, developmental toxicity studies may be performed in parallel to the clinical study.

**SLIDE 34**
Regarding the submission of toxicology studies to the FDA, we recommend that sponsors submit protocols for CBER review prior to initiation of animal studies. Additionally, toxicity study reports should be submitted with the new IND or Master File and should contain:
• the full tabulation of data, summary and line listings, and well-organized tables;
• Certificates of Analysis for test articles and supporting stability data; and
• the final draft version of studies are acceptable. The final QA/QC version is due 120 days after submission of the IND.

FDA may recommend that additional toxicity studies may be necessary as the product and clinical development proceed.

As mentioned, the OVRR-update slides shown here incorporate CBER's "current thinking" on particular aspects of the topics covered in the OVRR training presentations shown in this series.

**SLIDE 35**
Another CBER office is the Office of Compliance and Biologics Quality, or OCBQ. The OCBQ organization, shown on this slide, has four divisions: The Division of Inspections and Surveillance (or DIS); the Division of Manufacturing and Product Quality (or DMPQ); the Division of Biological Standards and Quality Control (or DBSQC); and the Division of Case Management (or DCM). OCBQ's immediate Office of the Director also includes a policy team.

In the next few slides, we will discuss the updates within OCBQ since 2009.

**SLIDE 36**
In 2010, the Division of Product Quality, which resided in the Office of Vaccines Research and Review, was reorganized into OCBQ. The new name for this division is Division of Biological Standards and Quality Control, or DBSQC.

DBSQC is the product office for licensing activity for Limulus Amebocyte Lysate, or LAL Reagent kit manufacturers. DBSQC manages the distribution of reference standards and test materials. DBSQC is one of four essential regulatory laboratories under the World Health Organization.

Lot release testing is performed, per Testing Plans, in DBSQC laboratories, using test methods that are accredited by A2LA to ISO 17025 standards.

**SLIDE 37**
This chart shows the number of compliance actions that OCBQ issued per fiscal year, from 2011 until August 2017. In fiscal year 2017, as of August 2017, OCBQ has sent four warning letters and five untitled letters. In some cases, where a single manufacturer operates more than one facility, FDA may combine violations found in any of those facilities into a single Warning letter.

**SLIDE 38**
OCBQ has issued orders to cease manufacturing of HCT/Ps. As of 2017, there are four orders to cease manufacturing which are still in effect. OCBQ issued an order to cease manufacturing of HCT/Ps to Amniotic Therapies in 2016. It then issued an amended order to cease manufacturing to Amniotic Therapies in 2017.

**SLIDE 39**
This chart shows the number of CBER recalls per product type and fiscal year from 2012 until 2016. In fiscal year 2016, blood products were the most recalled products. The total number of recalls in fiscal year 2016 was 575.

**SLIDE 40**
In March 2009, the Direct Recall Classification program went into effect in order to utilize current information technology to streamline recall classification of biological products. By using an electronic interface between two existing agency databases, the time and resources previously needed to review and classify recalls of biological products were greatly reduced.

**SLIDE 41**
If you are a consumer, DRC means that recalls of biological products are posted in the public domain in a more timely manner.

If you are member of the biologics industry, you will be able to provide information to FDA electronically regarding a recall you are conducting of biological products. This reduces the burden of copying manual records and sending them to an FDA district

office. DRC also facilitates communications with the agency to answer questions or to gather more information regarding a recall.

For the agency, DRC has decreased the amount of time previously used by the district office and CBER to gather, evaluate, review, and classify a firm's recall action. The average amount of time from learning of a firm's recall action to classification of the recall has decreased from years to weeks and, through the use of DRC, continues to decrease.

For the agency, as well as for the public, DRC decreased the resources needed to classify and publish recalls, and allows the reallocation of resources to other agency priorities related to protection of the public health.

**SLIDE 42**

This chart shows the number of recalls in comparison to the recalls that were captured in the Direct Recall Classification. As can be seen from the graph, the number of recalls in fiscal year 2017 now very closely match with the recalls captured in the DRC.

**SLIDE 43**

Another computer program that we now utilize is the Biologics Export Certification Application and Tracking System, or BECATS, which was implemented in October 2013.

BECATS is CBER's web-based application for accepting requests, reviewing, processing, managing, tracking, and administering export certificates. At this time, BECATS is available only for Certificates to Foreign Governments. BECATS automates many of the steps that exporters and CBER perform when submitting and processing export document requests. Advantages to exporters include reduction in certificate processing time; real-time validation that eliminates the need to return submissions; certificate print preview; elimination of the cost of mailing the request; and real-time status updates available via email.

**SLIDE 44**

The chart shows the top ten countries that United States companies producing CBER-related products exported to in 2017. These counts are as of September 27, 2017. The chart on the right shows the top 10 product types that were exported from United States companies in 2017. Blood Source-Plasma were the product type exported most in 2017.

For additional information on the regulatory oversight of the Office of Compliance and Biologics Quality, please view the OCBQ training presentations shown in this series.

**SLIDE 45**

We now move to CBER's Office of Biostatistics and Epidemiology, or OBE.

The Office of Biostatistics and Epidemiology is composed of two divisions: the Division of Biostatistics, and the Division of Epidemiology. Each division has two branches.

Within the Immediate Office of the Director are additional teams. These include the Analytics and Benefit Risk Assessment Team, the High-Performance Integrated Virtual Environment Team, also known as HIVE, and the Business Management Team.

**SLIDE 46**

The Division of Biostatistics provides
statistical evaluation of study protocols for scientific soundness, comprehensive statistical review for medical product applications, and development and evaluation of novel study design approaches. The Division of Epidemiology analyzes adverse event information and epidemiology studies, assesses applicant Pharmacovigilance Plans, and determines the need for post-market studies and risk mitigation. The Analytics and Benefit Risk Assessment Team provides benefit-risk assessments and management, data mining, bioinformatics and genomics, and Real World Evidence, such as effectiveness studies.

**SLIDE 47**

The FDA Amendments Act of 2007 (known as FDAAA), in section 905, required that FDA establish an active post-market risk identification and analysis system.

The objective of this system is to enhance FDA's capability to identify and investigate safety issues in a reasonable amount of time and to estimate a measure of association between medical products exposure and adverse outcomes.

The main data source includes claims and administrative data with a small proportion from electronic health records, all of which are provided by private insurance companies.

**SLIDE 48**

CBER has its own Sentinel program. The CBER Sentinel Program consists of 3 components: The Post-licensure Rapid Immunization Safety Monitoring, or PRISM, component focuses on vaccine surveillance. Blood Safety Continuous Active-surveillance Network, or BloodSCAN, focuses on surveillance of blood and blood-derived products, and Surveillance of Tissues and Advanced Therapeutics performs surveillance on tissues and advanced therapeutics.

The OBE slides presented here include recent regulatory updates. For more information, please view the OBE training presentation shown in this series.

**SLIDE 49**

This concludes our high-level overview of recent updates over the past few years. We encourage you to view the entire web-based foreign regulators training program series for a full understanding of how CBER regulates biologics. Also, please visit the FDA CBER public website for more useful information on all the CBER Offices, as well as

CBER's international webpages for global outreach.  Here, we've listed some other helpful references.

**SLIDE 50**

We would like to acknowledge the Offices which contributed to the development of this presentation. Thank you.