HUMAN DRUGS

(Dollars in Thousands)	FY 2018 Enacted	FY 2018 Actual	FY 2019 Annualized CR	FY 2020 President's Budget	FY 2020 +/- FY 2019
Human Drugs	**1,633,743**	**1,755,609**	**1,713,629**	**1,980,030**	**266,401**
Budget Authority	***495,395***	***495,384***	***495,395***	***713,895***	***218,500***
User Fees	***1,138,348***	***1,260,225***	***1,218,234***	***1,266,135***	***47,901***
Center	1,432,054	1,554,711	1,510,169	1,749,191	239,022
Budget Authority	359,226	359,222	359,226	551,084	191,858
User Fees	1,072,828	1,195,489	1,150,943	1,198,107	47,164
Prescription Drug (PDUFA)	*658,620*	*790,598*	*732,096*	*770,854*	*38,758*
Generic Drug (GDUFA)	*376,601*	*366,873*	*382,803*	*391,330*	*8,527*
Biosimilars (BsUFA)	*37,028*	*36,605*	*35,416*	*35,001*	*-415*
Outsourcing Facility	*579*	*1,413*	*628*	*922*	*294*
Field	201,689	200,898	203,460	230,839	27,379
Budget Authority	136,169	136,162	136,169	162,811	26,642
User Fees	65,520	64,736	67,291	68,028	737
Prescription Drug (PDUFA)	*8,101*	*7,753*	*9,003*	*8,801*	*-202*
Generic Drug (GDUFA)	*55,915*	*55,355*	*56,808*	*57,430*	*622*
Biosimilars (BsUFA)	*1,150*	*1,158*	*1,100*	*1,363*	*263*
Outsourcing Facility	*354*	*470*	*380*	*434*	*54*
FTE	**6,335**	**6,335**	**6,560**	**6,715**	**155**

Authorizing Legislation: Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321-399); Public Health Service Act of 1944 (42 U.S.C. 201); Federal Advisory Committee Act (FACA) of 1972 as amended; Orphan Drug Act of 1983 (21 U.S.C. 360ee); Drug Price Competition and Patent Term Restoration Act of 1984 (Section 505(j) 21 U.S.C. 355(j)) (a.k.a. "Hatch Waxman Act"); Prescription Drug Marketing Act (PDMA) of 1987 (21 U.S.C. 353); Anti-Drug Abuse Act of 1988; Clinical Laboratory Improvement Amendments of 1988 (42 U.S.C. 201); Orphan Drug Amendments of 1988; Generic Drug Enforcement Act of 1992; Prescription Drug User Fee Act (PDUFA) of 1992; FDA Export Reform and Enhancement Act of 1996; Food and Drug Administration Modernization Act (FDAMA) of 1997; Public Health Security and Bioterrorism Preparedness and Response Act of 2002; Best Pharmaceuticals for Children Act (BPCA) of 2002; Freedom of Information Act (FOIA) as amended in 2002 (5 U.S.C. § 552); Pediatric Research Equity Act (PREA) of 2003; Project Bioshield Act of 2004 (21 U.S.C. 360bbb-3); Food and Drug Administration Amendments Act (FDAAA) of 2007; Biologics Price Competition and Innovation Act (BCPI) of 2009; Public Health Service Act of 2010 (42 U.S.C. 262); Protecting Patients and Affordable Care Act of 2010; Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA); Drug Quality and Security Act (2013); Sunscreen Innovation Act (2014); Adding Ebola to the FDA Priority Review Voucher Program Act (2014); 21st Century Cures Act (Cures Act) (2016); and Food and Drug Administration Reauthorization Act of 2017 (FDARA) (P.L. 115-52); Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act (SUPPORT) (2018).

Allocation Methods: Direct Federal/Intramural

PROGRAM DESCRIPTION AND ACCOMPLISHMENTS

FDA's Human Drugs Program is responsible for:

- Ensuring the safety and efficacy of new and generic prescription and over-the-counter (OTC) drug products
- Monitoring the safety of marketed drugs
- Overseeing drug quality to prevent and detect substandard or counterfeit drugs in the U.S. market.

FDA's Human Drugs Program consists of the Center for Drug Evaluation and Research (CDER) and Office of Regulatory Affairs (ORA) field drugs program. The Program operates with funding from budget authority and user fees.

The Program's mission is to promote and protect public health by ensuring that human drugs are safe and effective for their intended uses, meet established quality standards, and are available to patients. The Human Drugs Program supports FDA's priorities of improving health care quality and reducing health care costs.

The following selected accomplishments demonstrate the Human Drugs Program's delivery of its regulatory and public health responsibilities in the context of current priorities.

Figure 2 Medicine for a Patient

REDUCE THE BURDEN OF ADDICTION CRISES THAT ARE THREATENING AMERICAN FAMILIES

Opioids

Opioids are effective medications that can help manage pain when properly prescribed for the right condition and used properly. Addressing the opioid crisis is one of FDA's highest priorities. FDA's regulates the drugs and devices used in the treatment of pain, as well as opioid addiction and overdose, to assure that the actions taken are in the best interest of public health.

FDA is taking immediate steps to reduce the scope of the opioid addiction epidemic. We continuously examine our role and policies in the regulation of opioids, drugs and devices used in pain treatment, and in opioid addiction and overdose to assure we act in the best interest of public health. In addition, FDA continues to accomplish goals laid out under the HHS Opioid Strategy, launched in April 2017. This plan is a comprehensive, evidence-based strategy that provides the overarching framework to leverage the expertise and resources of Health and Human Services agencies in a strategic and coordinated manner.

As part of the HHS Opioid Strategy, FDA is committed to examining all facets of the epidemic: opioid abuse, misuse, addiction, overdose, and death, in the US. FDA has identified four priority areas in confronting the opioid epidemic:

- Decreasing Exposure and Preventing New Addiction
- Supporting the Treatment of Those with Opioid Use Disorder
- Fostering the Development of Novel Pain Treatment Therapies
- Improving Enforcement and Assessing Benefit-Risk.

FDA is working to improve the transparency of our benefit-risk paradigm for opioids, ensuring that we continue to consider appropriately the wider public health effects of prescription opioids. We are engaged in many ongoing activities aimed at furthering the overarching strategy, including:

- Working more closely with its advisory committees before making critical product and labeling decisions
- Enhancing safety labeling; requiring new data on long-term opioid analgesic use
- Seeking to improve treatment of both addiction and pain.

On October 24, 2018, the President signed into law the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment (SUPPORT) for Patients and Communities Act. The bipartisan legislation grants FDA additional authorities that will meaningfully advance our efforts to combat the opioid crisis. Through the SUPPORT Act, CDER is advancing efforts to:

- Address the challenges and barriers of developing non-addictive medical products intended to treat pain or addiction
- Promote the development of evidence-based opioid prescribing guidelines to treat acute pain resulting from specific conditions or procedures
- Implement our new authority to issue a mandatory recall for any controlled substance if there is a probability that it would cause serious adverse health consequences or death
- Implement our new authority to require certain packaging and disposal for opioids and other drugs, to mitigate the risk of abuse and misuse
- Implement our new authority to require post-market studies of the long-term efficacy of opioid analgesics to help FDA advance our understanding of opioid pain medicines.

FDA recognizes both the risks of opioid use and the benefits of these drugs for patients who need them, including those with debilitating chronic pain conditions. Opioid misuse and abuse remains one of our highest priorities, and we believe it is going to take carefully developed, sustained, and coordinated action by everyone involved to reduce the tide of opioid addiction and death afflicting our communities; while maintaining appropriate prescribing for patients in medical need.

FOSTER COMPETITION AND INNOVATION

The goal of the Human Drugs Program is to promote the public health by ensuring that prescription and OTC human drug products, including brand-name and generic products, are safe and effective. In addition, FDA aims to ensure that novel prescription drugs become available in a timely manner while maintaining FDA's high standards for safety and efficacy.

Novel drugs are often innovative products that serve previously unmet medical needs or otherwise advance patient treatment and public health. In calendar year 2018, CDER approved 59 novel drugs. From 2009 through 2017, CDER has averaged about 33 novel drug approvals per calendar year. More than 75% of novel drugs approved by CDER were approved in the U.S. before other countries, providing Americans first access to treatment.

The Human Drugs Program employs multiple regulatory tools including FDA's expedited development and review programs – fast track, priority review, accelerated approval, and new breakthrough therapy designations. Early and repeated communications between FDA and sponsors have also helped expedite products to market.

FDA is working to increase speed and efficiency in several areas of the clinical trial phase of drug development including:

- Assisting with establishing flexible clinical development designs and accepting such designs when they support the high standards for demonstrating safety and efficacy
- Meeting frequently and working closely with industry sponsors throughout the development process to plan efficient clinical trial programs and agree on needed data
- Helping create clinical trial networks and "master protocols," to streamline clinical trials, reduce the cost of conducting, and reduce the time needed to carry them out.

Drug Shortages

Drug shortages can delay or prevent patients from getting needed care. Drugs in short supply may also lead health care professionals to rely on alternative drug products that may be less effective or associated with higher risks. The Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) granted authorities that enabled FDA to coordinate with manufacturers to help prevent or mitigate drug shortages. These authorities included requiring manufacturers to provide early notification of permanent discontinuances or interruptions in manufacturing of covered prescription drugs that are likely to lead to a meaningful disruption in supply of those drugs in the U.S. These requirements helped FDA work with industry early on to address problems before shortages occur and resulted in decreasing numbers of new shortages in recent years.

FDA continues to make significant progress in reducing the number of drug shortages, from 251 new shortages in 2011 to 26 new shortages in 2016 and 39 new shortages in 2017. Specifically, in 2017, multiple hurricanes impacted drug manufacturing in Puerto Rico. In 2017 and early 2018, a large manufacturer made decisions resulting in discontinuances and delays for multiple medications, including IV opioid analgesic drugs.

FDA has been working with manufacturers to resume production and has expedited review of new submissions, helping to increase supplies. FDA was able to help prevent 145 shortages in 2017 and continues these important prevention efforts in 2018. To continue transparency on the Agencies processes, an update to the Manual of Policies and Procedures (MAPP 41901.1 Rev. 3) on CDER Drug Shortage Management was posted to our website on December 4, 2018.[31] To further address shortages, FDA has created a new Task Force, comprising senior leaders from FDA, the Centers for Medicare and Medicaid Services, and the Department of Veterans Affairs to identify the root causes and holistic solutions for this critical public health problem. A report on this issue will be delivered to Congress by the end of 2019.

On November 27, 2018 the Drug Shortages Task Force under a cooperative agreement with the Robert J. Margolis, MD, Center for Health Policy at Duke University held a public meeting with stakeholders on "Identifying the Root Causes of Drug Shortages and Finding Enduring Solutions". This public meeting built on the earlier listening sessions and one-on-one stakeholder meetings and allowed FDA to obtain valuable feedback from additional stakeholder groups, including health care professionals, patients, manufacturers, wholesalers, pharmacists, insurers, academic researchers and the public.

[31] Updated MAPP is available at https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM079936.pdf.

Drug Pricing and Access - Biosimilars

In July 2018, FDA released the Biosimilars Action Plan[32] (BAP) to provide information about the key actions FDA is taking to encourage innovation and competition among biologics and the development of biosimilars. The BAP builds on the progress in implementing the approval pathway for biosimilar and interchangeable products. The BAP is focused on four key areas:

- Improving the efficiency of the biosimilar and interchangeable product development and approval process
- Maximizing scientific and regulatory clarity for the biosimilar product development community
- Developing effective communications to improve understanding of biosimilars among patients, clinicians, and payors
- Supporting market competition by reducing gaming of FDA requirements or other attempts to unfairly delay competition.

BsUFA supports the review process for biosimilar biological product applications. The Biosimilar Product Development (BPD) Program was created as a part of BsUFA to provide a mechanism and structure for the collection of development-phase user fees to support FDA's biosimilar review program activities. As of December 3, 2018, 65 programs were in the BPD Program. CDER has received meeting requests to discuss the development of biosimilar products for 33 different reference products. As of December 3, 2018, FDA has licensed 15 biosimilar products. These accomplishments represent the next step to increasing treatment options for patients.

During June and July 2018, FDA issued two draft guidances and one final guidance for industry. The final guidance entitled, "Labeling for Biosimilar Products" provides FDA's recommendations for labeling for biosimilar products and is intended to assist applicants in developing prescription drug labeling for proposed biosimilar products.

In September 2018, FDA held a public hearing on FDA's approach to enhancing competition and innovation in the biological products marketplace, including by facilitating greater availability of biosimilar and interchangeable products. In December 2018, FDA hosted a webinar for health care professionals to provide an overview of the regulatory framework for biosimilar and interchangeable products, including the general approval requirements for biosimilars, the approach and scientific concepts used in the development of biosimilar products, and clinical and practical considerations when using biosimilar and interchangeable products.

In December 2018, FDA issued two draft guidances and two final guidances for industry. The final guidance entitled, "Biosimilars: Questions and Answers on Biosimilar Development and the BPCI Act of 2009" and the draft guidance entitled, "New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2)" are companion guidance documents that through a question and answer (Q&A) format is intended to inform prospective applicants and facilitate the development of proposed *biosimilars* and *interchangeable biosimilars*, as well as to describe FDA's interpretation of certain statutory requirements added by the Biologics Price Competition and Innovation Act of 2009 (BPCI Act). The final guidance entitled, "Interpretation of the

[32] For additional information visit https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm613761.pdf

'Deemed To Be a License' Provision of the Biologics Price Competition and Innovation Act of 2009" and the draft guidance entitled, "The 'Deemed to be a License' Provision of the BPCI Act: Questions and Answers" describe and provide answers to common questions about FDA's interpretation of the statutory provision under which an application for a biological product approved under the Federal Food, Drug, and Cosmetic Act (FD&C Act) as of March 23, 2020, will be deemed to be a license for the biological product under the Public Health Service Act (PHS Act) on March 23, 2020.

Harnessing Real-world evidence

FDA uses real world evidence to monitor postmarket safety and adverse events, and to make regulatory decisions. This includes integrating evidence such as electronic health records, registries, and claims and billing data into regulatory decision making and to answer questions relevant to broader populations of patients.

Sentinel

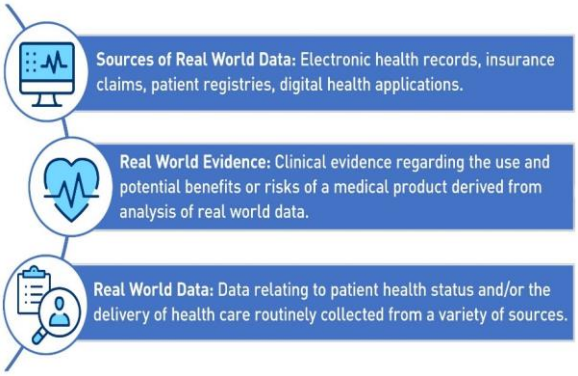

Figure 3 Data used to support postmarket safety activities

The 2007 Food and Drug Administration Amendments Act (FDAAA) required FDA to establish an active postmarket risk identification and analysis (ARIA) system to analyze drug and biologic safety data from multiple sources. In response to this requirement, FDA launched the Sentinel Initiative in 2008, which led to the development and implementation of the Sentinel System. The Sentinel Initiative provides significant public health benefits by developing new approaches and methods to actively monitor the safety of marketed medical products to complement existing FDA surveillance capabilities. The Sentinel System includes access to large quantities of electronic healthcare data and enhances the FDA's ability to detect and better understand safety signals to better inform patients and healthcare providers on the safe use of regulated medical products.

In FY 2018, the Sentinel System expanded surveillance to 292 million patients, which is an increase of 69 million patients from FY 2017. Each year, the Sentinel distributed database naturally grows as more data accumulates within the existing data partners. Effective in FY 2020, FDA will begin to assess performance of the Sentinel System according to the number of investigations of priority drug safety questions analyzed using the Sentinel ARIA System.

In February 2018, FDA held the Tenth Annual Sentinel Initiative Public Workshop to bring the stakeholder community together to discuss a variety of topics on active medical product surveillance and current and emerging Sentinel projects. To date, the Sentinel Initiative has contributed to multiple safety communications and labeling changes to better inform patients and providers about safe use of drugs and vaccines.

FDARA and 21st Century Cures Act Implementation

FDARA provided the second authorizations of the Generic Drug User Fee Amendments (GDUFA II), the Biosimilars User Fee Act (BsUFA II), and the sixth authorization of the Prescription Drug User Fee Act (PDUFA VI). The five-year reauthorizations ensured FDA

continued to receive consistent funding from FY 2018 through FY 2022 to support program innovation, evaluation, and improvement. GDUFA II, BsUFA II and PDUFA VI continue to deliver tremendous public health benefits by:

- Providing timely access to more affordable generic drugs and biosimilar biological products
- Providing patients with more affordable treatments
- Enhancing FDA's capacity to fulfill its mission of bringing novel drug products to market.

Generic Drug Review

Many Americans face challenges with access to medically necessary drug products due the rising healthcare costs fueled largely by extravagant prescription drug pricing. The availability of safe and effective generic drugs can help reduce the cost of drug products. As such, generic drug review is a high priority for the Human Drugs Program. The review function supports the larger FDA mission of promoting and protecting public health.

GDUFA II includes important features to modernize the generic drug program. For example, under GDUFA II, certain applications may be eligible for a shorter review time, including applications for drug shortage products. Our GDUFA II commitment also included a pre-Abbreviated New Drug Application (pre-ANDA) program designed to support development of complex generic drug products under GDUFA II. The pre-ANDA program features meetings between FDA and sponsors at various stages of drug development to help clarify regulatory expectations early in product development and during application review.

Commitment to the GDUFA program led to a record number of combined approvals and tentative approvals in FY 2018.[33] FY 2018 was the third consecutive year that FDA set a combined approvals and tentative approvals record. FDA achieved these successes by providing greater predictability, transparency, and efficiency, along with improved timeliness, to the generic drug review process.

Under GDUFA II, FDA uses "real time" communications such as information requests and discipline review letters issued during the review of an original ANDA to give applicants an opportunity to correct certain deficiencies within the current review cycle. These communications help minimize the number of review cycles necessary for approval and promote transparency in the review process.

FDA has also taken several actions under the agency's Drug Competition Action Plan (DCAP) to help remove barriers to generic drug development and market entry to spur competition so that consumers can get access to the medicines they need at affordable prices. FDA has focused efforts under the DCAP on three key areas:

- Improving the efficiency of the generic drug development, review and approval processes
- Maximizing scientific and regulatory clarity with respect to generic versions of complex drug products
- Closing loopholes that allow brand drug companies to "game" the Hatch-Waxman Amendments in ways that forestall the generic competition that Congress intended.

[33] See the Activities Report of the Generic Drug Program (FY 2018) at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm625314.htm. During FY 2018, OGD approved or tentatively approved 971 ANDAs.

In FY 2018, FDA established policies under the DCAP to promote generic drug development in areas where there is inadequate competition. This included developing 208 new and revised drug development guidance documents. Of these, 74 address the development of generic versions of complex, difficult-to-copy, drugs. The agency also published two updates to the List of Off-Patent, Off-Exclusivity Drugs without an Approved Generic. FDA maintains this list to improve transparency and encourage the development and submission of generic drug applications for products in markets with little competition.

The agency also approved the first three generic drugs designated as competitive generic therapies, which are a new category of drugs for which there is inadequate generic competition. In addition, FDA began prioritizing the review of generic drug applications for which there are no blocking patents or exclusivities and for which there are no more than three approved drug products. This prioritization policy is supported by data that shows a significant price decrease when there are at least three generic drugs on the market, which lowers the costs to consumers.

Under GDUFA II and the DCAP, FDA will continue modernizing the generic drug program and ensuring that Americans have timely access to safe, effective, high quality, and lower cost human generic drugs.

Generic Product Approvals

Below are some of CDER's recent generic product approvals. This list does not represent any degree of importance or priority ranking of products.[34]

Product Category	Approved	Product Name	FDA-Approved Use on Approval Date
Opioid Dependence	Apr 2018	Hydromorphone Hydrochloride Injection (generic of Dilaudid)	For the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate
	Jul 2018	Morphine Sulfate Injection (generic of Infumorph)	For the management of pain severe enough to require use of an opioid analgesic by intravenous administration and for which alternative treatments are not adequate
Infections	Apr 2018	Ertapenem Sodium for Injection (generic of Invanz)	For the treatment of certain moderate to severe infections caused by susceptible bacteria
	Aug 2018	Cefepime Hydrochloride for Injection (generic of Maxipime)	For the treatment of infections caused by susceptible strains of microorganisms

[34] For more information on product approvals and designations visit http://www.fda.gov/NewsEvents/ProductsApprovals//.

Product Category	Approved	Product Name	FDA-Approved Use on Approval Date
Cancer	Aug 2018	Arsenic Trioxide Injection (generic of Trisenox)	For induction of remission and consolidation in certain patients with APL who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy
	Sep 2018	Carmustine for Injection (generic of BiCNU)	For palliative therapy in certain brain tumors, multiple melanoma, relapsed or refractory Hodgkin's and non-Hodgkin's lymphoma
Other	Jan 2018	Potassium Chloride Extended-Release Tablets (generic of K-Tab)	For the treatment of patients with hyperkalemia, with or without metabolic alkalosis
	May 2018	Methylphenidate Hydrochloride for Extended-Release Oral Suspension (generic of Quillivant XR)	For the treatment of ADHD
	Oct 2018	Nitric Oxide Gas for Inhalation (generic of INOmax)	For improved oxygenation and to reduce the need for extra corporeal membrane oxygenation in term and near-term neonates with hypoxic respiratory failure

New Drug Review

With PDUFA V, FDA created a new review program for new molecular entity (NME) new drug applications (NDAs) and original biologics license applications (BLAs) for applications received between October 1, 2012, through September 30, 2017. The goals of the Program are to increase the efficiency and effectiveness of the first review cycle and decrease the number of review cycles necessary for approval. To accomplish these goals, the Program provides new opportunities for communication between applicants and the FDA review team, as well as 60 days review clock time for FDA to meet with the applicant as well as address review activities for these highly complex applications.

PDUFA VI contained many enhancements designed to build on the achievements of earlier agreements. One of the key programs continuing under PDUFA VI is the Enhanced Review Transparency and Communication for NME NDAs and Original BLAs (the Program). As of September 2018, FDA has received 355 applications through this Program since its inception on

October 1, 2012, which involves more communication and transparency between the applicant and the FDA review team during review of marketing applications. The FY 2018 Program cohort has received 75 applications to date.

FDA is using vital PDUFA resources to continue to support early and meaningful communication between FDA and drug sponsors, including through the popular, highly successful, and resource-intensive Breakthrough Therapy program. Seventy-two percent of the novel drugs approved in 2018 were approved in United States before any other country. Thirty-five percent of novel drugs approved in 2018 were first-in-class, which is one indicator of the drug's potential for strong positive impact on the health of the American people. Additionally, 72% of the novel drugs approval in 2018 were designated in one or more expedited categories of Fast Track, Breakthrough, Priority Review, and/or Accelerated Approval.

During FY 2018, FDA published 35 draft and final guidance documents including the submission procedures for human factors protocols for new drug, and biologics license applications and guidance on adaptive design for clinical trials. FDA also conducted 8 public meetings related to the process for the review of human drug and biologics license applications.

PDUFA VI continues to support drug development oversight and marketing application review for the new drugs regulatory program. Some important components of the PDUFA VI agreement include:

- Resources for the highly successful and resource-intensive Breakthrough Therapy program
- Commitments regarding FDA's ongoing Patient-Focused Drug Development Initiative
- Enhanced use of real-world evidence for use in regulatory decision making
- Additional postmarket funding for FDA's Sentinel system
- Process improvement work related to combination product review.

FDA will also continue to apply the Program to the review of all NME NDAs and BLAs, including applications that are resubmitted following a Refuse-to-File (RTF) decision and have addressed the deficiencies that led to the RTF, received from October 1, 2017 through September 30, 2022.

New Product Approvals

Below are some of CDER's recent new product approvals. This list does not represent any degree of importance or priority ranking of products.[35]

Product Category	Approved	Product Name	FDA-Approved Use on Approval Date
Autoimmune Disease	May 2018	Olumiant	To treat moderately to severely active rheumatoid arthritis
Opioid Dependence	May 2018	Lucemyra	For the non-opioid treatment for management of opioid withdrawal symptoms in adults

[35] For more information on product approvals and designations visihttp://www.fda.gov/NewsEvents/ProductsApprovals//.

Product Category	Approved	Product Name	FDA-Approved Use on Approval Date
Liver Disease	Jul 2018	Mulpleta	To treat thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure
Infectious Diseases	Oct 2018	Nuzyra	To treat community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections
	Jul 2018	TPOXX	The first drug ever to treat smallpox and therefore help in the event of a bioterror attack with this virus
Other	Feb 2018	Erleada	To treat a certain type of prostate cancer using novel clinical trial endpoint
	Feb 2018	Lokelma	To treat hyperkalemia.
	Apr 2018	Crysvita	To treat adults and children ages 1 year and older with x-linked hypophosphatemia (XLH), a rare, inherited form of rickets.
	May 2018	Palynziq	To treat a rare and serious genetic disease known as phenylketonuria (PKU)
	Jun 2018	Epidiolex	To treat rare, severe forms of epilepsy
	Aug 2018	Pifeltro	To treat HIV-1 infection in adult patients
	Nov 2018	Yupelri	To treat patients with chronic obstructive pulmonary disease (COPD)
	Nov 2018	Daurismo	To treat newly-diagnosed acute myeloid leukemia (AML) in adult patients

21st Century Cures

The Cures Act supports our innovation and evidence framework to expedite the delivery, discovery, development, and evaluation of beneficial new medical products for the American public. The Cures Act authorizes FDA to prioritize and enhance ongoing activities including efforts to:

- Facilitate greater patient engagement in drug development
- Advance innovative clinical trials through adaptive designs and novel statistical modeling
- Foster the generation of evidence derived from real-world experience and evaluate its applicability to drug development
- Support the advancement of emerging manufacturing technologies
- Qualify new drug development tools.

Additionally, the Cures Act provides new hiring authorities to improve FDA's ability to compete with industry and academia in hiring and retaining scientific experts.

The Cures Act included authorization of the limited population pathway for antibacterial and antifungal drugs (LPAD). This facilitates development and approval of antibacterial and antifungal drugs intended to treat serious or life-threatening infections in a limited population of patients with unmet needs. In June 2018, FDA published draft guidance describing the recommended criteria, processes, and other general considerations for demonstrating the safety and effectiveness of drugs approved under the LPAD pathway. FDA is working to revise this draft guidance and meet the statutory deadline for publication of the final guidance by February 2020. The Cures Act clarified FDA's authority to:

- Remove the breakpoint information from antimicrobial drug labeling
- Leverage the work done by standards development organizations
- Take advantage of online tools to modernize and streamline the updating of breakpoints information for these antimicrobial drugs.

In December 2017, FDA launched the susceptibility test interpretive criteria ("breakpoints") webpages also required by the Cures Act to enable up-to-date breakpoints for the reports provided to physicians to inform appropriate treatment choices. In 2018, FDA opened a public docket to receive comments on the FDA-recognized breakpoints listed on the web page.

In accordance with the Cures Act, FDA is establishing an updated qualification process for drug development tools (DDT) including biomarkers, clinical outcome assessments (COAs), and animal models for proposed contexts of use for drugs and biologics. Once a DDT is qualified under the new process, it can be used for its qualified context of use to support regulatory decisions. For biomarkers, FDA's work is primarily focused in two distinct areas:

- Supporting use of surrogate endpoints in individual drug and biological product development programs, including by cataloguing those previously used as well as a process to develop novel surrogate endpoints
- Facilitating a public process to support biomarker qualification as a drug development tool.

In July 2018, FDA published a list of surrogate endpoints (SE) which were the basis of approval or licensure (as applicable) of a drug or biological product for both accelerated and traditional approval. FDA Collaborated with the Foundation at FNIH Biomarkers Consortium, Critical Path Institute, FDA CERCI program, National Biomarker Development alliance. The outcomes of these collaborations have been over six workshops and two White Papers. The Cures Act requires FDA to publish a guidance describing the standards, process, and timeframes for DDT qualification. FDA must also establish a taxonomy for the classification of biomarkers for use in drug development. These topics were discussed at a public workshop in December 2018.

The Cures Act allows FDA to issue grants to study continuous manufacturing – a technologically advanced and automated manufacturing method. Continuous manufacturing provides a faster, more reliable way to make drugs and biological products and can help reduce drug shortages and recalls related to problems with product or facility quality. In 2017, FDA granted an award to the University of Connecticut to develop and build a continuous manufacturing platform with modular components for complex dosage forms. In July 2018, FDA awarded new 3-year grants to Rutgers, Georgia Tech and MIT for studying and recommending improvements to the process

of continuous manufacturing of drugs and biological products and similar innovative monitoring and control techniques. This research is likely to advance FDA's regulatory science and facilitate production of high-quality, cost-effective complex drug products for the benefit of the public.

The Cures Act supports FDA's evaluation of the potential use of utility of real-world evidence (RWE) to support the approval of new indications of approved medical products or to satisfy post-approval study requirements for marketed products. FDA is actively working to integrate RWE such as electronic health records, registries, and claims and billing data into regulatory decision making and to answer questions relevant to broader populations of patients. In December 2018 FDA developed and published a framework to evaluate the use of RWE gathered from industry, academia and patient advocacy stakeholders to support regulatory decisions.

International Harmonization

FDA leads and engages in work conducted by the International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) to pursue international harmonization of scientific and technical standards for drugs, including both innovator and generic drugs. Harmonizing the drug development process allows drug developers to implement a single global drug development program and utilize common elements of applications to file for approval in multiple markets. In the case of generic drugs, further harmonization of bioequivalence standards will offer particular opportunities. Harmonization could allow manufacturers to use the data submitted in support of a generic drug marketing application to meet other regions' regulatory requirements for approval. In addition, harmonization may increase the size of markets and thereby attract more competition from manufacturers, lower costs by increasing the number of market entrants, and expand patient access in jurisdictions in which generic drug manufacturers otherwise may have decided not to pursue marketing authority due to differences in scientific and technical standards that require additional expensive studies in each jurisdiction.

To advance this initiative, FDA submitted a proposal, or "reflection paper", to ICH outlining a new strategic approach for developing and enhancing ICH guidelines to support the harmonization of scientific and technical standards for generic drugs. As part of this approach, this paper outlines recommendations to:

- Develop a series of ICH guidelines on bioequivalence standards for simple dosage forms
- Develop a series of ICH guidelines on bioequivalence standards for complex dosage forms
- Survey existing ICH Efficacy and Multidisciplinary guidelines for revision or modernization work
- Develop additional guidelines, as needed, that will advance the harmonization of standards for generic drugs
- Establish a generic drug discussion group

The paper was reviewed and endorsed by the ICH Assembly in November 2018. An ICH generic drug discussion group will soon be formed and the ICH-endorsed paper will soon be posted on the ICH website.

FDA continues to collaborate with regulatory authorities and the pharmaceutical industry under ICH to identify areas where there is a commonly recognized need for regulatory harmonization,

to develop guidelines to improve the quality and efficiency of drug development, manufacturing, and post-market safety oversight across multiple regulatory regions.

FDA believes that harmonizing scientific and technical standards for human drugs will help advance markets that drives product competition and increase patient access to high-quality drugs worldwide. FDA will continue pursuing other ways to harmonize international standards for both brand and generic drugs to lower barriers for global entry, expand the opportunities for U.S. drug developers and improve the economic framework for drug development and competition.

Combating Antibiotic Resistant Bacteria

Over the last few decades, antibacterial drug development has not kept pace with patient need. Patients and clinicians are increasingly confronting infections caused by pathogens resistant to many oral antibacterial drugs in both the inpatient and outpatient settings. Antibacterial products are challenging to develop because of the need to study a new therapy in an acute serious disease setting. For example, patients with serious infections are likely to be acutely ill and in need of urgent therapy, which results in challenges in obtaining informed consent and completing trial enrollment procedures in a timely manner. In addition, many patients with serious infections have significant comorbidities that may render them less likely to be enrolled in a clinical trial. Furthermore, antibacterial products are challenging to develop because of limited economic returns.

Despite these considerable challenges in developing an antibacterial drug, FDA approved eight new antibacterial drugs over the past four years, all of which were designated as *qualified infectious disease products* pursuant to section 505E(d) of the FD&C Act. The antibacterial product pipeline nevertheless remains very fragile. The regulatory science research projects described below help to facilitate development and informed use of antibacterial drugs.

CDER has awarded external contracts, through FDA's Broad FDA Announcement, to fund the following research:

- A clinical study and development of tools to improve patient enrollment in clinical trials of new drugs in patients with hospital-acquired and ventilator-associated bacterial pneumonia
- Clinical studies needed to develop patient-reported outcome questionnaires for use in pneumonia and skin infection clinical trials
- The development of a data collection method using electronic medical records from patients with blood infections to update laboratory standards for reporting drug resistance
- Clinical and animal model studies to more quickly develop antibacterial drug dosing recommendations for newborns with meningitis and other serious infections
- Animal model studies to assist the development of new antibacterial drugs targeting high priority resistant pathogens.

CDER has awarded Interagency Agreements to work with other federal agencies to fund the following research:

- CDC studies to understand the microbiome disruption potential for antibacterial drugs and CDC will generate data for antibiotic breakpoints decisions.

- ASPE studies to understand the market for antibacterial drugs, the incentives for developing new antibacterial drugs, and the social value of developing new antibacterial drugs.

CDER's coordinated activities address some important gaps in knowledge for antibacterial drug development. Other important areas of work are needed to provide dependable pathways for studying new antibacterial drugs.

Drug Quality and Security Act Implementation

Title I - Compounding

In November 2013, after a fungal meningitis outbreak linked to contaminated compounded drugs caused more than 60 deaths and 750 cases of illness, the Drug Quality and Security Act (DQSA) was enacted, providing FDA with additional responsibilities to oversee compounding. The DQSA added a new section 503B to the Federal Food, Drug, and Cosmetic Act (FD&C Act), creating a new category of compounders known as outsourcing facilities. Seventy-four firms were registered with FDA as outsourcing facilities at the end of fiscal year 2018. The DQSA also amended section 503A of the FD&C Act to remove provisions that the U.S. Supreme Court held to be unconstitutional in 2002.

Following the enactment of the DQSA, FDA has acted quickly to increase its drug compounding oversight through inspections and enforcement, developing policies regarding the compounding provisions of Federal law, convene and obtain input from an advisory committee, collaborate and coordinate with state regulators, and conduct stakeholder outreach.

Since enactment of the DQSA, FDA has completed the following actions:

- Conducted over 600 inspections of compounders, including over 160 inspections of compounders registered as outsourcing facilities
- Issued over 220 warning letters to compounders, including one warning letter that addressed violations identified at four facilities
- Issued over 100 letters to state agencies, referring findings from inspections of pharmacies in situations where FDA believes that any necessary follow-up can be overseen appropriately by the state
- Issued over 200 recall notices regarding compounded drug products.

FDA has issued 24 draft and revised draft guidance documents regarding compounding and related activities, 16 of which have been finalized. FDA also issued three proposed rules, two of which have been finalized, a Federal Register Notice regarding the list of bulk drug substances that may be used in compounding under section 503B, and a draft and revised draft memorandum of understanding. The policy documents address many significant compounding and related provisions of the FD&C Act and are an important part of FDA's efforts to communicate with stakeholders about its regulatory policies, and to protect patients' health from the risks associated with compounded drugs.

In addition, FDA re-established the Pharmacy Compounding Advisory Committee (PCAC), which provides advice on scientific, technical, and medical issues concerning drug compounding under sections 503A and 503B of the FD&C Act. FDA has held two meetings in FY 2015, three meetings in FY 2016, two meetings in FY 2017, and one meeting in FY 2018.

Further, FDA continued to support stakeholder outreach and collaboration activities. FDA meets with stakeholder organizations including pharmacy, medical, hospital, insurer, and industry organizations, as well as consumer groups and outsourcing facilities, to hear their views on matters related to compounding. FDA has held six sets of listening sessions with more than 75 stakeholder organizations. FDA also hosts intergovernmental working meetings with representatives of the state boards of pharmacy to increase and improve our collaborative efforts to oversee compounding facilities throughout the United States. FDA has held seven such intergovernmental working meetings and has also held two teleconferences with state regulators to discuss emerging issues. FDA also held a meeting with its Federal partners on drug compounding in FY 2018. FDA also announced in FY 2018 its intent to hold a public meeting the following year on certain policy matters related to compounding. In addition, FDA responds to numerous inquiries from stakeholders, including consumers, about compounding.

FDA continues to receive reports of serious adverse events associated with compounded drugs and to identify poor drug production practices that could cause widespread patient harm. Therefore, FDA will continue these efforts, which are critical to protect the public health.

Title II - Drug Supply Chain Security Act

The Drug Supply Chain Security Act (DSCSA) enhances FDA's ability to protect consumers from exposure to potentially harmful drugs through improved detection and removal of such products from the drug supply chain. DSCSA requires FDA to establish the regulatory framework to implement the law, and outlines critical steps to build an electronic, interoperable system to identify and trace certain human, finished, prescription drug products as they are distributed within the United States.

Two critical areas of DSCSA implementation are Product Identification and Tracing, and Licensing.

Product Identification and Tracing: FDA will collaborate with prescription drug manufacturers, wholesale distributors, repackagers, and many dispensers (primarily pharmacies) to develop the new system for enhanced drug distribution security by 2023. The 2023 system is expected to enable:

- Secure tracing of product at the package level
- Verification of product identifiers at the package level
- Prompt response to suspect and illegitimate products when found
- Improved efficiency of recalls
- Transparency and accountability in the drug supply chain.

Licensing: FDA is working on regulations to implement the new licensing standards set forth in the DSCSA for wholesale drug distributors and third-party logistics providers, as well as preparing to establish an FDA licensing and inspection program. FDA also issued guidance specific to reporting requirements for wholesale distributors and third-party logistics providers and will continue to engage stakeholders through stakeholder meetings, public comments on guidances, and through questions received by FDA staff.

Since enactment of the DSCSA, FDA has worked to develop regulations, standards, policies, and programs to implement the law.[36] FDA has issued ten draft guidance documents and six final guidances, including two final guidances to assist stakeholders in understanding when a product without a product identifier is grandfathered and when requirements will be enforced. FDA also continued its stakeholder outreach and communications holding six public meetings as well as multiple stakeholder meetings to increase awareness of the DSCSA. In 2018, FDA completed a series of three public meetings with stakeholders, including members of the supply chain, state authorities, standards organization, and solution providers, on various strategies and issues related to the enhanced drug distribution security provisions of the DSCSA.

FDA continues to develop a long-term program schedule for implementing the multiple statutory requirements of the law. As the phased in requirements of DSCSA go into effect over the next five years, FDA will continue to engage supply chain stakeholders as we develop the enhanced drug distribution security by 2023.

Guidances

Below are notable drug guidances recently issued by FDA. These guidances help address various issues. This list reflects notable guidances published most recently and does not represent any degree of importance or priority ranking among the published guidances.[37]

Date	Docket #	Title	Description
Apr 2018	FDA-2018-D-1334	Opioid Dependence: Developing Depot Buprenorphine Products for Treatment Guidance for Industry (Draft)	Addresses drug development and trial design issues relevant to the study of depot buprenorphine products
Aug 2018	FDA-2018-D-2382	Opioid Use Disorder: Endpoints for Demonstrating Effectiveness of Drugs for Medication-Assisted Treatment	Intended to assist sponsors in developing drugs for medication-assisted treatment of opioid use disorder
Sep 2018	FDA-2014-D-2138	Adverse Event Reporting for Outsourcing Facilities under Section 503B of the FD&C	Communicates FDA's current thinking on adverse event reporting for outsourcing facilities
Dec 2018	FDA-2014-D-0779	Current Good Manufacturing Practice – Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act	Addresses considerations of how cGMP requirements should be applied according to the size and scope of an outsourcing facility's operations

[36] For more information on FDA's DSCSA-related activities, please visit https://www.fda.gov/Drugs/DrugSafety/DrugIntegrityandSupplyChainSecurity/DrugSupplyChainSecurityAct/default.htm

[37] Full list of FDA guidance documents is available at http://www.fda.gov/RegulatoryInformation/Guidances.

Date	Docket #	Title	Description
Dec 2018	FDA-2011-D-0611	Biosimilars: Questions and Answers on Biosimilar Development and the Biologics Price Competition and Innovation Act	Describes FDA interpretation of certain statutory requirements and facilitates the development of proposed biosimilars and interchangeable biosimilars
Dec 2018	FDA-2018-D-4627	Biomarker Qualification: Evidentiary Framework	Discusses general considerations to address when developing a biomarker for qualification under the 21st Century Cures Act

Rules

Below are some rules recently published by CDER. Rules help address various issues. This list does not represent any degree of importance or priority ranking among the published rules.[38]

Date	Docket #	Purpose or Benefit
Nov 2016	FDA-2011-N-0697	Amendments to Regulations on Citizen Petitions, Petitions for Stay of Action and Submission of Documents to Dockets
Nov 2016	FDA-2005-N-0343	Medical Gas Containers and Closures; Current Good Manufacturing Practice Requirements
Nov 2016	FDA-2016-N-0543	Food and Drug Administrative Review and Action on Over-the- Counter Time and Extent Applications
Dec 2016	FDA-2016-N-3464	List of Bulk Drug Substances That Can Be Used to Compound Drug Products in Accordance with Section 503A of the Federal Food, Drug, and Cosmetic Act; Proposed Rule
Dec 2017	FDA-2015-N-0101	Safety and Effectiveness of Health Care Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use
Sep 2018	FDA-2017-N-6924	Repeal of Regulation Requiring an Approved New Drug Application for Drugs Sterilized by Irradiation

EMPOWER CONSUMERS AND PATIENTS

Patient-Focused Drug Development

Patient-focused drug development (PFDD) is a systematic approach to help ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation. The primary goal of PFDD is to better incorporate the patient's voice in drug development and evaluation, including but not limited to:

[38] For more information on FDA rules please visit http://www.fda.gov/RegulatoryInformation/RulesRegulations/default.htm

- Facilitating and advancing use of systematic approaches to collecting and utilizing robust and meaningful patient and caregiver input to more consistently inform drug development and regulatory decision-making
- Encouraging identification and use of approaches and best practices to facilitate patient enrollment and minimizing the burden of patient participation in clinical trials
- Enhancing understanding and appropriate use of methods to capture information on patient preferences and the potential acceptability of tradeoffs between treatment benefit and risk outcomes
- Identifying the information that is most important to patients related to treatment benefits, risks, and burden, and how to best communicate the information to support their decision making.

Through the PFDD initiative FDA has been addressing the need to better enable patients to provide meaningful input into drug and biologic development. The Cures Act created a new subsection "Patient Experience Data". This requires reviewers to include a brief statement regarding patient experience data and related information if it is submitted and reviewed as part of an application. FDA has implemented an approach to record and track the submission and review of patient experience data. A new subsection called "Patient Experience Data" has been included in drug review documents, which will require reviewers to include a brief statement regarding patient experience data and related information that is submitted and reviewed as part of an application.

As described in the plan published in June 2017 FDA will issue a series of guidances to address methodological PFDD topics required by Section 3002 of the Cures Act, including how patient experience data and other relevant information from patients and caregivers can be collected and used for medical product development and regulatory decision-making.[39] To inform the first guidance, FDA conducted a public workshop in December 2017 to convene a stakeholder discussion on methodological approaches that can be used by a person seeking to collect patient experience data for submission to FDA to inform regulatory decision making. FDA issued the first draft guidance in June 2018, addressing sampling methods for collecting representative information on patient experience to inform the development and evaluation of medical products throughout the medical product lifecycle. This guidance also discusses methods to operationalize and standardize the collection, analysis and dissemination of patient experience data. It also includes a glossary of terms that will be used in one or more of the four draft guidance documents.

In October 2018, FDA hosted a two-day PFDD workshop with stakeholders including patients, expert practitioners, drug developers and other interested persons to obtain stakeholder feedback on methods to be addressed in the second and third PFDD guidance documents to:

- Identify what is important to patients regarding the burden of disease, treatment and the benefits and risks in the management of the patient's disease; and
- Select, develop or modify Fit-for-Purpose Clinical Outcome Assessments to measure the patent experience in clinical trials.

[39] Full plan is available at https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM563618.pdf

This two-day workshop included discussion of FDA discussion papers and public input received from the docket will inform the development of the second and third methodological PFDD guidance documents as outlined in the plan published in June 2017.[40]

In addition to the work related to the four methodological PFDD guidances, in December 2018, FDA also issued a draft guidance on developing and submitting proposed drug guidance relating to patient experience data.[41] This guidance, also required under Section 3002 of the Cures Act, is intended to assist stakeholders seeking to develop and submit a proposed draft guidance relating to patient experience data for consideration by FDA. To inform the development of this draft guidance, a public workshop was conducted in March 2018 to obtain input from external stakeholders.

To complement the PFDD guidance work and accomplishments outlined above, FDA plans to further advance the quality and utility of sponsor-submitted patient experience data for regulatory decision making by establishing a competitive grant program to begin in FY 2019.

STRENGTHEN SCIENCE AND EFFICIENT RISK-BASED DECISION MAKING

Improving the Efficiency of Medical Product Development and Regulation with In Silico Tools

FDA recognizes that science has enabled fundamental advances in our understanding of human disease. Furthermore, we recognize that efficient regulatory processes informed by the most up-to-date science enables us to develop treatments that target the underlying mechanisms that drive diseases. Applying in silico (computational) approaches - such as modeling and simulation - to drug development enables applicants to apply predictive models in early drug development and provides regulators with tools to conduct critical premarket and postmarket analyses.

In silico clinical trials use computer models and simulations to develop and evaluate drugs. Modeling and simulation play a critical role in organizing diverse data sets and exploring alternate study designs, enabling safe and effective new therapeutics to advance more efficiently through the different stages of clinical trials. CDER is currently using modeling and simulation to:

- Predict clinical outcomes
- Inform clinical trial designs
- Support evidence of effectiveness
- Optimize dosing
- Predict product safety
- Evaluate potential adverse event mechanisms
- Select appropriate endpoints
- Optimize clinical development programs (e.g., efficacy extrapolation based on PK matching in pediatric patients)
- Enrich patients.

CDER addresses a variety of drug development, regulatory, and therapeutic questions through modeling and simulation strategies. CDER's Office of Translational Sciences (OTS) uses these

[40] For additional detail, visit https://www.fda.gov/downloads/Drugs/NewsEvents/UCM620708.pdf

[41] Guidance available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM628903.pdf

same strategies in the review of Investigational New Drugs Applications (INDs) and New Drug Applications (NDAs). These approaches help assess the combined effect of drug interactions, renal impairment, and hepatic insufficiency in patients, with clinical management strategies described in drug labeling where appropriate.

CDER also uses modeling and simulation to support the creation of natural history databases to for model-based drug development. FDA is currently collaborating with scientists to develop such natural history models in Parkinson's disease, Huntington's disease, Alzheimer's disease, and muscular dystrophy to better evaluate the behavior of new treatments in rare disease populations that are inherently hard to study due to their small size.

Modeling and simulation is also used by CDER in the premarket setting for predictive safety assessments. This includes quantitative structure activity relationship (QSAR) to make predictions of whether a drug or drug impurity is likely to have mutagenic (cancer-causing) effects based on the chemical structure. In addition, quantitative systems pharmacology models are used for safety assessment. An example in CDER is the use of a cardiac physiology/pharmacology model to predict the risk of a drug to cause abnormal heart rhythms. An implementation working group with the ICH led by FDA is working toward global implementation of this approach to eliminate the need for certain cardiac safety clinical trials.

FUNDING HISTORY[42]

Fiscal Year	Program Level	Budget Authority	User Fees
FY 2016 Actual	$1,451,570,000	$487,299,000	$964,271,000
FY 2017 Actual	$1,549,170,000	$488,626,000	$1,060,544,000
FY 2018 Actual	$1,755,609,000	$495,384,000	$1,260,225,000
FY 2019 Annualized CR	$1,713,629,000	$495,395,000	$1,218,234,000
FY 2020 President's Budget	$1,980,030,000	$713,895,000	$1,266,135,000

[42] Numbers reflect comparability adjustments for FY 2018, FY 2019, and FY 2020 consistent with budget figures.

BUDGET REQUEST

The FY 2020 Budget Request is $1,980,030,000, of which $713,895,000 is budget authority and $1,266,135,000 is user fees. The budget authority is increased by $218,500,000 compared to the FY 2019 Continuing Resolution level and user fees increased by $47,901,000. The Center for Drug Evaluation and Research (CDER) amount in the request is $1,749,191,000. The Office of Regulatory Affairs amount is $230,839,000. The FY 2020 Budget allows the Human Drugs Program to uphold its public health mission of ensuring that new, generic, biosimilar, and OTC drugs are safe and effective.

The FY 2020 Budget will enable FDA to continue to carry out rigorous science-based premarket drug reviews of new, generic, and biosimilar biological drug products. Identifying and developing new scientific methods, models, and tools to improve the quality, safety, predictability, and efficiency of new drug development is a core mission of FDA. FDA will continue to promote patient and health professional awareness of drug benefits and risks through effective communication of drug information.

FDA will continue to conduct postmarket surveillance to enable early detection of drug safety signals. FDA oversees drug promotion and marketing to help ensure that marketed drug labeling and advertising are truthful and not misleading. FDA will also continue its efforts related to opioids with abuse-deterrent properties. FDA is committed to making progress on setting and applying appropriate regulatory incentives and expectations regarding opioids with abuse-deterrent properties.

FDA will continue oversight of human drug compounding through inspections and enforcement, policy development and implementation, obtaining input from an advisory committee, state collaboration and coordination, and stakeholder outreach. The FY 2020 Budget will also support FDA's ability to improve the integrity of the drug supply chain. FDA will continue to establish the regulatory framework to support the implementation of the Drug Supply Chain Security Act by developing policy and programs, drafting proposed rules, drafting guidance documents and conducting public meetings.

The FY 2020 Budget will support FDA's efforts to minimize public health risks associated with counterfeit and substandard drugs. FDA is educating consumers and the health care community about the risks of, and minimizing exposure to, counterfeit and substandard drug products in addition to implementing regulatory and enforcement tools to improve the security of the drug supply chain.

Budget Authority

Human Drugs - FY 2020 Budget Request

FDA intends to focus its resources on promoting innovation and competition, and advancing the health and safety of American families. The targeted budget increases for FDA are intended to support these goals in a way that would also help American businesses capitalize on recent and emerging breakthroughs in technology and scientific knowledge. These breakthroughs include medical product innovation, improvements in manufacturing processes, and advances in scientific knowledge and data-gathering techniques.

The requested funding would enable FDA to implement regulatory improvements intended to advance these outcomes across a wide range of industries. FDA believes that these regulatory

improvements would better enable industry to pursue innovation that will lead both to better health outcomes for American families and to U.S. economic development.

FDA proposes the following targeted budget requests for special initiatives. These novel initiatives will require new investments, advance the Agency's strategic priorities, and align with the Department's broader policy goals. In many cases, the improvements that would be made possible by a single request would help to advance multiple priorities simultaneously.

Foster Advancements in Manufacturing Innovation

Innovations in medical product manufacturing have the potential not only to improve the quality of the products being made-with direct benefits for the health of American families, but also to make the manufacturing process more efficient. Such improvements in efficiency can lead to lower costs for manufacturers which make it more attractive and feasible for manufacturers to locate their manufacturing and jobs in the U.S. and ultimately lower prices for consumers.

Promote Domestic Manufacturing: Advancing Modern Drug and Biological Product Manufacturing Technologies: + $25.0 million / 10 FTE

Center: + $25.0 million / 2 FTE

FDA recognizes that the U.S. pharmaceutical and biotechnology industries are moving toward advanced manufacturing technologies such as continuous manufacturing for both small-molecule drugs and biological products (e.g., monoclonal antibodies or vaccines) to improve the agility, flexibility, cost, and robustness of their manufacturing processes. This has great potential to enhance product quality, reduce product failures, avoid drug shortages, significantly reduce vulnerabilities in the U.S. drug supply, and enable rapid responses to domestic and global pandemic needs, thereby enhancing national security. Additional funding for this initiative will support advanced manufacturing technologies to also help accelerate product development and support new clinical development related to targeted therapies.

FDA promotes innovation in this area by evaluating innovative manufacturing technologies and creating a robust scientific base to define the impact of these new technologies on product quality, safety, and effectiveness. This improved analytical framework would allow FDA to develop clear scientific standards, guidance, and policy to support effective and efficient regulatory evaluation of advanced manufacturing technologies. Specifically, there are urgent needs to support advances in manufacturing science and research from a regulatory perspective by providing better regulatory guidance and scientific frameworks in several key areas and funding is critical to make these advancements.

These areas include new processes for active pharmaceutical ingredients and final dosage forms that benefit from continuous manufacturing. For both small-molecule drugs and biological products, modular or plug-and-play type manufacturing equipment design with re-usable, flexible, or interchangeable parts will allow different types of continuous manufacturing process integration. Other processes may also include end-to-end continuous manufacturing from the raw material(s) to final product without isolated intermediates; enhanced in-line process analytical technologies to monitor critical quality attributes and provide feedback in real-time for rapid decision making regarding product quality; and advanced control systems and enhanced modeling for robust and efficient processes. FDA needs sufficient resources, including personnel who have the expertise and capacity to build a foundation for this initiative.

Based on the knowledge gained from research in novel manufacturing technologies, FDA is currently developing a guidance on continuous manufacturing for solid oral dosage forms to facilitate a broader implementation of these new manufacturing technologies in the pharmaceutical industry and simultaneously encouraging the industry to relocate drug manufacturing to the United States. Investments in FDA's work in this area will foster manufacturing innovations that will lead to lower drug prices, and improve the reliability and quality of the drug supply chain.

Advance a New Drug Industry: Establishing the Outsourcing Facility Sector as a Robust and Reliable Source of Compounded Products: + $12.0 million / 27 FTE

Center: +$ 10.0 million / 17 FTE

The Drug Quality and Security Act of 2013 created "outsourcing facilities" – a new sector of drug compounders held to higher production standards to protect patient health. Outsourcing facilities are intended to offer a more reliable supply of compounded drugs needed by hospitals, clinics, and other health care providers. It is particularly important that this sector be able to meet providers' needs for "office stock drugs" (compounded drug products that a provider holds in the office in anticipation of patients who will present with a medical need for a compounded drug), as it has the unique ability under the law to prepare such products. After three years, this domestic sector is still relatively small (approximately 70 entities), is experiencing growth challenges, and is not yet fulfilling its potential. Businesses have encountered market challenges and state regulatory complexities that limit entry and advancement, and FDA continues to find concerning quality and safety problems during inspections.

The FY 2020 Budget request will allow the Human Drugs Program to establish a Center of Excellence on Compounding for Outsourcing Facilities, increase direct engagement with this sector to provide much-needed education and training, conduct research to help inform regulatory decision-making, and implement programs to harmonize and strengthen state oversight of compounding facilities.

The Center of Excellence on Compounding for Outsourcing Facilities created through a public-private partnership would provide training on current good manufacturing practice (CGMP) – the quality standard applicable to outsourcing facilities. The CGMP training would include in-depth, hands-on instruction and demonstrations offered in small settings to members of the sector with minimal cost to participants. The Center of Excellence would also conduct market research to help inform regulatory decision-making by FDA and its external partners, including identification of key challenges and opportunities, as well as growth potential. FDA staff would work closely with a partner organization on engagement with outsourcing facilities, development of research initiatives and developing and executing CGMP training.

Increased direct FDA engagement is also essential. Outsourcing facilities consistently seek more in-depth information, prompt feedback, and timely inspections and site visits from the Agency. They frequently request FDA's views on, for example, facility design, production and testing methods, and new technologies. The requested resources will allow the Human Drugs Program to offer new programs for FDA review of method and process design and study protocols upon request, as well as conduct more meetings to provide prompt in-depth feedback. This approach has the potential to significantly reduce future compliance failures, thus improving confidence in the sector, and would also support technical advancements and encourage market entry and growth.

As part of our increased engagement initiative, FDA will also expand efforts to work with states to harmonize and streamline their approach to the outsourcing facility sector and improve the quality of compounded drugs. State quality requirements for compounding pharmacies not registered with FDA as outsourcing facilities also vary, as do the frequency and duration of inspections, often due to budgetary constraints. FDA often observes insanitary conditions at state-licensed compounding pharmacies. Additional funding will support training and outreach initiatives to strengthen state oversight of compounding facilities, as well as a pilot program of contracted state inspections. This pilot program would fund eligible states to conduct inspections under federal standards, to help ensure that compounding pharmacies not registered as outsourcing facilities provide solely patient-specific compounded drugs prepared under appropriate quality conditions (not insanitary) and outsourcing facilities become the sole source of compounded drugs for office stock prepared under CGMP.

Field: +$2.0 million / 10 FTE

The Office of Regulatory Affairs (ORA) is a critical partner in each of the activities described above. ORA will support the Center of Excellence on Compounding for Outsourcing Facilities and provide hands-on assistance to these facilities to improve compliance. ORA also will support training and outreach initiatives to strengthen state oversight of compounding, as well as a pilot program of contracted state inspections.

In addition, ORA will establish a specialized group of investigators who will spend a majority of their time on outsourcing facility inspectional activities. As discussed above, outsourcing facilities are in their early growth years and would benefit from more frequent FDA inspections and site visits, which outsourcing facilities in the past have requested. These visits would not only help the sector come into compliance, but also help address regulatory hurdles in states that refuse to license these facilities unless they receive annual inspections by FDA. Furthermore, outsourcing facilities are distinct from conventional manufacturers in numerous ways and require specialized knowledge to inspect. A specially trained group of investigators who spend a majority of their time on outsourcing facility oversight will develop a highly sophisticated expertise; will become intimately familiar with the facilities, systems, and technologies that they routinely inspect; and will provide timely, consistent, substantive feedback when compliance issues are identified. This initiative will also help FDA meet annual inspection targets and conduct additional facility visits when requested by the outsourcing facility.

All of these ORA efforts will yield more substantive and efficient interactions with the outsourcing facilities, stimulating entry of new entities and expansion of existing outsourcing facilities.

Compounding: + $13.5 million / 30 FTE

Center: + $10.7 million / 20 FTE

FDA seeks funding to catalyze development of policies and regulations for the outsourcing facilities, including advancement of the list of bulk drug substances that outsourcing facilities may use in compounding and current good manufacturing practice guidance and regulation specific to outsourcing facilities.

Development of the List of Bulk Drug Substances

Development of the list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the FD&C Act ("the 503B Bulks List") is a laborious initiative. The number of bulk drug substances that will require evaluation is significant. In 2013 and 2014, FDA issued Federal Register notices soliciting nominations for bulk drug substances for inclusion on the 503B Bulks List and, in 2015, a Federal Register notice opening a docket for submission of new nominations or renominations. FDA has identified for evaluation approximately 300 unique bulk drug substances, and many of those substances have been proposed for multiple uses, dosage forms and routes of administration. In addition, bulk drug substances continue to be nominated and renominated.

The evaluation of bulk drug substances is complex. In March 2019, FDA issued a final guidance describing a two-part analysis that the Agency intends to use when determining whether to include a nominated bulk drug substance on the 503B bulks list because of a clinical need for an outsourcing facility to use it in compounding. The first part of the analysis involves pharmacists, medical officers, regulatory counsels, and other Agency staff conducting in-depth review of nominated substances, engaging with the nominators, researching the availability of FDA-approved drugs containing the bulk drug substance, and gathering information about whether a compounded drug is needed and whether it can be compounded from FDA-approved drugs.

The second part of the analysis draws on the expertise of medical officers, chemists, pharmacists, and other technical experts throughout the Agency. FDA's chemists evaluate physical and chemical characterization of substances; medical officers research and review any safety issues raised by the use of the substance in compounding and the available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists; and pharmacists research information about the historical use of the bulk drug substance in compounding. The experts produce extensive reviews detailing a thorough analysis of each bulk drug substance and the dosage forms and routes of administration the nominators proposed.

The process for developing the 503B Bulks List also involves other resource-intensive procedures and expertise. FDA must publish a notice in the Federal Register proposing bulk drug substances to be included on the 503B Bulks List, including the rationale for such proposal. FDA must then provide a comment period of at least 60 calendar days. After reviewing the public comments submitted in response to that notice, FDA may decide to consult with the Pharmacy Compounding Advisory Committee (PCAC). The Agency will then make a determination of which bulk drug substances will be placed on the list, and publish a notice in the Federal Register designating bulk drug substances for inclusion on the list. FDA is also identifying in the Federal Register bulk drug substances that will not be placed on the list. In March 2019, FDA issued its first Federal Register notice that two bulk drug substances had been evaluated and are not included on the 503B Bulks List.

Funding will enable FDA to hire staff with the relevant scientific, analytical, and regulatory expertise needed to evaluate substances and develop the 503B Bulks List. Timely establishment of the 503B Bulks List will provide outsourcing facilities and compounders considering registering as outsourcing facilities with more immediate certainty about the bulk drug substances that may be used in compounding and facilitate the compounding of drug products to meet the clinical needs of healthcare providers and patients.

Current Good Manufacturing Practice Guidance and Regulation for Outsourcing Facilities

The Drug Quality and Security Act of 2013 created outsourcing facilities to supply healthcare providers with compounded drugs made under current good manufacturing practice (CGMP) requirements. Before becoming outsourcing facilities, many entities were compounding drugs under a lower quality standard as state-licensed pharmacies and not yet accustomed to CGMP. Stakeholders, especially those currently registered as outsourcing facilities and compounders potentially interested in registering as outsourcing facilities, are awaiting FDA final guidance and regulations addressing the CGMP requirements applicable specifically to outsourcing facilities. In December 2018, FDA issued a revised draft guidance describing FDA's proposed policies regarding outsourcing facility compliance with the CGMP regulations in 21 CFR Parts 210 and 211. FDA's draft guidance explains that FDA intends to promulgate more specific CGMP regulations pertaining solely to outsourcing facilities. Funding would enable FDA to issue final guidance regarding compliance with 21 CFR Parts 210 and 211and proposed and final regulations relating specifically to the CGMP requirements for outsourcing facilities at a faster pace. This would give outsourcing facilities and those contemplating becoming outsourcing facilities clarity on CGMP requirements for outsourcing facilities, thereby assisting them in meeting healthcare providers' and patients' needs for quality compounded drugs.

Field: + $2.8 million / 10 FTE

Supporting Outsourcing Facilities' Efforts to Improve Compounding Quality

Outsourcing facilities would benefit from more frequent FDA inspections and site visits. These visits not only help the sector come into compliance, but also help address regulatory hurdles in states that refuse to license these facilities unless they receive annual inspections by FDA. Outsourcing facilities are distinct from conventional manufacturers in numerous ways and require specialized knowledge to inspect. Establishing a specialized group of investigators who would spend most their time on outsourcing facility inspectional activities would allow the investigators to develop a highly sophisticated expertise with cGMP requirements and policies specific to outsourcing facilities; become intimately familiar with the facilities, systems, and technologies that they routinely inspect; provide timely, consistent, substantive feedback when compliance issues are identified; and improve the efficiency of their inspections. It also would help FDA meet annual inspection targets and conduct additional facility visits when requested by the industry. In addition, further training can be provided to this specialized group of investigators, including cGMP requirements.

Promote Innovation in Product Development and Scientific Knowledge

FDA is proposing measures to foster innovation and other scientific advancements in medical products for human and animal use. These advancements will help American families to lead healthier lives, including through medical breakthroughs leading to new treatments that were previously unavailable. Moreover, the more FDA can do to foster innovation, the more likely it will be that new technologies – and new jobs – will take hold in the U.S.

Create a New Medical Data Enterprise: Advance the Use of Real World Evidence to Improve Human and Animal Health: + $20.0 million / 2 FTE

Center: + $20.0 million / 2 FTE

Expanding FDA's capacity to utilize real world evidence to evaluate the safety and effectiveness of medical products would generate data that could be used to improve the efficiency of the regulatory process and reduce the burdens that drive up the time and cost required to bring

innovative and life-saving products to the market. Leveraging real world evidence is also integral to advancing the public health where human and animal health challenges intersect, such as the public health threats posed by increasing antimicrobial resistance.

Within the Sentinel Initiative, the FDA has built a cost-effective and scalable system, allowing FDA to answer numerous questions simultaneously and in a matter of weeks and months, rather than years. The per-study costs are a fraction of historical costs. FDA has completed 254 analyses using the Sentinel Common Data Model and reusable modular programs since the full activation of the Sentinel System in 2016, including 116 in 2016 and 138 in 2017. This is many more than would have been possible without the improvements brought about by the Sentinel System. The creation of the Sentinel System and the companion Innovation in Medical Evidence and Development Surveillance (IMEDS) program, that provides access to the Sentinel infrastructure to stakeholders, has reduced the burden on pharmaceutical sponsors for conducting postmarketing studies.

Although large database systems, such as Sentinel, have been developed to help evaluate postmarket safety, their utility for the evaluation of complex issues related to safety and their potential utility to evaluate effectiveness is less than optimal because to date Sentinel has relied primarily on claims data due to challenges with linking to more complete clinical data held in patients ' medical records. Other systems, such as the National Evaluation System for health Technology (NEST), that rely primarily on registries, have been leveraged to evaluate safety and effectiveness, in some cases resulting in first in the world approvals, but also face challenges because they do not link to electronic health records.

Expanding on these successful distributed database models, the further development of a robust near-real-time real-world evidence capability would serve to facilitate the development of drugs, biologics, and devices by allowing FDA and eventually sponsors to obtain critical information on aspects of the safety and effectiveness of marketed products.

Building on the accomplishments of the Sentinel System and NEST, the requested FY 2020 funding would be used to 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 for at least ten million individuals in a broad range of healthcare settings in the United States for a broad range of medical products. The healthcare settings would be carefully selected to cover data gaps in the Sentinel and NEST systems for FDA-regulated products not currently easily assessed using existing systems. ln addition to accessing more detailed clinical data, this effort would apply modem computational techniques, such as natural language processing and machine learning, to efficiently use these data elements for evaluating safety and effectiveness of marketed medical products. This would create a sustainable platform that could then be expanded through public-private partnerships.

This expanded real-world evidence capability would serve to facilitate the development of drugs, biologics, and devices by allowing FDA and eventually sponsors to obtain critical information on aspects of the safety and effectiveness of marketed products. Near-real-time access to data would result in the ability to shift more data collection into the postmarket setting to address residual uncertainties, to more rapidly identify and confirm relevant safety signals, and to facilitate product label expansion into new indications. Given the relatively large sample size, it would also allow FDA, potentially in collaboration with other federal partners, to rapidly evaluate emerging diseases potentially affecting the blood or tissue supplies.

A by-product of the development of a robust natural language processing and machine learning system also would be to significantly augment the efficiency of the existing manual review of passively reported adverse events by FDA staff. This would allow the optimization of human safety expert review while freeing resources to be redirected toward advancing product development, review, and approval. FY 2020 funding to support the activities above will enable FDA to address this critical initiative.

Applying Cutting Edge Science to Advance Drug Development and Review: Drug Innovation Platform: + $45.0 million / 5 FTE

Center: +$45.0 million / 5 FTE

Rapidly advancing science in drug development requires FDA to have up to date scientific standards and assessment tools, as well as evolving technologies, methods, and approaches. Without these tools the Agency's ability to support innovation and review applications lag behind and inhibit innovation. Currently, FDA has several drug development guidances where updates to assure new scientific information and new approaches to drug development are incorporated. In addition, guidances are needed in a number of disease areas where there is no existing guidance and therefore no articulated pathway to market for new treatments. FDA's decision-making rests on the regulatory and statutory framework, and on the scientific expertise of its staff, but would be supported and facilitated by a comprehensive knowledge management system that provides access to and analysis of prior regulatory decisions and previously submitted clinical trials information and other relevant datasets.

FDA requires a comprehensive knowledge management approach to its significant number of precedential decisions, and to the underlying data, including data from trials, data generated by FDA, and real-world data. Additional funding would support development of a knowledge management system that would provide rapid access to and in-depth analysis of the vast and diverse information submitted to FDA. Such a knowledge management system would advance FDA's ability to rapidly develop scientific evidence as questions arise, including questions about drug safety or quality.

With this investment, FDA would build a knowledge management system and portal to previously submitted and ever-expanding information on drug development and regulatory precedents, advancing FDA's ability to provide consistent and fully-informed responses to regulatory questions. Such a knowledge management system may also help to enhance FDA's ability to rapidly respond to issues that arise, whether related to a regulatory decision or a safety signal, and support innovations in drug development by fully leveraging prior experience. This could also enable safety issues to be monitored along all phases of the drug lifecycle from animal studies to premarketing clinical trials to postmarketing adverse events. FDA would also expand its capability to quickly evaluate new questions, using laboratory research or other appropriate methods.

Funding for this initiative would support a variety of components which includes building reliable, connected environments that allow reviewers/users to access data, tools, and knowledge. This includes templates, standardized data, tools and regulatory review knowledge and intelligence.

Additional FY 2020 funding would also support recruitment efforts of technical experts to help understand the requirements for scientific review and to develop the specifications for a future

integrated platform for innovation that would also improve data sharing and allow testing of state-of-the-art tools and technologies. Such a platform would also support the enforcement of data standards and the acquisition of advanced analytical tools.

The FY 2020 funds requested would support refined oversight for investment and contract management functions to enable improved IT infrastructure to support regulatory review and knowledge management. In addition, FDA would have the capability to build IT environments that allow real-time testing of the latest tools and technologies including data visualization and business intelligence tools.

With the advent of enforceable guidance, the Agency must be prepared to accept and assess "data quality" and "data fitness" to fully utilize standardized data to support core analyses. This will entail increased infrastructure to support data management and data quality assessments as well as infrastructure to prepare data for standard analyses with core tools/technologies. In addition, with various data sources that can influence regulatory decision making, the Agency will need additional resources to have scientific computing environments enabled to support real time data analysis with state-of-the-art tools. FDA will also need considerable funding to develop and enhance regulatory intelligence systems to fully interface with the review work product to seamlessly capture metadata about the review.

Investments in this area would also facilitate training and understanding of advanced methodologies and emerging science to increase capacity to evaluate and propose innovative strategies for clinical outcome assessments and the endpoints derived from them. FDA would also have the additional capacity to develop advanced analytical methods/tools for the quantitative assessment of safety and increase training and exposure to quantitative assessment of complex innovative designs to increase capacity to evaluate, propose, and refine innovative strategies. Additional funding would support new and essential efforts to build a knowledge management framework that would enhance the overall drug development and review cycle within the Agency.

Overall, the development of this Drug Innovation Platform would make the review of drug applications and the management of postmarketing safety and efficacy supplements exponentially more efficient and effective, resulting in shorter review cycles and the ability to continuously evaluate and adopt innovative technologies and methodologies to support drug development and surveillance.

Stimulating Medical Product Development for Rare Diseases: +$20.0 million / 5 FTE

Center: +$20.0 million / 5 FTE

A disease is considered rare if it has a prevalence of fewer than 200,000 affected individuals in the United States. There is great unmet need with nearly 7,000 diseases that lack treatment for an estimated 30 million Americans. Currently, there are large and growing gaps in the evidence available to help providers and patients make treatment decisions due to a lack of clinical data and understanding of how to develop the treatments in a given disease, often compounded by the small number of patients impacted by rare diseases.

FY 2020 funding would support FDA's commitment to advancing the evaluation and development of medical products that demonstrate promise for the diagnosis and/or treatment of rare diseases or conditions. To foster innovation and medical product development for rare diseases, FDA would develop clinical trial networks to create an understanding of the natural

history and clinical outcomes of rare diseases and leverage this framework when promising medical products are identified on behalf of patients. FDA would stimulate medical product development for rare diseases by expanding and enhancing the understanding of rare diseases and related research and drug development processes.

FDA will also conduct assessments of current orphan drug incentives, including market exclusivity, to inform FDA's policy framework around primary and secondary drug indications. Included would be a better understanding of how FDA could best incentivize more drug development for ultra-rare diseases. The requested funding for this initiative will enable FDA to implement advances to support the public health mission of the Agency.

Modernizing Generic Drug Development and Review: +$27.0 million / 5 FTE

Center: +$27.0 million / 5 FTE

Timely development, review, and access to generic drugs are pivotal for enabling competition and providing affordable drugs for American patients. Currently, generic drug review is performed using text-based applications and assessments—in other words, 20th Century technology. An updated review platform would significantly modernize generic drug review and by improving clarity for generic sponsors and decreasing the rate of refusals-to-file, greatly increasing efficiency at FDA. This one-time platform investment would provide returns in the efficiency and effectiveness of the process for many years. As part of modernizing the regulatory processes for generic drugs, this investment would also support efforts to update generic drug labeling, with an initial focus on oncology products, as part of the FDA's efforts to ensure that patients and their providers have access to up-to-date information to inform clinical decisions.

The new Knowledge-aided Assessment & Structured Application (KASA) platform would support the capture and management of all the required information about a drug product, facilitate risk identification, mitigation and communication, and provide a structured template that would completely replace an unstructured text based narrative review. Instead of the current unstructured approach, information from the submission considered essential for the assessment would be structured and organized in tabular format. This would result in more consistent drug product evaluations and seamless knowledge management across generic and brand-name drugs that would enhance product surveillance based on quality risk. In addition, this new platform would enable the automation of elements of the application review that are currently performed manually, reducing overall application review cycle times.

The funding request for this new generic drug review platform would allow FDA to advance the quality assessment of sponsor-provided drug product applications and will lead to more predictability to the regulated industry, and thus facilitate generic entry. Additional funding would support resources and costs for IT investments as well as, structure for data management, contracts and grants. Taken together, these programs would allow FDA to advance the quality assessment of sponsor-provided drug product applications and ultimately improve patient care and facilitate access to new and generic therapies.

Opioids: + $55.0 million / 14 FTE

Center: +$33.2 million / 2 FTE

FDA requests $33.2 million to combat the opioid epidemic and to support the substantial work

that is needed to implement the SUPPORT Act, enacted in October 2018. The SUPPORT Act gives FDA new authorities to continue current epidemic-related efforts and develop and implement new actions to reduce the use, misuse, and abuse of opioid medicines. FDA will use the funding to develop and implement evidence-based actions targeted to:

- Decrease initial exposures to opioid medicines, thus preventing new addiction
- Support development and approval of treatments for individuals with opioid use disorder
- Foster the development of novel therapies without addictive properties to ensure that persons suffering from severe and chronic pain have the safe and effective medicines they need
- Improve enforcement and assess benefit-risk.

Critical areas related to the use and abuse of opioid drugs demand science-based study and analysis. For example, identified research studies include collecting, generating, and analyzing the pre-clinical, clinical, and real-world data needed to support safer analgesic packaging and rational prescribing through evidence-based treatment guidelines. FDA needs more information about pain and how to treat it more safely and effectively.

The requested funding will also support the development of surveillance programs that can help FDA assess the impact of its regulatory actions and treatment guidelines on opioid use, misuse, and abuse. FDA will use this evidence when developing regulatory policy, and targeted compliance and enforcement activities.

Funding will also support the development of a comprehensive systems model of the opioid crisis. This model is critical to harness the best available data to assess the potential effects and interdependencies of various interventions. FDA will also use funding to support development of studies to improve the evaluation of abuse-deterrent generic opioid products, and the development of mechanistic models and social and behavioral science research to help foster the safe use of opioids.

The FY 2020 Budget also requests funding to continue the activities critical to enhancing regulatory oversight of products entering the country through International Mail Facilities (IMF). With the requested resources, FDA will work to resolve a broad range of complex regulatory compliance and enforcement cases and issues related to importation of potentially unsafe medical products found at the IMFs. FDA will be required to respond to regulatory status consults on potential unapproved new drug and misbranding charges, follow up domestically on violative firms discovered from import surveillance and compliance work, and provide incident coordination and outreach related to imported products to protect public health.

FDA will also review and analyze imports data from the IMFs to identify trends and compliance issues for action to drive the IMF strategy. This includes the use of administrative destruction authority, establishing sampling plans, and deploying rapid screening technologies in the IMFs, and to ensure the effectiveness and consistency with risk-based imports policy and strategy to target higher risk products.

In addition, FDA will increase surveillance and cyber-driven intelligence based on drug information gathered at the IMFs. Also, ORA will compile the database of violative products and firms, and CDER will evaluate the products and websites and determine whether to issue a Warning Letter or other enforcement action to the person responsible for the website. The

requested resources will also support FDA's ability to have technical experts available to provide expert testimony in criminal trials.

Due to the complexity associated with the identification of these products, the wide range of natural and synthetic opioid drugs, FDA will need staff to sustain the critical efforts in this area.

The responsibilities of the additional staff will focus on supporting the IMFs and include but are not limited to:

- Method development, validation, development/maintenance of data libraries for current and future field instrumentation
- Confirmatory testing of samples
- Training of current and future import staff in the use of current and future field deployable instrumentation and methods
- Real time technical support to the IMFs remotely
- Participation as technical advisors during field operations
- Evaluation of new technology that can be applied to the analyses of opioids, drug products and supplements encountered daily in these facilities.

Field: + $21.8 million / 12 FTE

With the funding requested in the FY 2020 Budget, ORA will continue building out FDA presence at IMF facilities, improve product targeting, increase staff and safety, purchase equipment, and improve laboratory facilities.

After evaluating the needs of all IMFs, taking into consideration the corresponding divisions under program alignment, volume of parcel incoming by IMF and existing personnel, ORA began hiring to increase staffing to 125 FTE in support of the nine international mail facilities. The additional staff will provide the agency the manpower to increase its reviews from 15,000 to 100,000 per year. In addition, ORA is requesting additional staff and funds to support lab work related to the increased package screening.

Medical Countermeasures: +$1.0 million / 4 FTE

Center: + $1.0 million / 4 FTE

The FY 2020 Budget Request includes $1 million for FDA review and regulatory science capacity to facilitate the development and availability of MCMs to respond to CBRN and emerging infectious disease threats.

Performance

The Human Drugs Program's performance measures focus on premarket and postmarket activities, generic drug review actions, and drug safety in order to ensure that human drugs are safe and effective, and meet established quality standards, as detailed in the following table.

Measure	Year and Most Recent Result / Target for Recent Result (Summary of Result)	FY 2019 Target	FY 2020 Target	FY 2020 +/- FY 2019
223210: Review and act on 90 percent of standard NME NDA and original BLA submissions within 10 months of the 60-day filing date. *(Output)*	FY 2017: 100% Target: 90% (Target Exceeded)	90%	90%	Maintain
223211: Review and act on 90 percent of priority NME NDA and original BLA submissions within 6 months of the 60-day filing date. (*Output*)	FY 2017: 100% Target: 90% (Target Exceeded)	90%	90%	Maintain
223212: Review and act on 90 percent of standard non-NME original NDA submissions within 10 months of receipt. *(Output)*	FY 2017: 99% Target: 90% (Target Exceeded)	90%	90%	Maintain
223213: Review and act on 90 percent of priority non-NME original NDA submissions within 6 months of receipt. *(Output)*	FY 2017: 100% Target: 90% (Target Exceeded)	90%	90%	Maintain
223215: Review and act on 90 percent of standard original Abbreviated New Drug Application (ANDA) submissions within 10 months of receipt. *(Output)*	FY 2017: 96% Target: 90% (Target Exceeded)	90%	90%	Maintain
223216: Review and act on 90 percent of priority original Abbreviated New Drug Application (ANDA) submissions within 8 months of receipt. *(Output)*	New Goal	90%	90%	Maintain
224221: Percentage of Human and Animal[43] Drug significant inspection violations which receive appropriate follow-up after regulatory action was taken. (*Output*)	Baseline: 86% (New Measure)	80%	80%	Maintain

[43] Due to Program Realignment, ORA's Workplan now combines Human and Animal drug inspection activities together, so this combination performance goal is repeated in both the Human Drugs and Animal Drugs and Feed program narratives.

Measure	Year and Most Recent Result / Target for Recent Result (Summary of Result)	FY 2019 Target	FY 2020 Target	FY 2020 +/- FY 2019
224222: Percentage of Human and Animal[44] Drug follow-up inspections conducted due to regulatory action on significant inspection violations that moved toward compliance. (*Outcome*)	Baseline: 67% (New Measure)	55%	55%	Maintain
292202: Number of people for whom FDA is able to evaluate product safety through Mini-Sentinel/Sentinel system. *(Outcome)*	FY 2018: 292 million Target: 233 million (Target Exceeded)	N/A	N/A	N/A
292203: Number of medical product analyses conducted through FDA's Sentinel Active Risk Identification and Analysis (ARIA) System. *(Output) (New Measure)*	FY 2018: 74 (Historical Actual)	50	55	+5

The following selected items highlight notable results and trends detailed in the performance table.

REVIEW GOALS

The New Drug Review performance measures focus on ensuring that the public has access to safe and effective new treatments as quickly as possible. The goal of the PDUFA program is to increase the efficiency and effectiveness of the first review cycle and decrease the number of review cycles necessary for approval. The Agency will continually work to meet or exceed the review performance goals when possible moving forward.

The goal of the GDUFA program is to enhance the efficiency of the generic drug review process, promote transparency between FDA and generic drug sponsors, and enhance access to high-quality, lower cost generic drugs. The value of this investment in the Generic Drug Review program is reflected by FDA's performance on its review goals under GDUFA and FDA's commitment to meet shorter review goals (8 months) for priority submissions under GDUFA II.

SENTINEL

The FDA's Sentinel Initiative provides significant public health benefits by developing new approaches and methods to actively monitor the safety of marketed medical products to complement existing FDA surveillance capabilities. Through the Sentinel System, FDA is able to evaluate drug safety issues and inform regulatory decision making. To date, the Sentinel Initiative has contributed to multiple drug safety communications and labeling changes, providing vital information to patients and providers about the safety of drugs and vaccines.

[44] Due to Program Realignment, ORA's Workplan now combines Human and Animal drug inspection activities together, so this combination performance goal is repeated in both the Human Drugs and Animal Drugs and Feed program narratives.

Development of the Sentinel System has matured so that the number of people covered by the system is now sufficient to shift the focus of the performance goal to how the data are used to protect public health. Consequently, FDA has developed a new Sentinel performance measure that focuses on using the system to generate high quality evidence about the use of medical products and better understand their risks and benefits. The new measure leverages Sentinel's Active Risk Identification and Analysis (ARIA) system, which is comprised of pre-defined, parameterized, reusable routine querying tools, combined with the multi-site electronic data in the Sentinel Common Data Model. This enables safety analyses to be done more efficiently using a trusted distributed database that undergoes continuous quality checks and refreshes. The results of these analyses have been presented at FDA Advisory Committee Meetings, highlighted potential ways to intervene in the opioid crisis, informed responses to Citizens Petitions, and influenced numerous regulatory decisions.

The new goal is framed as the number of analyses conducted using the ARIA system. Given that this is a new goal, and that the analyses conducted each year can vary greatly in the number, timing, complexity and character of the safety issues, the initial targets have been set at 50 and 55 analyses for FY 2019 and 2020 respectively and will be reassessed periodically. These targets reflect the trend toward more complex analyses that employ more sophisticated analytical methods, which yield more meaningful inputs to public health and regulatory decision making.

NEW ORA FIELD PERFORMANCE MEASURES

ORA is embarking on an initiative to move from output focused performance goals such as inspection counts to public health outcome based performance goals. This initiative seeks to provide more meaningful performance goals for internal and external stakeholders, and to showcase more direct public health impacts for ORA. The new performance goals introduced for FY 2019 measure topics such as our commitment to follow-up on firms receiving significant inspection violations, as well as measurements related to ORA regulatory impact on violators, and are tracked on a 3-year rolling basis. Due to the nature of regulatory actions and subsequent follow-up conducted by FDA, the duration of these events can vary considerably. After regulatory action, FDA also works to schedule follow-up after a reasonable time has passed to allow the firm to correct for the original violations. A 3-year rolling timeline also ensures tracking of all significant violations that require attention and allows for a more robust analysis.

Program Activity Data

CDER Workload and Outputs	FY 2018 Actual	FY 2019 Estimate	FY 2020 Estimate
New Drug Review			
Workload – Submissions/Filings/Requests			
New Drug Applications/Biologic Licensing Applications (NDA/BLA)	153	153	153
Efficacy Supplements	248	248	248
Manufacturing Supplements	2,001	2,001	2,001
Commercial INDs (Drugs and Biologics) with Activity	7,387	7,387	7,387
Sponsor Requests: IND-Phase Formal Meetings	2,887	2,887	2,887
Sponsor Requests: Review of Special Study Protocols	155	155	155
Submissions of Promotional Materials	107,108	114,000	116,500
Outputs – Reviews/Approvals			
Reviews: Priority NDA/BLA	70	70	70
Reviews: Standard NDA/BLA	141	141	141
Approvals: Priority NDA/BLA	56	56	56
Approvals: Standard NDA/BLA	89	89	89
Mean time from Receipt to Approval: Priority NDA/BLAs (in months)	9.5	9.5	9.5
Mean time from Receipt to Approval: Standard NDA/BLAs (in months)	19	19	19
Median time from Receipt to Approval: Priority NDA/BLAs (in months)	7.9	7.9	7.9
Median Time from Receipt to Approval: Standard NDA/BLAs (in months)	11.9	11.9	11.9
Reviews: NDA Supplementals	3,095	3,095	3,095
Reviews: Clinical Pharmacology/ Bio-Pharmaceutic	6,033	6,335	6,652
Biologic Therapeutics Review			
Workload – Submissions/Filings/Requests			
Receipts: Commercial IND/IDE (Biologics Only)	193	193	193
Receipts: IND/IDE Amendments (Biologics Only)	23,648	23,648	23,648
Outputs – Reviews/Approvals			
Reviews: Total Original License Application (PLA/ELA/BLA)	16	16	16
Approvals: PLA/BLA	15	15	15
Reviews: License Supplement (PLA/ELA/BLA)	471	471	471
Generic Drug Review			
Workload – Submissions/Filings/Requests			
Receipts: Abbreviated New Drug Applications (ANDA)	1,044	1,000	1,000
Outputs – Reviews/Approvals			
Actions – ANDA	4,225	4,000	4,000
Approval Actions - ANDA (both Tentative and Full Approvals)	971	975	1,000
Median Review Time from ANDA Receipt to Approval (months)	29.84	30	30
Actions - ANDA Supplementals (Labeling and Manufacturing)	5,786	5,700	5,800
Over-the-Counter Drug Review			
OTC Monographs Under Development*	25	25	25
OTC Monographs Published*	2	4	4
*Category includes Proposed Rules and Final Rules; OTC Monographs published in FY 2018: Health Care Antiseptic Final rule (FR 82, 243; 20 December 2017) and Withdrawal notice for Proposed Amendment to the TFM for ibuprofen (83 FR 22224; 14 May 2017)			

CDER Workload and Outputs	FY 2018 Actual	FY 2019 Estimate	FY 2020 Estimate
Best Pharmaceuticals for Children Act			
Labels Approved with New Pediatric Information **	18	18	18
New Written Requests Issued**	22	21	22
Pediatric Exclusivity Determinations made**	13	9	9
Post Exclusivity Safety Report **	13	9	9
**Category includes Proposed Rules and Final Rules			
Patient Safety			
Workload – Submissions/Filings/Requests			
Submissions: Adverse Event Reports	2,081,903	2,367,288	2,691,606
Electronic Submissions: % of Total Adverse Drug Reaction Reports	100%	100%	100%
Electronic Submissions: % of Serious/Unexpected Adverse Drug Reaction Reports	100%	100%	100%
Submissions: Drug Quality Reports	17,944	20,000	21,000
Outputs – Reviews/Approvals			
Safety reviews completed by Office of Surveillance & Epidemiology	7,356	7,724	8,110
Number of drugs with Risk Communications	250	195	215
Administrative/Management Support			
Workload			
Number of Advisory Committee Meetings	33	33	33
Number of FOI Requests	3,235	3,300	3,300
Number of FOI Requests Processed	3,229	3,325	3,325
Number of Citizen Petitions Submitted (excluding suitability petitions and OTC monograph-related petitions)	116	123	123
Number of Citizen Petitions Pending on Last Day of Fiscal year (excluding suitability petitions and OTC monograph-related petitions)	202	190	190
Number of Citizen Petitions Completed [1] (excluding suitability petitions and OTC monograph-related petitions)	97	107	107

[1] Citizen Petitions completed may include petitions filed in prior years.

FIELD HUMAN DRUGS PROGRAM ACTIVITY (PAD)

Field Human Drugs Program Workload and Outputs	FY 2018 Actuals	FY 2019 Estimate	FY 2020 Estimate
FDA WORK			
DOMESTIC INSPECTIONS			
UNIQUE COUNT OF FDA DOMESTIC HUMAN DRUG ESTABLISHMENT INSPECTIONS	***1,662***	***1,709***	***1,709***
Pre-Approval Inspections (NDA)	81	100	100
Pre-Approval Inspections (ANDA)	90	90	90
Bioresearch Monitoring Program Inspections	667	600	600
Drug Processing (GMP) Program Inspections	632	650	650
Compressed Medical Gas Manufacturers Inspections	42	50	50
Adverse Drug Events Project Inspections	73	88	88
OTC Monograph Project and Health Fraud Project Inspections	19	70	70
Compounding Inspections[1]	127	142	142
Domestic Laboratory Samples Analyzed	1,041	1,300	1,300
FOREIGN INSPECTIONS			
UNIQUE COUNT OF FDA FOREIGN HUMAN DRUG ESTABLISHMENT INSPECTIONS [2]	***1221***	***1360***	***1360***
Foreign Pre-Approval Inspections (NDA) incl PEPFAR	102	98	98
Foreign Pre-Approval Inspections (ANDA) incl PEPFAR	159	190	190
Foreign Bioresearch Monitoring Program Inspections incl PEPFAR	280	255	255
Foreign Drug Processing (GMP) Program Inspections	743	900	900
Foreign Adverse Drug Events Project Inspections	8	10	10
TOTAL UNIQUE COUNT OF FDA HUMAN DRUG ESTABLISHMENT INSPECTIONS	***2,883***	***3,069***	***3,069***
IMPORTS			
Import Field Exams/Tests	8,607	10,000	10,000
Import Laboratory Samples Analyzed	735	620	620
Import Physical Exam Subtotal	**9,342**	**10,620**	**10,620**
Import Line Decisions	871,212	845,143	904,303
Percent of Import Lines Physically Examined	1.07%	1.26%	1.17%
GRAND TOTAL HUMAN DRUG ESTABLISHMENT INSPECTIONS	***2,883***	***3,069***	***3,069***

[1] The number of compounding inspections includes inspections of compounders that are not registeredwith FDA as outsourcing facilities.

[2] The FY 2018 actual unique count of foreign inspections includes 115 OIP inspections (48 for China and 67 for India).

3 ORA is currently evaluating the calculations for future estimates.