BIOLOGICS

(Dollars in Thousands)	FY 2016 Final	FY 2016 Actuals	FY 2017 Annualized CR	FY 2018 President's Budget	FY 2018 President's Budget +/- FY 2017 CR
Biologics	**354,775**	**329,156**	**339,082**	**366,230**	**27,148**
Budget Authority	***215,317***	***215,308***	***214,907***	***95,893***	***-119,014***
User Fees	***139,458***	***113,848***	***124,175***	***270,337***	***146,162***
Center	311,094	286,622	295,735	325,101	29,366
Budget Authority	173,937	173,929	173,606	61,398	-112,208
User Fees	137,157	112,693	122,129	263,703	141,574
Prescription Drug (PDUFA)	*123,801*	*102,934*	109,704	*226,459*	*116,755*
Medical Device (MDUFA)	*11,475*	*9,731*	10,508	*34,010*	*23,502*
Generic Drug (GDUFA)	*1,072*	*26*	1,088	*1,502*	*414*
Biosimilars (BsUFA)	*809*	*2*	829	*1,732*	*903*
Field	43,681	42,534	43,347	41,129	-2,218
Budget Authority	41,380	41,379	41,301	34,495	-6,806
User Fees	2,301	1,155	2,046	6,634	4,588
Prescription Drug (PDUFA)	*2,084*	*1,152*	1,847	*5,311*	*3,464*
Medical Device (MDUFA)	*217*	*3*	199	*1,323*	*1,124*
FTE	**1,341**	**1,341**	**1,379**	**1,409**	**30**

Authorizing Legislation: Public Health Service Act; Federal Food, Drug, and Cosmetic Act; Medical Device Amendments of 1976; Clinical Laboratory Improvement Amendments of 1988 (42 U.S.C. 201); Safe Medical Devices Act of 1990; Medical Device Amendments of 1992; Food and Drug Administration Modernization Act of 1997; Medical Device User Fee and Modernization Act of 2002; Public Health Security and Bioterrorism Preparedness Response Act of 2002; Project Bioshield Act of 2004; Medical Device User Fee Stabilization Act of 2005; Food and Drug Administration Amendments Act of 2007 (FDAAA); Patient Protection and Affordable Care Act of 2010; Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA); Drug Quality and Security Act of 2013; Pandemic and All-Hazards Preparedness Reauthorization Act of 2013, 21st Century Cures Act of 2016 (Cures Act)

Allocation Methods: Direct Federal/Intramural

PROGRAM DESCRIPTION AND ACCOMPLISHMENTS

The Biologics Control Act, passed in 1902, established the Biologics Program in the Department of Treasury's Hygienic Laboratory, which later became part of the National Institute of Health (NIH) in 1930. In 1972, the Biologics Program was transferred from NIH to FDA and became the Bureau of Biologics. In 1988, the Bureau became the Center for Biologics Evaluation and Research (CBER) which, with the Office of Regulatory Affairs' (ORA) field program, comprises the FDA Biologics Program.

The mission of CBER is to ensure the safety, purity, potency, and effectiveness of biological products including vaccines, allergenics, blood and blood products, and cells, tissues, and gene therapies for the prevention, diagnosis, and treatment of human diseases, conditions, or injury. Through our mission, we also seek to protect the public against the threats of emerging infectious diseases and bioterrorism. CBER uses sound science and regulatory expertise to:

- Protect and improve public and individual health in the United States and, where feasible, globally
- Facilitate the development, approval of, and access to safe and effective biological products and promising new technologies
- Strengthen CBER as a preeminent regulatory organization for biological products.

CBER has developed an interim strategic plan for 2017-2019 to contribute to the improvement of public health and to provide a framework for how CBER can most effectively allocate its fiscal and human resources to successfully navigate the challenges and opportunities of 21st Century medicine,. This plan aligns with FDA's Strategic Priorities and the Department of Health and Human Services' strategic plan and reflects new legislative mandates, expanded roles in addressing global health needs, recent innovations in regulatory science and technology, and expanded opportunities for collaboration. The CBER goals include:

- Increase the nation's preparedness to address threats as a result of terrorism, pandemic influenza, and emerging infectious diseases.
- Improve global public health through international collaboration including research and information sharing.
- Utilize advances in science and technology to facilitate development of safe and effective biological products.
- Ensure the safety of biological products.
- Advance regulatory science and research.
- Manage for organizational excellence and accountability.

During 2016, the Biologics Program contributed to the improvement of public health with the following accomplishments:

- In response to the Zika virus outbreak, FDA contributed with the development of blood and tissue safety guidances and took rapid steps to help ensure safety of the blood supply.
- FDA approved noteworthy biological products including Imlygic, the first FDA-approved oncolytic virus therapy to treat melanoma lesions that cannot be removed completely by surgery.
- FDA issued a Warning Letter regarding three stem cell treatment centers for operating without a valid biologics license or investigational new drug application in effect.

The following selected accomplishments demonstrate the Biologics Program's delivery of its regulatory and public health responsibilities within the context of current priorities. [26]

Improve and Safeguard Access

Within this Goal area, the Biologics Program addresses the following FDA Strategic Priorities: Safety and Quality, Regulatory Science, Globalization, and Smart Regulation. FDA's Biologics Program is committed to facilitating the development of new biological products for a broad range of complex and life-threatening diseases. The program seeks to expedite the development of innovative and complex biological products, including those representing the exciting medical promise of precision medicine; additional vaccines against pandemic influenza and other infectious diseases; cellular and gene therapies; and new technologies to enhance the safety and availability of blood and blood products.

Facilitate Product Development through Regulatory Science

FDA contributes to, and draws on, advances in science and technology to design better ways of predicting the safety, purity, potency and effectiveness of biological products early in their life cycle and conducts mission-related research to facilitate product development. The Biologics

[26] Please visit FDA.gov for additional program information and detailed news items.

Program has a cadre of scientific experts who understand the regulatory process to conduct proactive research to address regulatory science gaps and provide effective regulatory responses to public health emergencies and new technologies. FDA leverages this considerable scientific expertise to develop new methods and technologies designed to expedite product development.

FDA conducted research to model the impact of removing risk assessment questions for HIV and rely solely on HIV nucleic acid testing in order to protect the blood supply. The study found these changes would potentially increase the risk of exposure to HIV four-fold to blood recipients.[27]

In response to the Zika virus outbreak, FDA participated in the 7th meeting of the World Health Organization (WHO) Collaborating Centers to support development of WHO Biological Reference Preparations, including the Zika virus for the development of blood products and in vitro diagnostics devices used to test blood and blood components in March of 2016.

FDA also supported Zika diagnostic test development to help ensure diagnostic tests for Zika virus provide accurate and reliable results. FDA created Zika Virus RNA reference materials that were distributed to manufacturers to qualify blood screening methods.

Influenza Vaccine

To address potential bottlenecks in the production of seasonal and pandemic influenza vaccines**,** FDA has developed novel alternative methods to generate reagents needed to measure vaccine potency for lot release testing of vaccines. When the avian influenza viruses (H7N9) emerged in China in 2013, FDA overcame an unexpected bottleneck in the preparation of H7N9 vaccine reagents with the first use of an alternative approach to the standard procedure for producing an influenza vaccine potency reagent. Since the results were less than optimal with the traditional method, scientists used a method developed in FDA laboratories where the influenza H7N9 hemagglutinin (HA) glycoprotein is expressed as a virus-like particle and used to generate the H7-specific antiserum needed for potency testing.

FDA scientists are studying how to define the key properties of stem cell-derived therapies that would correlate with safety, potential for efficacy, and product quality in the clinical application of these cells. The scientists are testing the feasibility of innovative methodological approaches to characterize the cells. One recent example is the development of a new method to predict the ability of human mesenchymal stem cells (also known as multipotent mesenchymal stromal cells) to differentiate into bone cells (a term referred to scientifically as osteogenic induction).

In November 2016, two FDA scientists were awarded the Patent for Humanity award from the US Patent and Trademark Office for developing an improved meningitis vaccine production process that has been used to produce a vaccine for African countries to protect against meningococcal type A disease. 235 million people in high-risk Africa countries have been immunized with this vaccine, and thereby tens of thousands of deaths have been prevented.

In June 2016, FDA released a study on multiplex detection and identification of viral, bacterial, and protozoan pathogens in human blood and plasma using a high-density resequencing pathogen microarray platform, published in *Transfusion*. The results indicate that the technology

[27] Modeling complete removal of risk assessment questions in the USA predicts the risk of HIV exposure in blood recipients could increase despite the use of nucleic acid testing. Vox Sanguinis 2016 May (Epub 2016 Jan 14); Yang H, Anderson SA, Forshee R, Williams A, Epstein JS, Marks PW.

has potential for use in blood safety to identify nucleotide changes in the target pathogen and its potential utility in confirmatory testing for a wide variety of blood-borne pathogens.

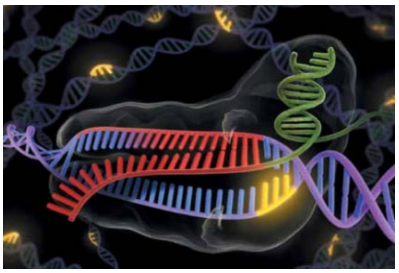
In January 2016, the Allergenic Products Advisory Committee met in open session to discuss approaches to establish the safety and effectiveness, including challenge study endpoints, to support the licensure of food allergy immunotherapy products and the clinical development of aeroallergen immunotherapy products for the prevention of respiratory allergic disease.

Improve the Development of Advanced Technologies and Methods

Advances in science and technology show great promise for the development of safe and effective biological products. The Biologics Program is working to expedite the use of advanced technologies and methods, such as newly identified clinical biomarkers, innovative clinical trial designs, and genomics, through the development of regulatory policy and guidances for industry. FDA is also identifying opportunities to expand the use of new scientific technologies in genomics, proteomics, and structural biology to strengthen science-based regulatory review.

Building on the FDA's existing expedited programs available to regenerative medicine products, the Regenerative Medicine Advanced Therapy (RMAT) Designation was established though the Cures Act, signed into law in December of 2016. Drugs that are regenerative medicine therapies may obtain the RMAT designation if the drug is intended to treat serious or life-threatening diseases or conditions and if there is preliminary clinical evidence indicating that the drug has the potential to address unmet medical needs for that disease or condition. RMAT-designated products are eligible for increased interactions with the FDA, similar to those interactions available to sponsors of breakthrough-designated therapies. In addition, they may be eligible for priority review and accelerated approval.

To improve the effectiveness of the product development process, FDA convened the public workshop "Scientific Evidence in the Development of Human Cells, Tissues, and Cellular and Tissue-Based Products Subject to Premarket Approval" on September 8, 2016, to identify and discuss scientific considerations and challenges to help inform the development of human cells, tissues, and cellular and tissue-based products (HCT/Ps) subject to premarket approval, including stem cell-based products. The importance of rigorous science for the development of stem cell therapies and product review and approval, risk-based approaches to review or change a product, and correct identification of stem cells were discussed.



Complex Therapies

FDA also held a Part 15 hearing, on September 12-13, 2016, to obtain feedback from stakeholders on four draft guidances relating to the regulation of HCT/Ps with over 90 presenters and close to 500 attendees. This feedback will be used to clarify and finalize Agency guidance on these complex yet critical issues related to the regulation of HCT/Ps.

Additionally, FDA hosted the 19th US-Japan Cellular and Gene Therapy Conference, on March 10, 2016, in conjunction with Japan's Ministry of Education, Culture, Sports, Science and Technology, under the US-Japan Cooperative Research Program. The theme of this meeting was three-dimensional (3D) modeling and printing of tissues and organs. The goal of the conference was to exchange ideas on cutting-edge areas of biomedical research, discuss the innovations in in

3D bioprinting of various anatomical structures and their potential use in regenerative medicine, and enhance opportunities for collaborations among scientists from the U.S. and Japan.

Efficiently Provide Access for Safe and Effective Products

FDA continuously evaluates and improves its business processes so that mission-critical work is performed in an effective and efficient manner. FDA also continues to provide scientific and regulatory advice to sponsors and stakeholders and to collaborate with other agencies and international regulatory authorities to advance the clinical development and licensure of biological products. To expedite the development and review of innovative products, established FDA programs such as fast track, breakthrough therapy, accelerated approval, and priority review are used for products that address an unmet medical need of a serious condition.

The Biologics Program exceeded its performance target by completing 100 percent of the standard and priority Biologics License Application/New Drug Application reviews, and standard and priority Efficacy Supplement reviews, within the specified review timeframes for the FY 2015 receipt cohort.

To improve efficiency in the review process, the Electronic Managed Review Process information technology system was developed and launched in September 2016. This system provides comprehensive workload, workflow, and regulatory information on Biologic License Application (BLAs) to supervisors, reviewers, and regulatory project managers to increase efficiency and reduce costs.

Selected Product Approvals in 2015 – 2017

FDA's Biologics Program has reviewed and approved an array of biological products to treat and prevent diseases. Below are selected recent Biological product approvals in date order.

Disease	Approved	Trade Name	Proper Name	Purpose or Benefit
Dust Mite Allergy	Mar 2017	Odactra	House Dust Mite Allergen Extract	The first allergen extract to be administered under the tongue to treat house dust mite induced nasal inflammation in people 18 through 65 years.
Full-thickness cartilage defects of the knee	December 2016	MACI	Autologous cultured chondrocytes on porcine collagen membrane	First FDA-approved product that applies the process of tissue engineering to grow cells on scaffolds using healthy cartilage tissue from the patient's own knee for repair.
Cholera	June 2016	Vaxchora	Cholera Vaccine Live Oral	Only FDA-approved vaccine for the prevention of cholera for adults traveling to cholera-affected areas. (Fast Track designation, Priority Review Status and Tropical Disease Priority Review Voucher)
von Willebrand disease	Dec 2015	Vonvendi	von Willebrand factor (Recombinant)	For adults, 18 years of age and older, diagnosed with von Willebrand disease. The first FDA-approved recombinant von Willebrand factor approved for the on-demand treatment and control of bleeding episodes. (Orphan Drug designation)
Influenza	Nov 2015	Fluad	Influenza vaccine, adjuvanted	The first adjuvanted trivalent seasonal influenza vaccine persons 65 years of age and older against influenza virus subtypes A and B. (Accelerated approval)

Disease	Approved	Trade Name	Proper Name	Purpose or Benefit
Melanoma lesions in the skin and lymph nodes	Oct 2015	Imlygic	talimogene laherparepvec	First FDA-approved genetically modified live oncolytic virus therapy used to treat melanoma lesions that cannot be removed completely by surgery.
Hereditary Factor X deficiency	Oct 2015	Coagadex	Coagulation Factor X (Human)	The first coagulation factor replacement therapy for treatment of adults and adolescents with hereditary Factor X deficiency for control of bleeding episodes. (Fast track designation, Priority Review Status, and Orphan Drug designation)

Enhance Oversight

Within this Goal area, FDA's Biologics Program addresses the following FDA Strategic Priorities: Safety and Quality, Regulatory Science, Globalization, and Smart Regulation. FDA's oversight of production, manufacturing, and the global supply chain, combined with surveillance of postmarket product use, plays a critical role in assuring the safety of FDA-regulated products.

As a part of regulatory oversight, FDA develops standards; assists industry in reducing risks in the manufacturing, production, and distribution of FDA-regulated products; strengthens the detection and surveillance of potential problems; and improves the response to identified and emerging problems with FDA-regulated products.

Compliance and Oversight

FDA's field work plays an integral role in helping to assure the safety of FDA-regulated products. The field staff provides additional surveillance through inspections at domestic and foreign manufacturing facilities and clinical study sites, including blood and tissue establishments, vaccine and allergenic facilities, device manufacturers, gene and cell therapy facilities, and plasma fractionators. FDA performs inspections to oversee clinical investigators and institutional review boards to ensure that the rights of human subjects participating in clinical trials are protected.

Postmarket inspections are conducted after products are approved. These inspections are performed to assure that products are manufactured in compliance with cGMP and other applicable FDA regulations. These efforts help to ensure that the biologics industry continuously reviews the quality standards of its manufacturing operations to maintain the safety and effectiveness of biological products on the U.S. market.

For example, in FY 2016, FDA issued a Warning Letter regarding three stem cell treatment centers for operating without a valid biologics license or investigational new drug application in effect. The treatment centers had recovered adipose tissue and processed into adipose-derived stem cells intended to treat a variety of medical conditions. The Warning Letter also identified violations of current Good Manufacturing Practice (cGMP) and current Good Tissue Practice (CGTP).

Develop Guidance to Ensure Product Safety

FDA is responsible for ensuring that blood, blood components, and HCT/Ps remain free of infectious agents and contamination, which may be spread, through contact with infected individuals, travel to endemic areas, arthropod vectors, contaminated food, risk behaviors and

many other mechanisms. FDA plays a critical role in the United States' preparedness for and response to infectious diseases including issuing guidance documents to help protect the safety of FDA regulated biological products. FDA also works proactively to prepare for and respond to threats and potential problems, collaborating with Department of Health and Human Services (DHHS) agencies, federal government partners, the World Health Organization (WHO), National Regulatory Authorities, and stakeholders from the private and public sector.

For example, FDA has been working aggressively to combat the Zika virus outbreak. In February 2016, FDA issued guidance recommending the deferral of individuals from donating blood if they have been to areas with active Zika virus transmission, may have been exposed to the Zika virus, or had a confirmed Zika virus infection.[28] In August 2016, revised guidance was issued, recommending nationwide testing of individual units of blood components for Zika virus or the use of a pathogen reduction device for plasma and platelet products.[29]

Mosquito Borne Virus

FDA also issued guidance in March 2016, providing "Donor Screening Recommendations to Reduce the Potential Transmission of Zika Virus by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)." This guidance addresses donation of HCT/Ps from both living and deceased donors, including donors of reproductive cells/tissue (semen, oocyte, embryos) and gestational tissues such as umbilical cord blood, placenta, and amniotic membrane.

In January of 2017, FDA issued the final guidance for industry, "Recommendations for Assessment of Blood Donor Suitability, Donor Deferral and Blood Product Management in Response to Ebola Virus." This guidance provides blood establishments recommendations for assessing blood donor eligibility, donor deferral and blood product management in the event that an outbreak of Ebola virus disease.

In December 2015, FDA published the final guidance "Revised Recommendations for Reducing the Risk of Human Immunodeficiency Virus Transmission by Blood and Blood Products," changing the blood donor deferral period for men who have sex with men from an indefinite deferral to 12 months. AABB and Plasma Protein Therapeutics Association developed revised donor history questionnaires to facilitate blood establishments' implementation of the final guidance. FDA reviewed the questionnaires and recognized them as acceptable mechanisms for collecting donor history information in FDA guidance issued in May, 2016, "Implementation of Acceptable Full-Length and Abbreviated Donor History Questionnaires and Accompanying Materials for Use in Screening Donors of Blood and Blood Components."

FDA is committed to reevaluating and updating its blood donor deferral policies to reduce the risk of HIV transmission as new scientific data become available. In July 2016, FDA established a public docket for comment on the Agency's blood donor deferral recommendations described in the December 2015 guidance. FDA invited the submission of scientific evidence on the feasibility of moving from the existing time-based deferrals related to risk behaviors to alternate options, including the use of individual risk assessments.

[28] Guidance for Industry: Recommendations for Donor Screening, Deferral, and Product Management to Reduce the Risk of Transfusion-Transmission of Zika Virus, Feb 2016
[29] Guidance for Industry: Revised Recommendations for Reducing the Risk of Zika Virus Transmission by blood and Blood Components

Collaboration with Industry and Public Health Organizations

Each year, the FDA, WHO, CDC and other public health experts collaborate on the review of influenza disease surveillance and laboratory data collected from around the world in an effort to identify influenza strains that may cause the most illness in the upcoming season. Based on that information and the recommendations of the FDA's Vaccines and Related Biological Products Advisory Committee, which met on March 9, 2017, FDA selected the strains that should be included in the influenza virus vaccines for the 2017-2018 influenza season.

FDA participated in meetings with WHO to facilitate regulatory capacity building of national regulatory authorities in developing countries. In May 2016, FDA participated in a consultation meeting on the development of a guideline for Ebola vaccine development.

FDA continues to engage with trade organizations to discuss the concerns from the blood collection industry over the sustainability of the blood collection industry due to decreased demand for red blood cells for transfusion, causing significant reductions in collections of Whole Blood and Red Blood Cells. FDA representatives also participate as ex officio members of the HHS Advisory Committee on Blood and Tissue Safety and Availability to discuss the sustainability of the blood collection industry.

Guidances

Below are selected recent guidances issued by CBER, listed in date order. These guidances help address various issues.[30]

Date	#	Title	Description
Nov 2016	FDA-2016-D-3750-0001	Revised Recommendations for Determining Eligibility of Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products Who Have Received Human -Derived Clotting Factor Concentrates	Supplements the August 2007 guidance. FDA no longer considers FDA licensed Human-Derived Clotting Factor Concentrates a risk factor for HIV, HBV, or HCV.
Sep 2016	FDA-2013-D-1143-0097	Use of Nucleic Acid Tests to Reduce the Risk of Transmission of West Nile Virus (WNV) from Living Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)	Makes recommendations for eligibility determinations for HCT/Ps, for testing living donors for WNV. Supplements recommendations and supersedes the "WNV" section in the August 2007 guidance.
Aug 2016	FDA-2016-D-0545-00010049/0050	Revised Recommendations for Reducing the Risk of Zika Virus Transmission by Blood and Blood Components	Supersedes February 2016 "Recommendations for Donor Screening, Deferral, and Product Management to Reduce the Risk of Transfusion-Transmission of Zika Virus" guidance and March 2016 Q&A.

[30] Complete information on CBER guidances can be found at:
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances
Complete information on CBER rules can be found at:
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ActsRulesRegulations/default.htm

Date	#	Title	Description
Mar 2016	FDA-2013-D-0811-0022	Donor Screening Recommendations to Reduce the Risk of Transmission of Zika Virus by Human Cells, Tissues, and Cellular and Tissue-Based Products	Identifies Zika virus as a relevant communicable disease agent or disease and provides recommendations to reduce the risk of transmission of the virus by HCT/Ps.
Jan 2016	FDA-2012-D-0307-0007	Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease by Blood and Blood Products	Provides manufacturers of plasma-derived products with revised recommendations for how to report labeling that accurately reflects the potential risk for vCJD in products.

Monitor the Safety, Quality, and Availability of Licensed Biological Products

The Biologics Program's vision for postmarket safety monitoring entails expanding access to information regarding patients' use of a biological product and health outcomes in automated databases, enabling optimal detection and analysis of potential biologics safety concerns. FDA is working to expand the use of large databases from healthcare providers, insurers, and other partners to identify safety problems associated with biologic product use. Using large datasets that reflect real life experiences of consumers treated with the product allows a comprehensive approach to product safety surveillance. Combined with enhanced scientific tools such as genomics, advanced statistics, and mathematical modeling, FDA is using powerful tools of bioinformatics to develop new scientific data and methods to evaluate safety signals. Recent accomplishments are highlighted below.

FDA has launched initiatives to facilitate new "real time" surveillance of vaccines and blood products. In September 2016, FDA in collaboration with the National Heart, Lung and Blood Institute, and the DHHS Office of the Assistant Secretary for Health, launched the Transfusion-Transmissible Infections Monitoring System (TTIMS). This system provides invaluable data for estimating the incidence and prevalence of HIV, hepatitis B virus, and hepatitis C virus infection. TTIMS is actively assessing transfusion-transmitted infection markers, behavioral risk factors, and other epidemiologic variables among voluntary U.S. blood donors that may be used to reflect changes in future blood safety policies. FDA has awarded multi-year contracts to US blood centers for data and provides a sample collection representing more than 50 percent of the total US blood supply.

The Blood Safety Continuous Active Surveillance Network (BloodSCAN), a component of the Sentinel System, is an active surveillance system used to evaluate recipient safety of FDA-regulated blood components and plasma-derived products, utilizing billing electronic health record data and other electronic data to assess the risk of adverse health outcomes among large populations. In 2016, FDA expanded the data within BloodSCAN to include inpatient electronic health record data from Hospital Corporation of America. This assessment, which is the first Sentinel utilization of this new inpatient data source, examines the feasibility of utilizing this information to capture exposure to blood components and the outcome of transfusion-related

acute lung injury (TRALI), identify potential risk factors and estimate the incidence rates of TRALI subsequent to blood component exposure.

In September 2016, FDA issued the protocol and study report for the pilot study of TreeSCAN utilizing PRISM data for the HPV4 vaccine. The TreeSCAN method allows a wide range of unsuspected but potential adverse reactions to be simultaneously evaluated, helping to identify adverse events that may merit additional, careful epidemiologic investigation. FDA is also applying this method in the first protocol-based study designed to mine healthcare data in Sentinel to detect whether there are any serious, unexpected adverse events after vaccination for Gardasil 9.

In December, 2016, FDA held a public workshop entitled "The Sentinel Post-Licensure Rapid Immunization Safety Monitoring (PRISM) Program" to describe the Sentinel Initiative, illustrate how PRISM is used by FDA for regulatory responsibilities including the integration into FDA's regulatory review process, and discuss the future expansion and integration of PRISM.

Under FDASIA and the Drug Quality and Security Act, FDA gained additional authorities to enhance product safety through monitoring of drug shortages. From January 1 to September 30, 2016, the Biologics Program has documented 1 new drug product shortage, 9 prevented shortages, 2 ongoing shortages, 24 notifications of potential or actual shortages from 17 different manufacturers. CBER has used regulatory flexibility to prevent or mitigate 1 shortage, and expedited 6 reviews to prevent or mitigate a shortage.

FUNDING HISTORY

Fiscal Year	Program Level	Budget Authority	User Fees
FY 2014 Actual	$321,064,000	$210,912,000	$110,152,000
FY 2015 Actual	$326,290,000	$211,362,000	$114,928,000
FY 2016 Actuals	$329,156,000	$215,308,000	$113,848,000
FY 2017 Annualized CR	$339,082,000	$214,907,000	$124,175,000
FY 2018 President's Budget	$366,230,000	$95,893,000	$270,337,000

BUDGET REQUEST

The FY 2018 Budget Request for the Biologics Program is $366,230,000, of which $95,893,000 is budget authority and $270,337,000 is user fees. This level provides a net increase of $27,148,000. Budget authority decreases by -$119,014,000 compared to the FY 2017 Annualized CR level and user fees increase by $146,162,000. The Center for Biologics Evaluation and Research (CBER) amount in this request is $325,101,000. The Office of Regulatory Affairs amount is $41,129,000.

The FY 2018 budget allows the Biologics Program to advance public health through innovative regulation that promotes the safety, purity, potency, effectiveness, and timely delivery of biological products to the American public. FDA will continue to facilitate the development of new biological products for a broad range of complex and life-threatening diseases. FDA will work to reduce review times and regulatory burden by continuing to make every effort to enhance FDA-sponsor communications in its user fee programs and conducting Expedited

Reviews to promote timely access for critically needed therapies for patients that meet an important public health need, without compromising FDA's high standards for demonstrating the safety, efficacy, and quality of new medicines. The Biologics Program will continue to leverage all of the expedited medical programs, including Breakthrough Therapy designation, Regenerative Medicine Advanced Therapy Designation, Fast Track designation, Priority Review Status, and Accelerated approval, when appropriate. Building on the FDA's existing expedited programs available to regenerative medicine products, CBER will continue implementation of the Regenerative Medicine Advanced Therapy (RMAT) Designation, which was established though the Cures Act.

The regulatory science and research program will continue to engage in forward-looking priority setting to allocate its resources towards efforts that best support FDA's ability to respond to public health needs, use science to address the complexity of products and ever-changing scientific and technological advancements.

To foster manufacturing innovation, flexibility, and adaptation in the increasingly global regulatory environment, FDA works to modernize existing regulations and guidance. These guidances range from protecting the blood and tissue supply in the face of an emerging infectious disease, to addressing recent statutory mandates, to expediting the use of advanced technologies, such as newly identified clinical biomarkers, innovative clinical trial designs, and genomics. FDA continues to collaborate with federal partners and regulated industry when developing or updating new guidance, rules, and standards that provide important direction to manufacturers and distributors of regulated biological products. The Biologics Program will continue early engagement with manufactures through participation in workshops to identify and discuss scientific considerations and challenges to help inform the development of biological products subject to premarket approval.

FDA collaborates and establishes relationships with other regulators and health agencies in the U.S. and throughout the world to respond quickly to public health threats resulting from outbreaks of emerging infectious diseases, pandemic influenza, and terrorism. FDA also strategizes to harmonize existing regulatory standards and works with international scientific efforts to establish and maintain reference materials and standards for biologics.

FDA continues to expand the use of large databases from healthcare providers, insurers, and other partners using real time data and population-based systems to identify and then address safety problems associated with biologic product use. Working with others in FDA, CBER will also support the advancement and use of systematic approaches to collect and utilize robust and meaningful patient and caregiver input that can more consistently inform drug development and, as appropriate, regulatory decision making.

BUDGET AUTHORITY

Reductions (-$7.5 million)

Center: -$4.8 million (Medical Product Safety & Availability)
CBER will reduce its applied scientific research, which supports the development of innovative products, in order to preserve critical regulatory oversight of its non-user fee programs that address blood components, tissues, and allergenic products. Spending on equipment upgrades and maintenance will be reduced, as will the number of research fellows hired to support the regulatory science program. Research fellows bring innovative ideas, talents, and skills to FDA

and fill gaps in emerging and targeted regulatory science areas. FDA's goal is to minimize the impact of these reductions on FDA's core mission activities.

CBER will also reduce work on the development of laboratory standards, including reference materials, assays, and methodologies that improve product quality and provide standards and guidance to address new technologies and emerging diseases.

Additionally, CBER will reduce staff through attrition in its non-user fee activities that include the regulation of blood components, tissues, and allergenic products. Not backfilling critical positions will require CBER to reprioritize how it provides advice to sponsors and reduce resources dedicated to the review of blood components for transfusion and allergenic extracts as well as the ability to provide advice to sponsors of tissues that do not require premarket review. CBER may no longer be able to exceed its performance target to complete review and action on 90% of complete blood bank and source plasma Biologic License Application supplements within 12 months after submission date. CBER will also limit proactive work to respond to infectious disease outbreaks globally, including limiting its active participation in international collaboration activities.

Field: -$2.7 million (Medical Product Safety & Availability)
ORA will apply strategic reductions to its programs in order to preserve the highest priority activities and operations in support of protecting public health. ORA will reduce existing workforce levels through attrition.

In order to continue operations under the FY 2018 request levels, ORA will apply the necessary program reductions to areas such as training, IT and lab equipment, and across all program office operating budgets while protecting resources for inspections and compliance activities.

Medical Product Budget Authority Recalibration (-$111.5 million)

Center: -$107.4 million / Field: -$4.1 million (Medical Product Safety & Availability)
The FY 2018 President's Budget recalibrates FDA funding for medical product review and approval processes from budget authority to user fees.

USER FEES

Medical Product User Fee Recalibration and Regulatory Efficiencies (+$146.2 million)

Center: +$141.6 million / Field: +$4.6 million (Medical Product Safety & Availability)
The FY 2018 President's Budget recalibrates FDA funding for medical product review and approval processes from budget authority to user fees. The budget also includes a package of administrative actions designed to achieve greater regulatory efficiency and speed the availability of innovative, safe, and effective medical products in the market. These actions include the improvements are described in the PDUFA VI, MDUFA IV, GDUFA II, and BSUFA II commitment letters submitted to Congress in January 2017.

CBER will strive to reduce review times and regulatory burden by continuing efforts to enhance FDA-sponsor communications and conducting Expedited Reviews with the goal of promoting patients' timely access to life-saving therapies consistent with FDA's high standards and public health mission. CBER is also working to enhance the use of real world evidence to incorporate meaningful patient and caregiver input, as appropriate, into FDA's regulatory decision making on behalf of patients. As part of our commitment to being a global leader at the forefront of medical advances and bringing forward cutting-edge therapies for patients, CBER will continue

implementation of the Regenerative Medicine Advanced Therapy (RMAT) Designation, which was established though the 21st Century Cures Act. RMAT-designated products, cell therapy, therapeutic tissue engineering products, human cell and tissue products, and combination products, are eligible for increased interactions with the FDA, similar to those interactions available to sponsors of breakthrough-designated therapies and may be eligible for priority review and accelerated approval. The Center will also work in collaboration with federal partners and regulated industry to address infectious diseases that may emerge to threaten public health, such as novel influenza viruses.

PERFORMANCE

The Biologics Program's performance measures focus on biological product review, manufacturing diversity and capacity for influenza vaccine production, strengthening detection and surveillance of FDA-regulated products and postmarket inspections in order to ensure the safety, purity, potency, and effectiveness of biological products, as detailed in the following table.

Measure	Year and Most Recent Result / Target for Recent Result (Summary of Result)	FY 2017 Target	FY 2018 Target	FY 2018 +/- FY 2017
233207: Review and act on standard New Molecular Entity (NME) New Drug Application (NDA) and original BLA submissions within 10 months of the 60 day filing date. *(Output)*	FY 2015: 100% Target 90% (Target Exceeded)	90%	90%	Maintain
233208: Review and act on priority NME NDA and original BLA submissions within 6 months of the 60 day filing date. *(Output)*	FY 2015: NA (No submissions received)	90%	90%	Maintain
233209: Review and act on standard non-NME original NDA submissions within 10 months of receipt. *(Output)*	FY 2015: NA (No submissions received)	90%	90%	Maintain
233210: Review and act on priority non-NME original NDA submissions within 6 months of receipt. *(Output)*	FY 2015: NA (No submissions received)	90%	90%	Maintain
233205: Complete review and action on complete blood bank and source plasma BLA submissions within 12 months after submission date. *(Output)*	FY 2015: NA (No submissions received)	90%	90%	Maintain
233206: Complete review and action on complete blood bank and source plasma BLA supplements within 12 months after submission date. *(Output)*	FY 2015: 100% Target: 90% (Target Exceeded)	90%	90%	Maintain
233211: Review and act on new non-user fee, non-blood product applications within 12 months of receipt. *(Output)*	FY 2015: 100% Target: 60% (Target Exceeded)	60%	60%	Maintain

Measure	Year and Most Recent Result / Target for Recent Result (Summary of Result)	FY 2017 Target	FY 2018 Target	FY 2018 +/- FY 2017
234101: Increase manufacturing diversity and capacity for influenza vaccine production. *(Output)*	FY 2016: Continued evaluation of new methods to produce high-yield influenza vaccine reference strains. (Target Met)	Continue evaluation of new methods to produce high-yield influenza vaccine reference strains	Continue evaluation of new methods to produce high-yield influenza vaccine reference strains	Maintain
231301: Percentage of Lot Distribution Reports that were entered into the Regulatory Management System – Biologics License Applications (RMS-BLA) within 7 Days. *(Output)*	FY 2016: 96% Target 85% (Target Exceeded)	85%	85%	Maintain
234212: Percentage of registered domestic blood bank and biologics manufacturing inventory inspected (approximately 900 in total). *(Output)*	FY 2016: 992 Target: 900 (Target Exceeded)	99%	99%	Maintain
234213: Percentage of planned human foreign and domestic tissue establishment inspections (approximately 570 in total). *(Output)*	FY 2016: 703 Target: 570 (Target Exceeded)	82%	82%	Maintain

Influenza Performance Measure

This performance measure supports the Department's national preparedness efforts in combating seasonal influenza, by increasing manufacturing diversity and capacity for influenza vaccine production. In FY 2016, FDA met the target to continue evaluation of new methods to produce high-yield influenza vaccine reference strains. Activities to meet this target included the following:

FDA continued efforts to develop new methods for determining influenza vaccine potency, an important component in the evaluation of high-yield influenza vaccine viruses. An international collaborative study comparing several alternative methods and involving multiple manufacturers and regulatory agencies was completed. Most of the newer methods demonstrated feasibility in this study and a follow-up study is being planned for FY 2017 that will continue to evaluate and compare these alternative potency methods, with an emphasis on evaluating the capability of each technique to distinguish and quantify sub-potent vaccine.

FDA continued evaluation of methods to assess the relative yields of candidate vaccine viruses. FDA participated in an international collaborative study that compared the influenza virus yields and virus hemagglutinin (HA) production from several candidate vaccine strains. This study was

completed in FY 2016. In additional studies at FDA, designed to increase the yields of candidate vaccines by targeted manipulation, FDA produced and optimized potentially pandemic influenza vaccine viruses, such as H7N9 vaccine reference virus. H7N9 candidate vaccine viruses produce a relatively low protein yield when compared with other seasonal or pandemic viruses for the influenza vaccine production. The protein yield of a H7N9 vaccine reference virus was enhanced by multiple passaging in cells and eggs. The substitution mutations in the high yield virus will be confirmed by introduction of the mutation into the other low yield viruses and assessment their protein yield in FY 2017.

PROGRAM ACTIVITY DATA TABLES

CBER Workload and Outputs	FY 2016 Actual	FY 2017 Annualized CR	FY 2018 President's Budget
Original Biologics License Applications (BLA)			
Workload [1]	40	40	40
Total Decisions [2]	36	36	36
Approved	12	12	12
BLA Efficacy Supplements			
Workload [1]	27	27	27
Total Decisions [2]	35	35	35
Approved	19	19	19
BLA Manufacturing Supplements			
Workload [1]	1,403	1,403	1,403
Total Decisions [2]	1,230	1,230	1,230
Approved	1,054	1,054	1,054
BLA Labeling Supplements			
Workload [1]	145	145	145
Total Decisions [2]	161	161	161
Approved	152	152	152
Original New Drug Application (NDA)			
Workload [1]	0	0	0
Total Decisions [2]	0	0	0
Approved	0	0	0
NDA Efficacy Supplements			
Workload [1]	0	0	0
Total Decisions [2]	0	0	0
Approved	0	0	0
NDA Manufacturing Supplements			
Workload [1]	28	28	28
Total Decisions [2]	26	26	26
Approved	24	24	24
NDA Labeling Supplements			
Workload [1]	3	3	3
Total Decisions [2]	6	6	6
Approved	6	6	6
Original Abbreviated New Drug Application			
Workload [1]	1	1	1
Total Decisions [2]	0	0	0
Approved	0	0	0
ANDA Efficacy Supplements			
Workload [1]	0	0	0
Total Decisions [2]	0	0	0
Approved	0	0	0

CBER Workload and Outputs	FY 2016 Actual	FY 2017 Annualized CR	FY 2018 President's Budget
ANDA Manufacturing Supplements			
Workload [1]	2	2	2
Total Decisions [2]	3	3	3
Approved	2	2	2
ANDA Labeling Supplements			
Workload [1]	0	0	0
Total Decisions [2]	0	0	0
Approved	0	0	0
Device 510Ks			
Workload [1]	44	44	44
Total Decisions [2]	80	80	80
Final Decision - SE	31	31	31
Device Premarket Applications (PMA)			
Workload [1]	1	1	1
Total Decisions [2]	3	3	3
Approved	1	1	1
Device Premarket Applications (PMA) Supplements			
Workload [1]	48	48	48
Total Decisions [2]	29	29	29
Approved	26	26	26
Investigational New Drugs (IND)			
Receipts: IND (new)	402	402	402
Receipts: IND Amendments	9,898	9,898	9,898
Total Active IND [3]	2,421	2,421	2,421
Investigational Device Exemptions (IDE)			
Receipts: IDE (new)	20	20	20
Receipts: IDE Amendments	292	292	292
Total Active IDE [3]	153	153	153
Patient Safety			
Adverse Event Reports Received [4]	73,720	78,000	80,000
Biological Deviation Reports Received	51,230	51,000	51,000
Sponsor Assistance Outreach			
Meetings	481	481	481
Final Guidance Documents [5]	37	30	30
Admin/Management Support			
Advisory Committee Meetings Held	10	13	13
FOI Requests Processed	334	360	360

[1] Workload includes applications received and filed.

[2] Total Decisions include approved, denied, withdrawn, approvable, approvable pending inspection, not approvable, exempt, major deficiency, substantially equivalent (SE), not substantially equivalent (NSE), de novo and complete response (CR).

[3] Total Active includes investigational applications received and existing applications for which CBER has received at least one amendment (IND) or supplement (IDE) during the FY being reported.

[4] Includes MedWatch, Foreign reports and VAERS reports. Does not include Fatality Reports or Medical Device Reports for CBER-regulated medical devices.

[5] Includes all FDA final guidances issued by CBER and other FDA centers that pertain to biological products.

Field Biologics Program Activity Data (PAD)

Field Biologics Program Workload and Outputs	FY 2016 Actuals	FY 2017 Annualized CR	FY 2018 President's Budget
FDA WORK			
DOMESTIC INSPECTIONS			
UNIQUE COUNT OF FDA DOMESTIC BIOLOGICS ESTABLISHMENT INSPECTIONS	***1,875***	***1,909***	***1,909***
Bioresearch Monitoring Program Inspections	80	100	100
Blood Bank Inspections	895	900	900
Source Plasma Inspections	180	190	190
Pre-License, Pre-Market Inspections	61	55	55
GMP Inspections	38	28	28
GMP (Device) Inspections	4	7	7
Human Tissue Inspections	638	650	650
FOREIGN INSPECTIONS			
UNIQUE COUNT OF FDA FOREIGN BIOLOGICS ESTABLISHMENT INSPECTIONS	***68***	***47***	***47***
Bioresearch Monitoring Program Inspections	17	11	11
Foreign Human Tissue Inspections	2	0	0
Blood Bank Inspections	7	7	7
Pre-License, Pre-market Inspections	7	7	7
GMP Inspections (Biologics & Device)	34	20	20
TOTAL UNIQUE COUNT OF FDA BIOLOGIC ESTABLISHMENT INSPECTIONS	***1,943***	***1,956***	***1,956***
IMPORTS			
Import Field Exams/Tests	155	45	45
Import Line Decisions	151,911	162,545	173,923
Percent of Import Lines Physically Examined	0.10%	0.03%	0.03%
GRAND TOTAL BIOLOGICS ESTABLISHMENT INSPECTIONS	***1,943***	***1,956***	***1,956***

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