BIOLOGICS

(Dollars in Thousands)	FY 2017 Final	FY 2017 Actual	FY 2018 Annualized CR	FY 2019 President's Budget	FY 2019 +/- FY 2018
Biologics	**339,492**	**340,016**	**358,025**	**403,268**	**45,243**
Budget Authority	***215,317***	***215,443***	***213,854***	***251,854***	***38,000***
User Fees	***124,175***	***124,573***	***144,171***	***151,414***	***7,243***
Center	296,066	296,923	315,328	360,492	45,164
Budget Authority	173,937	174,052	172,755	210,755	38,000
User Fees	122,129	122,871	142,573	149,737	7,164
Prescription Drug (PDUFA)	*109,704*	*111,173*	*127,961*	*134,872*	*6,911*
Medical Device (MDUFA)	*10,508*	*10,826*	*13,405*	*13,639*	*234*
Generic Drug (GDUFA)	*1,088*	*872*	*1,032*	*1,048*	*16*
Biosimilars (BsUFA)	*829*	---	*175*	*178*	*3*
Field	43,426	43,093	42,697	42,776	79
Budget Authority	41,380	41,391	41,099	41,099	---
User Fees	2,046	1,702	1,598	1,677	79
Prescription Drug (PDUFA)	*1,847*	*1,517*	*1,397*	*1,472*	*75*
Medical Device (MDUFA)	*199*	*185*	*201*	*205*	*4*
FTE	**1,414**	**1,414**	**1,375**	**1,383**	**8**

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); Food and Drug Administration Reauthorization Act of 2017 (FDARA) (P.L. 115-52).

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 its mission, CBER also seeks 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 of, 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 navigate the challenges and opportunities of 21st Century medicine successfully. 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 2017, the Biologics Program contributed to the improvement of public health with the following accomplishments, among others:

- Established the Regenerative Advanced Medicine Therapy (RMAT) designation to expedite the development of certain cell therapies, therapeutic tissue engineering products, human cell and tissue products, and certain combination products that meet the designation criteria.
- Issued landmark approvals of the first cell-based gene therapies available in the United States, Kymriah, a treatment utilizing a patient's own T-cells to combat the patient's cancer, and Luxturna a directly administered gene therapy that works by delivering a normal copy of the defective gene directly to retinal cells.
- Effected the seizure of one product, and issued five Warning Letters and one Untitled Letter to manufacturers of biological products due to deviations from the Federal Food, Drug, and Cosmetic Act, Public Health Service Act, and the applicable regulations in Title 21, Code of Federal Regulations (21 CFR).

The following selected accomplishments demonstrate the Biologics Program's delivery of its regulatory and public health responsibilities within the context of current priorities.[36]

Improve and Safeguard Access

FDA's Biologics Program is committed to helping to expedite the development and review 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

[36] Please visit http://www.fda.gov/ for additional program information and detailed news items

those representing ground breaking treatments, the exciting medical promise of precision medicine; and treatment options where very limited options exist. These products can include additional vaccines against pandemic influenza and other infectious diseases; cellular and gene therapies; or new technologies to enhance the safety and availability of blood and blood products.

Modernizing the Regulatory Process

Advances in science and technology show great promise for the development of safe and effective biological products and FDA is taking steps to foster innovation. 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.

FDA programs such as the RMAT Designation, Fast Track, Breakthrough Therapy Designation, Accelerated Approval, and Priority Review are used when appropriate to expedite the development and review of innovative biological products. Since the inception of the Breakthrough Therapy Designation process in July 2012, CBER has granted 35 Breakthrough Therapy designations, with 25 of the 35 products being for rare diseases (Orphan Product designation).[37] In FY 2017, FDA granted nine Breakthrough Therapy designations, seven of which were cell or gene therapy products.

The Biologics Program has utilized a variety of regulatory programs to help facilitate therapies for the treatment of cancer and other serious and life-threatening diseases coming to market. Notable examples are the approvals of three separate cell-based gene therapies available for the first time in the United States. Kymriah and Yescarta are both part of an innovative class of cell based gene therapies for cancer patients with few other options. Each dose is a customized treatment created using an individual patient's own T-cells, a type of white blood cell. The patient's T-cells are collected and sent to a manufacturing center where they are genetically modified to include a new gene that directs the T-cells to target and kill cancer cells. Once the cells are modified, they are infused back into the patient to kill the cancer cells. FDA granted both therapies Priority Review and Breakthrough Therapy designation. They were reviewed using a coordinated, cross-agency approach with the clinical review coordinated by the FDA's Oncology Center of Excellence, and CBER conducting all other aspects of the reviews and final product approvals.

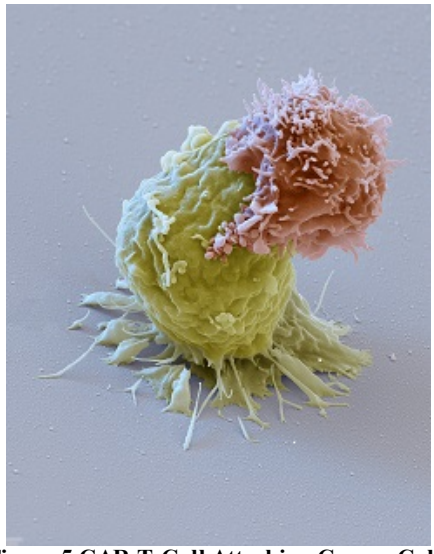

Figure 5 CAR-T Cell Attacking Cancer Cell

Luxturna is a directly administered gene therapy that works by delivering a normal copy of the defective gene directly to retinal cells. These retinal cells then produce the normal protein that converts light to electrical signal in the retina to restore patient's vision loss. FDA granted this therapy Priority Review and Breakthrough Therapy and Orphan drug designation. Luxturna is the first gene therapy in the U.S. that treats an inherited disease caused by mutations in a specific gene. This signals another development in the field of gene therapy and underscores the potential

[37] As of December 31, 2017

promise of the field of gene therapy for treating other serious and life-threatening diseases with no known cures.

In FY 2017, FDA established a new program to foster development and approval of regenerative medicine therapies: the RMAT Designation program. Upon receiving RMAT Designation, sponsors are eligible for increased and earlier interactions with FDA to help facilitate an efficient development program, including discussion of which approval pathways would be appropriate and advice on clinical trial design, including trial size and endpoints. The Agency has granted 13 RMAT Designations since program inception[38].

In November 2017, FDA announced its comprehensive policy framework for the development and oversight of regenerative medicine products, including novel cellular therapies. The framework, outlined in a suite of four guidance documents builds upon the FDA's existing risk-based regulatory approach and is intended to clarify what products are regulated as drugs, devices, and/or biological products. The suite of guidance documents also delivers on important provisions of the 21st Century Cures Act. This modern framework intends to balance the agency's commitment to safety with mechanisms to drive further advances in regenerative medicine so innovators can bring new, safe, and effective therapies to patients as efficiently as possible.

To improve efficiency in the review process, CBER expanded the capabilities of its Electronic Managed Review Process IT system to include electronic processing of efficacy supplements, uploading of approval letters and filing checklists, and expedited document sign-off. CBER also developed and implemented the Device Submissions Tracking System, to improve regulatory tracking of 510(k) device applications and expedite the medical device review process.

Facilitate Product Development Through Applied Research

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

Pathogen Reduction Technologies for blood components, are a potential solution to transfusion-transmitted sepsis or viral infections, however, there are still technical challenges with implementing them to avoid compromising the quality of the blood component. FDA is evaluating new and better photosensitizers, and new proofs-of-concepts as potential alternatives to existing technologies. To support the agency's efforts to fight the Zika virus, FDA has also undertaken efforts to evaluate the impact of red blood cell storage on virus infection, develop rapid, sensitive methods to assess vaccine effectiveness in animal studies and clinical trials, and explore how long the Zika virus persists in body tissues.

FDA hosted the 20th US-Japan Cellular and Gene Therapy Conference, on March 9, 2017, in conjunction with Japan's Ministry of Education, Culture, Sports, Science, and Technology, under

[38] As of December 31, 2017

the US-Japan Cooperative Research Program. Ideas were exchanged on cutting edge and diverse areas of biomedical research, and enhanced opportunities for collaborations, focusing on CRISPR (Clustered Regularly Interspaced Short Palindromic Repeat) methods.

CBER developed two new influenza vaccine potency assays as alternatives to the traditional potency assay. Both assays were evaluated in a large international collaborative study to compare alternative influenza vaccine potency assays on blinded vaccine samples. The International Federation of Pharmaceutical Manufacturers & Associations sponsored the study and participants included vaccine manufacturers, regulatory agencies, and other public health agencies. Data collected in FY 2017 demonstrated that both alternative assays were able to quantify proteins indicative of specific influenza strains in the vaccines, suggesting their promise as alternatives to the traditional potency assay.

To enhance the efficiency and accuracy of using next generation sequencing to detect adventitious viruses in cell substrates, CBER developed a new reference virus database (RVDB). In FY 2017, version 10.2 of the database was completed and made publicly available in the high-performance integrated virtual environment at the George Washington University. The RVDB is expected to detect existing and novel viruses by including nucleotide sequences of all viral sequences, complete or partial genomes, including endogenous retroviruses and retrotransposons. Members of the Advanced Virus Detection Interest Group performed test analysis of the database, which reported overall satisfaction and improvement compared to other public databases.

In May 2017, CBER convened the Vaccines and Related Biological Products Advisory Committee (VRBPAC) to discuss considerations for clinical trial evaluation of vaccines candidates to protect against Respiratory Syncytial Virus (RSV) disease, which is a leading cause of hospitalizations and health care visits in children less than five years of age. Currently, there are no vaccines licensed for the prevention of RSV. VRBPAC discussed the preclinical data needed to support studies and the need for standardized assays, viruses, and animal models. FDA is conducting research aimed at developing new serological assays (tests) to evaluate protective antibody responses to RSV. This research will facilitate the design and evaluation of vaccines, and help to identify vaccine candidates with the greatest potential for preventing RSV disease. Figure 6 is a graphic illustrating reduction of disease in the 21st century compared to the 20th century with the widespread use of vaccines.

A graphic of the impact of vaccines in the 20th and 21st centuries[39] follows:

[39] Source: Adapted from the CDC Epidemiology and Prevention of Vaccine-Preventable Diseases, 13th Edition "Pink Book". Available at: https://www.cdc.gov/vaccines/pubs/pinkbook/index.html

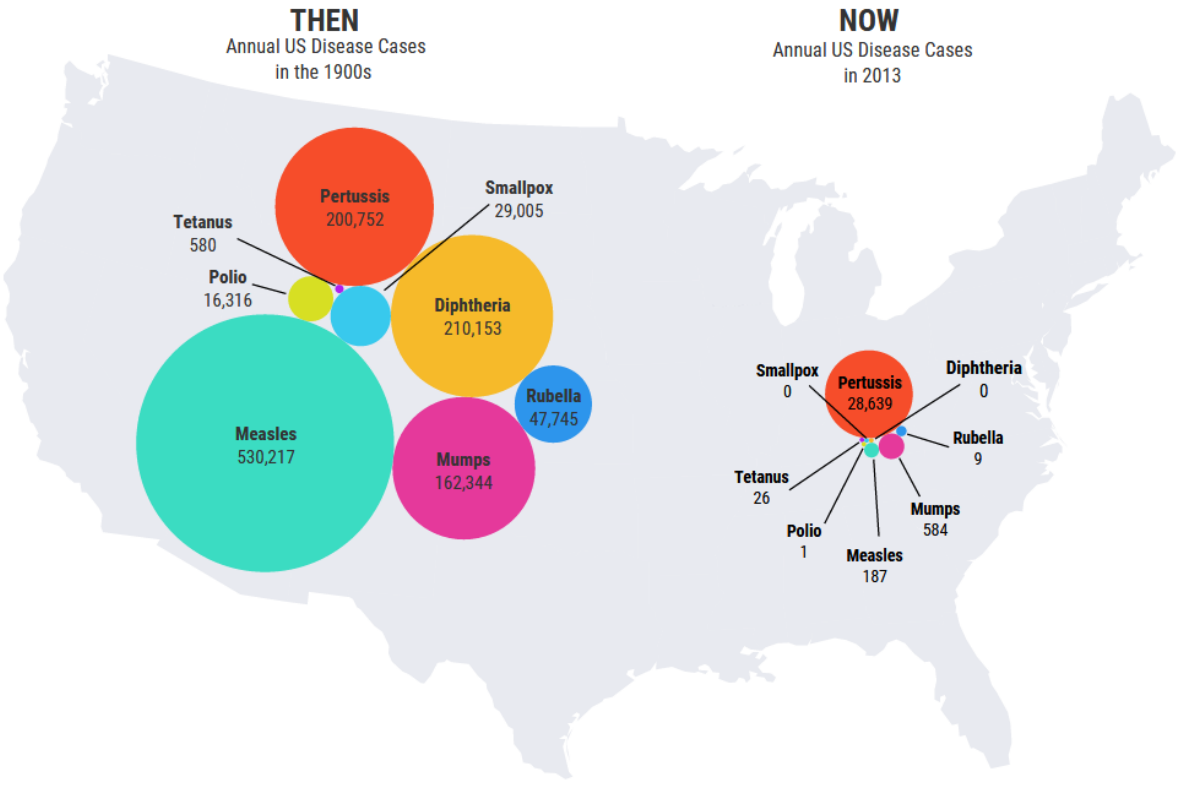

Figure 6 Impact of Vaccine in the 20th and 21st Centuries

Patient and Stakeholder Engagement to Bring Products to Market

To foster the development of innovative new therapies and address public health priorities, FDA engages a broad range of stakeholders. This includes fostering greater inclusion of patient engagement in the medical product development process, including regulatory decision-making for product review, post-market requirements, direct-to-consumer promotion, and risk communication.

FDA is working with the National Institute of Standards and Technology to coordinate and prioritize the development of standards and consensus definitions of terms for regenerative medicine advanced therapies. These standards and terms will help foster the development, evaluation, and review of regenerative medicine therapies, including with respect to the manufacturing processes and controls for such products.

In January 2017, FDA met with the Friedreich's Ataxia Research Alliance (FARA) to discuss potential gene therapies for Friedreich's Ataxia (FA), and to inform FARA and the research community of areas where more work may be needed to support development of gene therapies. In June 2017, an externally led Patient- Focused Drug Development Meeting gave patients with FA the opportunity to tell the FDA and drug developers about living with the disease.

In March 2017, in collaboration with NIH, CMS, and the Kidney Health Initiative FDA participated in, "Innovative Alternatives to Renal Replacement Therapy: Developing a Roadmap." This public workshop was held to discuss the scientific, technical, and regulatory

challenges needed to be addressed in a roadmap outlining steps towards bioartificial or bioengineered alternatives to dialysis. Topics included patient engagement, scientific challenges, and the path forward to address scientific barriers.

In June 2017, CBER participated in the Drug Information Association 2017 Annual Meeting held in Chicago, IL, chairing the forum entitled "Update from CBER: Advancing the Development of Complex Biologic Products." This meeting was held to foster the international exchange of actionable insights to improve health globally through the advancement of lifesaving medicines and technologies, enabling participants to build on their knowledge in the development of new therapies and accelerate efforts to enhance health and well-being.

In June, 2017 FDA with the University of California San Francisco-Stanford CERSI, and San Francisco State University Collaborative held a workshop with stakeholders to discuss whether Natural Language Processing can be applied to unstructured text in clinical notes. Potential uses could be used to identify indication or reason for medical product use, adverse outcomes or events associated with use of these products, and confounders or personal behaviors that may modify risks associated with use of these products. Protocol design, feasibility, recruitment efforts and execution of clinical trials was also discussed.

In July 2017, FDA and NIH/NIAID held a public workshop entitled ―Bacteriophage Therapy: Scientific and Regulatory Issues. The public workshop brought together government agencies, academia, industry, other stakeholders involved in research, development, and regulation of bacteriophages intended for therapeutic use in humans. The workshop stimulated discussion on this critical alternative to antibiotics in the treatment of infection and help facilitate development and rigorous clinical assessment of bacteriophage therapy products.

In September 2017, FDA held a public meeting on Patient-Focused Drug Development for Hereditary Angioedema (HAE), to obtain patient and caregiver perspectives on the impact of Hereditary Angioedema on daily life views on treatment options and participation in clinical trials.

FDA continues to provide scientific and regulatory advice to sponsors and stakeholders and to collaborate with other agencies and international regulatory authorities (WHO and EMEA) on the development and evaluation of vaccines for Zika virus. For example, FDA is actively engaged with NIH/NIAID and BARDA, and contributed to an HHS white paper outlining regulatory considerations for Zika vaccine licensure.

In October 2017, CBER representatives participated in the WHO Expert Committee on Biological Standardization meeting in Geneva Switzerland to establish WHO Biological Reference Preparations and written standards relevant to the manufacturing, licensing, and control of biological products. CBER representatives also serve as members of the WHO Blood Regulators Network, a forum for international blood regulatory authorities to share insights and address threats and opportunities to promote global blood product safety, efficacy, and availability, and attended the October 2017 meeting in Geneva.

Selected Product Approvals in 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
Biallelic RPE65 Mutation-Associated Retinal Dystrophy	Dec 2017	LUXTURNA	voretigene neparvovec-rzyl	First gene therapy in US that treats an inherited disease caused by mutations in specific gene (Priority Review, Breakthrough Therapy and Orphan drug)
Herpes Zoster (shingles)	Oct 2017	SHINGRIX	Zoster Vaccine Recombinant, Adjuvanted	For prevention of herpes zoster (shingles) in adults aged 50 years and older.
Large B-cell Lymphoma	Oct 2017	YESCARTA	Axicabtagene Ciloleucel	Second gene therapy available in the US for adults with large B-cell lymphoma.(Priority Review, Breakthrough Therapy Orphan drug)
Blood Screening	Oct 2017	cobas Zika	cobas Zika, Nucleic acid test for use on the cobas 6800/8800 systems	The first approval of a Zika virus detection test to screen donor samples for Zika virus RNA in plasma samples from individual human donors.
Acute Lymphoblastic Leukemia	Aug 2017	KYMRIAH	Tisagenlecleucel	First gene therapy available in the US for patients up to 25 years old with a form of acute lymphoblastic leukemia. (Priority Review, Breakthrough Therapy and Orphan drug)
Rabies Infection	Aug 2017	KEDRAB	Rabies Immune Globulin (Human)	For passive, transient post-exposure prophylaxis of rabies infection, given immediately after contact with a rabid animal and concurrently with full course of rabies vaccine.
Hereditary Angioedema	June 2017	HAEGARDA	C1 Esterase Inhibitor Subcutaneous (Human)	The first C1 Esterase Inhibitor for under the skin administration to prevent Hereditary Angioedema attacks in adolescent and adult patients.
Hemophilia B	May 2017	REBINYN	Coagulation Factor IX (Recombinant), GlycoPEGylated	Indicated for on-demand treatment and control of bleeding episodes, and for the perioperative management of bleeding in adults and children with hemophilia B.

Enhance Oversight

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.

Protect the Public Health from Infectious Disease

FDA collaborates with Department of Health and Human Services (DHHS) agencies, federal government partners, the WHO, National Regulatory Authorities, and stakeholders from the private and public sector to help ensure that blood, blood components, and HCT/Ps remain free of infectious agents and contaminants. This work helps decrease the spread of infectious disease, which may be spread through contact with infected individuals, travel to endemic areas, arthropod vectors, risk behaviors, and many other mechanisms.

Figure 7 is a graphic of Infectious Diseases and their Global Impact.[40]

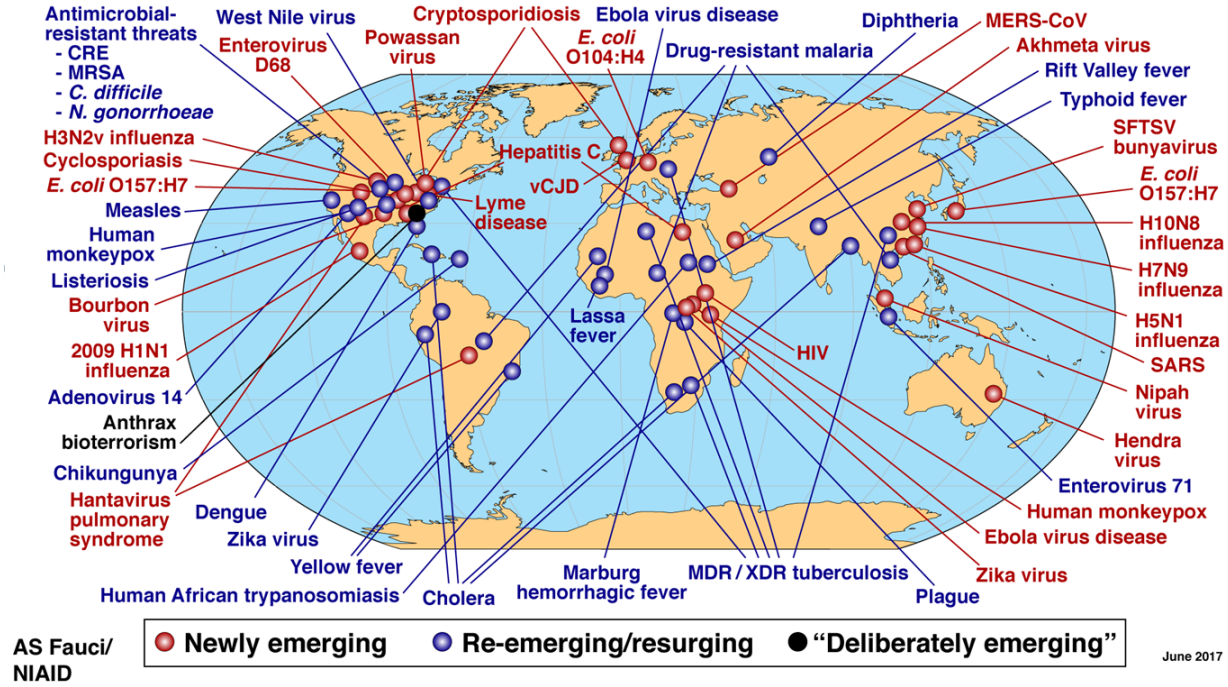

Figure 7 Infectious Diseases Globally

FDA has been working aggressively to combat the Zika virus outbreak. 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. FDA is continuing to monitor the evolving scientific and epidemiologic data on Zika virus and will

[40] "Global Examples of Emerging and Re-Emerging Infectious Diseases." Dr. Anthony S. Fauci, MD. National Institute of Allergy and Infectious Disease (NIAID)

update guidances as necessary to protect the safety of our nation's supply of blood and human cells, tissues, and cellular and tissue-based products.


Figure 8 Blood Donation

In October 2017, FDA approved the Roche Molecular Systems cobas Zika test, the first FDA-licensed donor screening test for Zika. The test is intended for use by blood collection establishments to detect Zika virus in blood donations, and for testing living organ donors, not for the individual diagnosis of Zika virus infection. Prior to this approval, several blood collection establishments used the cobas Zika test under IND to follow the recommendations in the FDA's 2016 guidance document. The approval is the result of a commitment by the manufacturer to work rapidly and collaboratively with the FDA and the blood collection industry to respond to a public health crisis and ensure the safety of blood in the U.S. and its territories.

In April 2017, FDA, in collaboration with the blood collection industry, the National Heart, Lung and Blood Institute, the Department of Defense and the Department of Health and Human Services, held a public workshop on emerging tick-borne diseases and blood safety. The workshop addressed tick-borne pathogens that continue to emerge as threats to blood safety, the effectiveness of current and potential mitigation strategies, and approaches to decision making on blood safety interventions.

Transfusion-transmitted babesiosis has emerged as a significant risk to the US blood supply. Human babesiosis is a disease transmitted primarily through tick vectors caused by Babesia microti, which is a rodent parasite. In response to this threat, FDA scientists developed a highly sensitive enzyme immunoassay test based on novel antigens for screening blood donors against Babesia microti, the causative agent of human babesiosis. B. microti is endemic prevalent in many parts of northeastern United States and is the most prevalent top ranking transfusion-transmissible infection for which no licensed donor screening test is available.

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 to gather scientific evidence on the feasibility of moving from the existing time-based deferrals related to risk behaviors as recommended in FDA's December 2015 guidance to alternative options, including the use of individual risk assessments. FDA presented a summary of responses submitted to the docket at its April 2016 Blood Products Advisory Committee meeting. FDA will assess the impact of current donor deferral recommendations and continue to gather the scientific evidence necessary for any future policy change.

Each year, FDA, WHO, CDC and other public health experts collaborate on the review of influenza disease surveillance and laboratory data collected from around the world to identify influenza strains that may cause the most illness in the upcoming season. Based on that information and the recommendations of FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC), which met on March 9, 2017, FDA selected the strains that should be included in the influenza virus vaccines for the 2017-2018 northern hemisphere influenza season. On October 4th, the VRBPAC met to select the strains to be included in an influenza virus vaccine for the 2018 southern hemisphere influenza season.

After the Ebola outbreak of 2014, it was recognized that the regulatory capacity and public health preparedness needed to be strengthened in African Countries. FDA worked with the WHO-coordinated committee African Vaccine Regulatory Forum to help revitalize the regional network to facilitate development and licensure of priority medical products in the region and increase capacity and preparedness to address future public health emergencies.

Selected Guidances in 2016 – 2017

Below are selected recent guidances issued by CBER, listed in date order. These guidances help address various issues.[41]

Date	#	Title	Description
Nov 2017	FDA-2017-D-6146-0001	Regulatory Considerations for Human Cell, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use; Guidance for Industry and Food and Drug Administration Staff	Intended to improve stakeholders' understanding of the definitions of minimal manipulation and homologous use in FDA's regulations. Finalizes two draft guidances and certain material related to adipose tissue.
Nov 2017	FDA-2014-D-1584-0221	Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception	Finalizes draft guidance dated October 2014, as well as, certain material related to adipose tissue that was included in the draft guidance from December 2014 (Adipose Draft Guidance).
Nov 2017	FDA-2017-D-6154-0001	Evaluation of Devices Used with Regenerative Medicine Advanced Therapies; Draft Guidance for Industry	When finalized, will provide information of Agency's current thinking of concepts related to evaluation of devices used in the recovery, isolation, and delivery of RMATs.
Nov 2017	FDA-2013-D-0575-0036	Expedited Programs for Regenerative Medicine Therapies for Serious Conditions; Draft Guidance for Industry	Provides information about expedited programs available for certain regenerative medicine therapies, including the Regenerative Medicine Advanced Therapy (RMAT) designation program established in the Cures Act.
Sep 2017	FDA-2015-D-4386-0011	Deviation Reporting for Human Cells, Tissues, and Cellular and Tissue-Based Products Regulated Solely Under Section 361 of the Public Health Service Act and 21 CFR Part 1271	Provides establishments manufacturing non-reproductive human cells, tissues, and cellular and tissue-based products (HCT/Ps) regulations and recommendations to comply with requirements to investigate and report HCT/P deviations.

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

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

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 Current Good Manufacturing Practices 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.

In August 2017, the U.S. Marshals Service seized five vials of Vaccinia Virus Vaccine (Live) – a vaccine that is reserved only for people at high risk for smallpox, such as some members of the military. The seizure came after FDA inspections at two stem cell clinics confirmed that the vaccine was used to create an unapproved stem cell product (a combination of excess amounts of vaccine and stromal vascular fraction – stem cells derived from body fat). The vaccine was then administered to cancer patients with potentially compromised immune systems and for those whom the vaccine posed a potential for harm, including myocarditis and pericarditis (inflammation and swelling of the heart and surrounding tissues). The unproven and potentially dangerous treatment was being injected intravenously and directly into patients' tumors.

In addition, Warning Letters were issued to two manufacturers of human cells, tissues, and cellular and tissue-based products (HCT/Ps) and one medical device manufacturer because their distributed products lacked appropriate FDA marketing authorization.

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 advance the use of real world experience, including large databases, from healthcare providers, insurers, and other partners to identify safety problems associated with biologic product use. In FY 2017 CBER launched a new pilot program, the Biologics Effectiveness and Safety system, as part of Sentinel to expand its use of electronic health record data in conducting post-market surveillance of biologic products in a more cost-effective and rapid manner. Using real world evidence may allow for a more comprehensive approach to product safety surveillance and help inform drug development and, as appropriate, regulatory decision making.

FDA, in collaboration with the National Heart Lung and Blood Institute and the DHSS Office of the Assistant Secretary launched the Transfusion Transmissible Infections Monitoring System (TTIMS) to help assure the continued safety of the US blood supply and monitor the effects of FDA's policy changes regarding donor deferral. TTIMS contractors are actively monitoring over 50 percent of the U.S. blood supply for HIV, hepatitis B virus and hepatitis C virus and conducting HIV recency testing.

Under FDASIA and the Drug Quality and Security Act, FDA gained additional authorities to enhance product safety through monitoring of drug shortages, including shortages of biologics products. For CY 2017, the Biologics Program has documented 4 new drug product shortages,

13 prevented shortages, 3 ongoing shortage, 50 notifications from 23 different manufacturers. CBER has used regulatory flexibility to prevent or mitigate 2 shortages, and expedited 16 reviews to prevent or mitigate a shortage.

As an active member of the AABB Interorganizational Task Force on Domestic Disasters and Acts of Terrorism, CBER worked proactively with the blood collection industry and device manufacturers to ensure the availability of blood and blood components in areas of the continental U.S., Puerto Rico, and the Virgin Islands impacted by the hurricanes in 2017.

FUNDING HISTORY

Fiscal Year	Program Level	Budget Authority	User Fees
FY 2015 Actual	$326,290,000	$211,362,000	$114,928,000
FY 2016 Actual	$329,156,000	$215,308,000	$113,848,000
FY 2017 Actual	$340,016,000	$215,443,000	$124,573,000
FY 2018 Annualized CR	$358,025,000	$213,854,000	$144,171,000
FY 2019 President's Budget	$403,268,000	$251,854,000	$151,414,000

BUDGET REQUEST

The FY 2019 Budget Request for the Biologics Program is $403,268,000, of which $251,854,000 is budget authority and $151,414,000 is user fees. This level provides a net increase of $45,243,000. Budget authority increases by $38,000,000 compared to the FY 2018 Annualized CR level and user fees increase by $7,243,000. The Center for Biologics Evaluation and Research (CBER) amount in this request is $360,492,000. The Office of Regulatory Affairs amount is $42,776,000.

The FY 2019 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 expedite the use of advanced technologies and methods to facilitate product development, production, and regulatory decision-making, such as newly identified clinical biomarkers, innovative clinical trial designs, and continuous manufacturing methodology for a broad range of complex and life-threatening diseases.

FDA will work to reduce review times and regulatory burden by enhancing FDA-sponsor communications in its user fee programs and continuing to use FDA's expedited programs such as the RMAT Designation, Fast Track Designation, Breakthrough Therapy Designation, Accelerated Approval, and Priority Review. These programs help expedite the development and review of innovative biological products, many of which address unmet medical needs in patients with rare, serious, or life-threatening conditions without compromising FDA's high standards for demonstrating the safety, efficacy, and quality of new medicines.

FDA will continue to protect the public against the threats of emerging infectious diseases and bioterrorism, including facilitating the development of prophylactic and therapeutic biologics and vaccines. Infectious diseases are not only spreading faster; they appear to be emerging more quickly than ever before. Since the 1970s, over 40 infectious diseases have been discovered. 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 current and emerging public health needs and meet ever-changing scientific and technological advancements. This program has helped CBER keep pace with the tremendous scientific advancements being made in the field.

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. This collaboration helps facilitate global access to vaccines and biological products that address critical health needs, including promoting research and sharing information to address global diseases and emerging threats impacting human populations. FDA also strategizes to harmonize existing regulatory standards and works with international scientific efforts to establish and maintain reference materials and standards for biologics.

To foster manufacturing innovation, flexibility, and adaptation, FDA will work in collaboration with federal partners and with input from regulated industry to develop or modernize regulations and guidances. These regulations and guidances range from protecting the blood and tissue supplies in the face of emerging infectious diseases, to addressing recent statutory mandates, to expediting the use of advanced technologies. The Biologics Program will continue early engagement to identify and discuss scientific considerations and challenges to help inform the development of biological products.

FDA will advance the use of real-world experience including large databases from healthcare providers, insurers, and other partners, to identify safety problems associated with biologic product use in a cost-effective and rapid manner. Using real world evidence may allow for a more comprehensive approach to product safety surveillance, and help inform drug development and, as appropriate, regulatory decision-making. Working with others in FDA, CBER will also support the 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

Medical Product Safety (+38 million / 8 FTE)

Promote Domestic Manufacturing: Advancing Modern Drug and Biological Product Manufacturing Technologies, Through the Development of Efficient Regulatory Pathways Center: +$15 million / 4 FTE

The budget increase will allow FDA to support new efforts to foster more investment and innovation in the development and creation of more modern, domestically-based manufacturing to improve the agility, flexibility, cost, and reliability of manufacturing processes. This includes continuous manufacturing of biological products, including vaccines and cell and gene-based therapies. With continuous manufacturing platforms, vaccine supply can be more easily ramped up on short notice, and certain vaccines can be rapidly modified to address infectious diseases, such as the flu. The application of this kind of enabling technology to vaccine production has long been a strategic priority for the U.S. Equipped with a robust scientific understanding of the requirements and the impact of these advanced manufacturing technologies, FDA can help industry make investments in these new technologies and grow these opportunities.

By developing a science-based framework that provides clarity for how products developed in these systems will be evaluated, and by funding research, development and testing of the enabling technologies, the agency can help reduce the cost and uncertainty of adopting these new manufacturing platforms, essentially de-risking them for adoption by industry. FDA would lead stakeholders in the development of clear scientific standards, policy, and guidance to support the effective and efficient adoption of these new manufacturing platforms, including the new inspectional methods they will require.

Create a New Medical Data Enterprise: Advance the Use of Real-World Evidence to Improve Human and Animal Health and Support Pre-Market Evaluation and Post-Market Safety

Center: +$23 million / 4 FTE

FDA will advance the use of real-world experience to better inform patient care and provide more efficient, robust, and potentially lower-cost ways to develop clinical information that can inform product review and promote innovation. FDA will establish a new capability, including the development of data and analytical tools, to conduct near-real-time evidence evaluation down to the level of individual electronic health records in a broad range of U.S. healthcare settings. FDA will also further explore the use of natural language processing and artificial intelligence to rapidly process information such as adverse event reports, allowing signal detection. Expanding FDA's capacity to utilize real-world evidence to evaluate the pre- and post-market safety and effectiveness of medical products would generate processes that could improve the efficiency of the regulatory process, better inform patients and providers about pre-and post-market safety, reduce some of the burdens that drive up the time and cost required to bring beneficial innovations to the market and address barriers that can make certain important safety and effectiveness information around the real-world use of products hard to collect and evaluate.

USER FEES

Current Law User Fees: +$7.243 Million

Center: +$7.164 million / Field: +$0.079 million

The Biologics Program request includes an increase of $7,243,000 for user fees authorized under FDARA, which will allow FDA to fulfill its mission of promoting and protecting the public health by ensuring safety and efficacy of medical products and accelerating innovation in the industry.

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 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 2018 Target	FY 2019 Target	FY 2019 +/- FY 2018
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 2016: 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 2016:100% Target 90% (Target Exceeded)	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 2016: 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 2016: 99% 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 2016: 67% Target: 60% (Target Exceeded)	60%	60%	Maintain

Measure	Year and Most Recent Result / Target for Recent Result (Summary of Result)	FY 2018 Target	FY 2019 Target	FY 2019 +/- FY 2018
234101: Increase manufacturing diversity and capacity for influenza vaccine production. *(Output)*	FY 2017: 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.	FY 2017: 99% Target 85% (Target Exceeded)	85%	85%	Maintain
234212: Percentage of planned registered domestic blood bank and biologics manufacturing inventory inspections. (Output)	FY 2017: 106% Target: 99% (Target Exceeded)	95%	95%	Maintain
234213: Percentage of planned human foreign and domestic tissue establishment inspections. (Output)	FY 2017: 100% Target: 82% (Target Exceeded)	85%	85%	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 2017, 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. A second international collaborative study comparing several alternative methods and involving multiple manufacturers and regulatory agencies was completed in FY 2017. Methods developed at CBER, including antibody capture-ELISA and receptor-binding assays, were shown to be feasible for quantifying H3N2 and influenza B hemagglutinin (HA) in vaccines. Additional development work on these methods is planned for FY 2018 and future years.

FDA continued evaluation of methods to assess the relative yields of candidate vaccine viruses. FDA investigated several methods to increase the yields of candidate vaccines by targeted manipulation, both for potential pandemic influenza vaccine viruses, such as H7N9 vaccine reference virus and seasonal influenza vaccine candidates. In particular, H7N9 candidate vaccine viruses, and seasonal influenza B candidate vaccine viruses produce relatively low influenza HA yields compared to other high yield seasonal vaccine viruses. Additional development work for H7N9 and influenza B candidate vaccine viruses is planned for FY 2018 and future years.

New ORA Field Performance Measures

ORA has been working to improve the field performance measures to better aligned with ORA's Program Alignment initiative. In this submission, ORA has completed the process of adjusting the performance goals, so that the FY 2018 and FY 2019 targets now complete a certain percentage of the planned inspections in ORA's annual Workplan. The ORA Workplan is the necessary mechanism that takes into account all the complex variables (geography, commodity, risk, availability, efficiency, etc.) that allows ORA to plan which inspections to do. With these newly formulated performance goals, ORA is committing to complete a certain percentage of the initially planned inspections. This revision strengthens the importance of the Workplan, but allows the flexibility to respond dynamically to changing circumstances during the year, to better handle emerging risks and evolving public health priorities (i.e. the heavy hurricane damage this past year). This is a significant departure from the previous performance goals, so FY 2018 will be an important year in resetting the new baselines. Also, since the targets are now based on a planned number of inspections, it is possible to inspect more than what was planned and thus have an actual inspection rate over 100%.

PROGRAM ACTIVITY DATA

CBER Workload and Outputs	FY 2017 Actual	FY 2018 Annualized CR	FY 2019 President's Budget
Original Biologics License Applications (BLA)			
Workload [1]	20	20	20
Total Decisions [2]	74	36	36
Approved	33	33	33
BLA Efficacy Supplements			
Workload [1]	17	17	17
Total Decisions [2]	46	46	46
Approved	37	37	37
BLA Manufacturing Supplements			
Workload [1]	1,322	1,322	1,322
Total Decisions [2]	1,441	1,441	1,441
Approved	1,239	1,239	1,239
BLA Labeling Supplements			
Workload [1]	142	142	142
Total Decisions [2]	113	113	113
Approved	105	105	105
Original New Drug Application (NDA)			
Workload [1]	0	1	1
Total Decisions [2]	1	1	1
Approved	1	1	1
NDA Efficacy Supplements			
Workload [1]	0	1	1
Total Decisions [2]	0	1	1
Approved	0	1	1
NDA Manufacturing Supplements			
Workload [1]	24	24	24
Total Decisions [2]	23	23	23
Approved	18	18	18
NDA Labeling Supplements			
Workload [1]	1	1	1
Total Decisions [2]	1	1	1
Approved	1	1	1
Original Abbreviated New Drug Application (ANDA)			
Workload [1]	0	1	1
Total Decisions [2]	1	1	1
Approved	0	1	1
ANDA Efficacy Supplements			
Workload [1]	0	0	0
Total Decisions [2]	0	0	0
Approved	0	0	0

CBER Workload and Outputs	FY 2017 Actual	FY 2018 Annualized CR	FY 2019 President's Budget
ANDA Manufacturing Supplements			
Workload [1]	1	1	1
Total Decisions [2]	3	3	3
Approved	2	2	2
ANDA Labeling Supplements			
Workload [1]	0	1	1
Total Decisions [2]	0	1	1
Approved	0	1	1
Device 510Ks			
Workload [1]	53	53	53
Total Decisions [2]	57	57	57
Final Decision - SE	39	39	39
Device Premarket Applications (PMA)			
Workload [1]	4	4	4
Total Decisions [2]	5	5	5
Approved	2	2	2
Device Premarket Applications (PMA) Supplements			
Workload [1]	59	59	59
Total Decisions [2]	65	65	67
Approved	17	17	17
Investigational New Drugs (IND)			
Receipts: IND (new)	456	456	456
Receipts: IND Amendments	10,848	10,848	10,848
Total Active IND [3]	2,624	2,624	2,624
Investigational Device Exemptions (IDE)			
Receipts: IDE (new)	17	17	17
Receipts: IDE Amendments	384	384	384
Total Active IDE [3]	161	161	161
Patient Safety			
Adverse Event Reports Received [4]	65,000	65,000	65,000
Biological Deviation Reports Received	52,250	50,000	50,000
Sponsor Assistance Outreach			
Meetings	453	453	453
Final Guidance Documents [5]	30	30	30
Admin/Management Support			
Advisory Committee Meetings Held	8	13	13
FOI Requests Processed	265	320	320

[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 2017 Actual	FY 2018 Annualized CR	FY 2019 President's Budget
FDA WORK			
DOMESTIC INSPECTIONS			
UNIQUE COUNT OF FDA DOMESTIC BIOLOGICS ESTABLISHMENT INSPECTIONS	***1,835***	***1,892***	***1,892***
Bioresearch Monitoring Program Inspections	75	100	100
Blood Bank Inspections	872	900	900
Source Plasma Inspections	192	190	190
Pre-License, Pre-Market Inspections	77	55	55
GMP Inspections	33	28	28
GMP (Device) Inspections	2	7	7
Human Tissue Inspections	621	650	650
FOREIGN INSPECTIONS			
UNIQUE COUNT OF FDA FOREIGN BIOLOGICS ESTABLISHMENT INSPECTIONS	***67***	***47***	***47***
Bioresearch Monitoring Program Inspections	22	11	11
Foreign Human Tissue Inspections	0	0	0
Blood Bank Inspections	7	7	7
Pre-License, Pre-market Inspections	5	7	7
GMP Inspections (Biologics & Device)	33	20	20
TOTAL UNIQUE COUNT OF FDA BIOLOGIC ESTABLISHMENT INSPECTIONS	***1,902***	***1,939***	***1,939***
IMPORTS			
Import Field Exams/Tests	197	45	45
Import Line Decisions	157,080	168,076	179,841
Percent of Import Lines Physically Examined	0.13%	0.03%	0.03%
GRAND TOTAL BIOLOGICS ESTABLISHMENT INSPECTIONS	***1,902***	***1,939***	***1,939***