OFFICE OF ORPHAN PRODUCTS DEVELOPMENT

(Dollars in Thousands)	FY 2017 Final	FY 2017 Actuals	FY 2018 Annualized CR	FY 2019 President's Budget	FY 2019 President's Budget +/- FY 2018 CR
Office of Orphan Products Development (Budget Authority) 1,2,3.....	29,099,000	29,099,000	29,099,000	29,099,000	---
FTE.....	34	34	34	34	---

[1] FY 2017 includes $3 million added to PDC grant funds.
[2] FY 2017 amounts include $1.2 million of OOPD program funds to support Orphan Product Grants. [3]
Assumes approximately 50 percent of non-grant budget from user fees in 2017.

Authorizing Legislation: Federal Food, Drug and Cosmetic Act (21 U.S.C. 321-399); PHS Act (42 U.S.C. 241) Section 301; Safe Medical Device Act of 1990 (as amended) (21 U.S.C. 351-353, 360, 360c-360j, 371-375, 379, 379e, 381); Pediatric Medical Devices Safety and Improvement Act of 2007, Section 305; Food and Drug Administration Safety and Innovation Act of 2013, Sections, 510, 620 and 908.

Allocation Method: Direct Federal/Extramural Grants

PROGRAM DESCRIPTION AND ACCOMPLISHMENTS

The public health programs of the Office of Orphan Products Development (OOPD) have promoted and advanced the development of innovative products – drugs, biologics, medical devices, and medical foods – that demonstrate promise for the prevention, diagnosis, and/or treatment of rare diseases or conditions. There are an estimated 7,000 rare diseases, with a public health impact that affects more than 25 million Americans and many millions more of family members in the United States. Between 85 and 90 percent of these cases are serious or life-threatening.

Leveraging Innovation

OOPD administers major provisions of the Orphan Drug Act and other relevant statutes, where Congress sought to provide incentives to promote the development of products for the treatment of rare diseases and for underserved populations. OOPD incentive program activities facilitate product development innovation and collaboration with private, public and academic entities. Further, the programs directly support the FDA's Strategic Policy Roadmap priority area to leverage innovation and competition to improve health care, broaden access, and advance public health goals.[45]

Orphan Product Grants Activity[46]

The Orphan Drug Act created the Orphan Product Clinical Trial Grants Program, which is administered by OOPD, to stimulate the development of promising products for rare diseases and conditions. Orphan product grants are a proven method of fostering and encouraging the development of new, safe and effective medical products for rare diseases and conditions. These grants support new and continuing extramural research projects that test the safety and efficacy of promising new drugs, biologics, devices, and medical foods through human clinical trials in extremely vulnerable populations often with life-threatening conditions.

[45] https://www.hhs.gov/about/strategic-plan/strategic-goal-4/index.htmlhttp://www.hhs.gov/about/strategic-plan/strategic-goal-2/index.html"

[46] FY 20187 and FY 2019 each includes $1.2 million of OOPD program funds to support Orphan Product Grants

Clinical Trial Grants Program

Over 700 new clinical trials have been funded by the Orphan Products Grants Program to date. This OOPD Grants Program has supported the marketing approval of more than 60 orphan products for serious or life threatening orphan indications. In FY 2018, OOPD received 79 clinical trial applications. OOPD funded 12 new grants, including studies to treat Stargardt Disease (a rare retinal disease that typically causes vision loss in childhood), and Head & Neck Squamous Cell Carcinoma. In addition, in FY 2018, OOPD provided funding or continued support for 75 other ongoing clinical study projects, including several Phase 3 trials.

OOPD published a new RFA for FY 2019 that will increase the impact of the program and allow for patient input into study designs.

These grants are a modest investment to better ensure that product development occurs in a timely manner and helps reduce risk in the process for industry in these rare disease fields. However, FDA appropriated grant funds, which are less than the $30 million congressionally authorized amounts, are covering less and less of the total cost for conducting clinical trials. Increases in the costs of clinical trials have reduced the capacity of the program to provide the needed monetary support to researchers actively conducting clinical trials that increase the number of new, safe and effective diagnostic and therapeutic options for patients with rare diseases.

Natural History Grants Program

The Natural History Grant Program, launched in FY 2016 supports studies that advance rare disease medical product development through characterization of the natural history of rare diseases/conditions, identification of genotypic and phenotypic subpopulations, and development and/or validation of clinical outcome measures, biomarkers and/or companion diagnostics. OOPD received 89 applications in the first cycle of this new program, including 29 applications for Neurology focused studies and funded six new research grants for natural history studies in rare diseases, including studies for Friedreich's ataxia and sickle cell anemia. Two of the six grants were awarded through a partnership with the National Institutes of Health (NIH) National Center for Advancing Translational Sciences (NCATS). OOPD published a new RFA for FY 2019. These studies will add valued data to help develop targeted therapies and lead to more efficient and better designed clinical trials.

Orphan Drug Designation Activity

The Orphan Drug Act also created the orphan drug designation program to provide financial incentives to sponsors for developing drugs and biologics for rare diseases and conditions. Rare diseases and conditions are, in part, defined as one affecting fewer than 200,000 persons in the United States. OOPD evaluates requests from sponsors who are developing drugs to treat rare diseases to determine eligibility for orphan drug designation. Sponsors of designated orphan drugs are eligible for significant tax credits for clinical trial costs, user fee waiver of marketing applications and, upon approval, consideration for seven years of marketing exclusivity.

Over 4,700 orphan drug designations OOPD issued since 1983 have resulted in over 700 marketing approvals, the majority having been awarded orphan exclusivity. In contrast, the decade prior to 1983 saw fewer than ten such products developed by industry make it into the market. For FY 2018, OOPD received 521 new applications and designated 339 orphan drugs.

These included potential treatments for many kinds of rare cancers, sickle cell disease, and Ebola. FDA approved 88 orphan designated drugs for marketing indications in FY 2018 to date.

The number of requests for orphan designation has quintupled since FY 2000. Not only are the requests rapidly increasing, but the complexity of the science associated with these orphan drugs is increasing due, in part, to advances in pharmacogenomics and precision medicine.

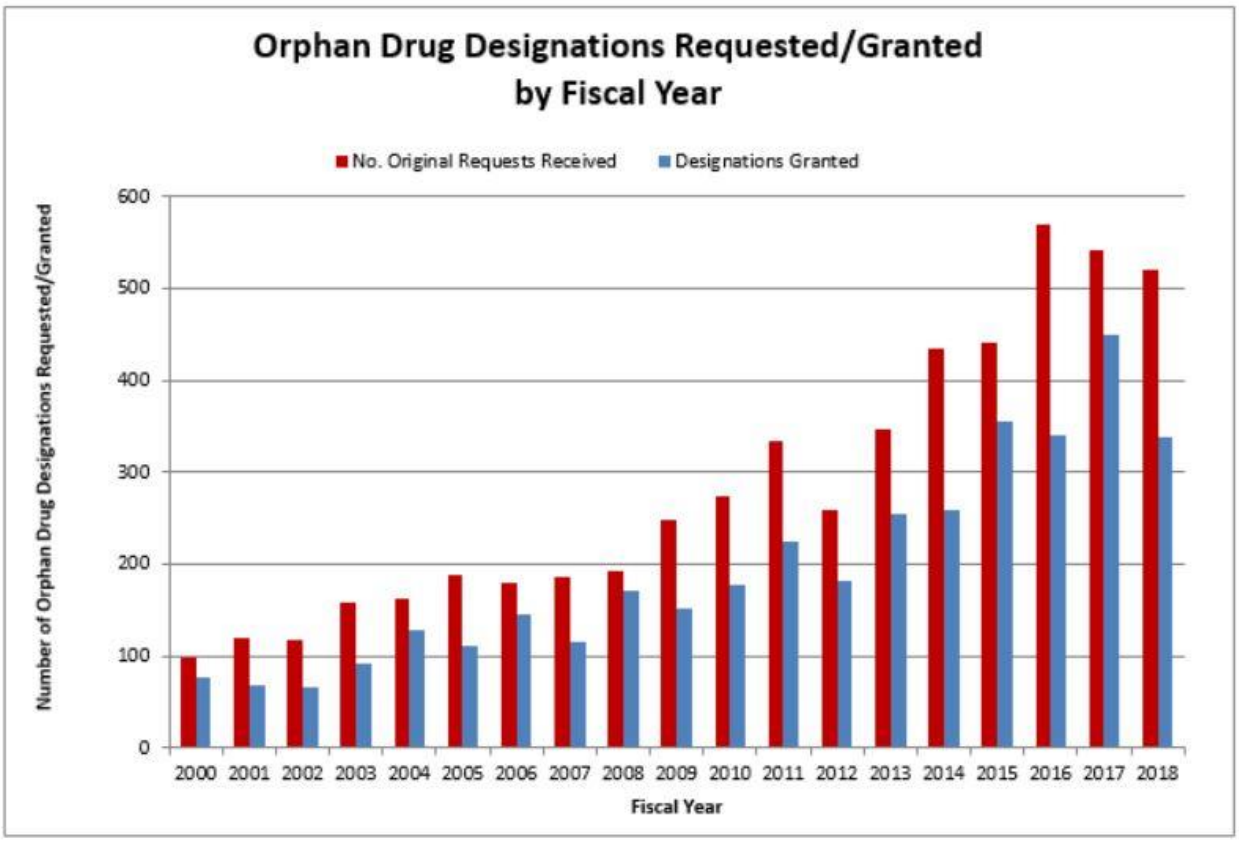

Figure 4 Orphan Drug Designations Requested/Designated by Fiscal Year

Product Designations

Below are examples of Orphan Product designations that occurred in 2018.[47]

Date	**Product**	**Purpose or Benefit**
July 2018	Gene Therapy	Treatment of Spinal Muscular Atrophy (SMA)
August 2018	Autologous Mesenchymal Stem Cells	Treatment of Amyotrophic Lateral Sclerosis (ALS)

Rare Pediatric Disease Priority Review Voucher Designation

The Food and Drug Administration Safety and Innovation Act (FDASIA) added Section 529 to the FD&C Act to encourage development of new drug and biological products ("drugs") for the prevention and treatment of qualifying rare pediatric diseases. This legislation created the Rare Pediatric Disease Priority Review Voucher (PRV) program wherein the sponsor of an approved

[47] For more information on designations and product approvals, visit http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm

drug to prevent or treat a rare pediatric disease may receive a voucher for a priority review of a subsequent drug.

Sponsors who are interested in receiving a rare pediatric disease priority review voucher may first request a "rare pediatric disease" designation through OOPD. While such a designation is not required to receive a voucher, requesting designation in advance may expedite a sponsor's future request for a priority review voucher. OOPD partners with the Office of Pediatric Therapeutics in making rare pediatric disease determinations. In FY 2018, OOPD received 51 new rare pediatric disease designation requests plus two consults from submitted marketing applications needing rare pediatric disease determinations. OOPD determined that 52 requests/consults met the definition of a "rare pediatric disease." On September 29, 2016, the Advancing Hope Act revised the definition of a "rare pediatric disease," and was implemented immediately thereafter. In FY 2018, a total of four rare pediatric disease priority review vouchers were issued.

On December 13, 2016, Congress extended the designation aspect of the program to September 30, 2020.

Humanitarian Use Device Designation Activity

The HUD program, created from provisions of the Safe Medical Devices Act, encourages the development of devices for rare diseases and is administered by OOPD.

OOPD reviews applications from sponsors requesting HUD designation. A device that has received HUD designation is eligible for Humanitarian Device Exemption (HDE) approval if, among other criteria, the device will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from use of the device outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of available devices or alternative forms of treatment. FDA approval of an HDE application authorizes the applicant to market the device. This marketing approval is subject to certain profit and use restrictions set forth in Section 520(m) of the FD&C Act. Since 1990, 74 HUD devices have been approved for marketing through the HDE pathway.

Except in certain circumstances, a HUD approved under an HDE cannot be sold for an amount that exceeds the costs of research and development, fabrication, and distribution of the device (for profit). Under Section 520(m)(6)(A)(i) of the FD&C Act, as amended by FDASIA, a HUD is eligible to be sold for profit after receiving HDE approval if the device meets certain criteria. As of the end of FY2018, 16 manufacturers have received approval to market their devices for profit and other sponsors have submitted requests to qualify for the exemption from profit prohibition.

In FY 2018, OOPD received 17 new HUD applications and designated 17 devices. Of the 17 devices that were designated, nine designations were based on HUD applications originally submitted in prior years. In FY 2018, two devices received an HDE approval from CDRH. Also, in FY 2018, one manufacturer who previously had HDE approval was authorized to market their device for profit.

Additionally, on December 13, 2016, Section 3052 of the 21st Century Cures Act (Pub. L. No. 114-255) changed the population estimate required to qualify for HUD designation from "fewer than 4,000" to "not more than 8,000." Accordingly, a HUD is now defined as a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in not more than 8,000 individuals in the United States per year. Since this change,

11 devices have received HUD designation for population estimates between 4,000 and not more than 8,000.

Pediatric Device Consortia Grants Activity

There is a significant public health need for medical devices designed specifically for children. This need is due in part to the lack of commercial incentives and market forces to drive pediatric medical device development, as well as the challenges of pediatric device development including differences in size, growth, development, and body chemistry that impact pediatric device requirements. Section 305 of the Pediatric Medical Device Safety and Improvement Act of 2007 (part of the 2007 FDAAA legislation) mandates demonstration grants for improving pediatric device availability through pediatric device consortia. The Consolidated Appropriations Act, 2017 (House and Senate Committee Reports) increased the appropriations of the program to a total of $6 million from $3 million. On August 18, 2017, FDA Reauthorization Act of 2017 extended the program through September 30, 2022.

On January 16, 2018, FDA posted a new Request for Applications for the Pediatric Device Consortia Grants Program, administered by OOPD, with the goal to facilitate the development, production, and distribution of pediatric medical devices through funding of pediatric device consortia. In FY 2018, FDA awarded five consortia funding $6 million per year over the next five years. Of the estimated $6 million granted this year, approximately $1 million will be used for real-world evidence projects to develop, verify, and operationalize methods of evidence generation, data use and scalability across device types in the pediatric device ecosystem. The consortia funded in this program are based out of Philadelphia, PA; Washington, DC; Houston, TX; Los Angeles, CA; and San Francisco, CA.

Since the program's inception in 2009, a total of $37.4 million has been awarded to the consortia. Collectively, the consortia have supported the development of more than 1000 potential pediatric devices, many of which are in the early stages of development. Over 20 new devices are now available for use in pediatric patients as a result of advisory assistance received from the consortia, including the PIVO, a needle-free blood collection device that attaches to peripheral IV systems; the JustRight Surgical Vessel Sealing System designed for use in open and laparoscopic general surgical procedures to seal blood vessels and vascular bundles; and the Lifeflow Rapid Infusion to deliver fluids to a patient's vascular system. The consortia collectively have also raised more than $150 million of additional non-FDA funds to support pediatric device development research.

Promote Informed Decisions

OOPD participates in significant communication and outreach activities by:

- providing information on incentives available to develop products for rare diseases to external stakeholders including industry, the patient community, advocacy groups, and international regulatory agencies
- speaking at meetings and conferences on the FDA designation and approval processes, the OOPD grant programs, and the science of developing therapeutic products for rare diseases and conditions
- assisting patients and advocacy groups on issues of concern related to rare diseases and orphan products, such as pediatric device needs and orphan drug shortages

- providing web-based rare disease and orphan product resources and information to various stakeholders such as industry, the patient community, advocacy groups, and international regulatory agencies

In FY 2018, OOPD participated in 35 individual industry outreach and patient oriented meetings. In addition, OOPD received 60 invitations to speak and participate at orphan product stakeholder meetings and conferences to discuss different rare disease issues. OOPD made presentations and participated in 25 of these meetings, often to explain how orphan drugs and humanitarian devices could be developed with ODA incentives and HDE provisions, as well as FDARA, the 21st Century Cures Act, and FDASIA requirements for rare diseases.

At these meetings, the missions of OOPD and FDA were explained, and questions and concerns from stakeholders were addressed. Examples of public health related OOPD outreach activities in FY 2018 include conducting training courses for researchers and reviewers, and presentations to national and international rare disease patient groups. In FY 2019 through FY 2021, OOPD will continue the mission critical outreach efforts to enhance all stages of the development and approval process for products to treat rare disease patients.

FUNDING HISTORY

Fiscal Year	Program Level	Budget Authority	User Fees
FY 2016 Actuals	$29,099,000	$29,099,000	$0
FY 2017 Actual	$29,099,000	$29,099,000	$0
FY 2018 Actual	$29,099,000	$29,099,000	$0
FY 2019 Annualized CR	$29,099,000	$29,099,000	$0
FY 2020 President's Budget	$29,099,000	$29,099,000	$0

Funding History table is not comparably adjusted.

BUDGET REQUEST

The FY 2020 Budget Request is $29,099,000. With this funding level, OOPD will fund approximately 10-12 new clinical trials grant awards and provide funding or continued support for approximately 75 other ongoing clinical study projects. In addition, OOPD plans to continue to fund six grants for natural history studies targeted on expediting the development of products for these rare conditions.

PROGRAM ACTIVITY DATA

Office of Orphan Products Development Program Activity Data			
Program Workload and Outputs	**FY 2018 Actual**	**FY 2019 Estimate**	**FY 2020 Estimate**
Grant Programs			
Total Orphan Product Grant (New and Continuations)	87	90	90
Total Pediatric Consortia Grants (New and Continuations)	5	5	5
Total Natural History Grants (New and Continuations)	6	7	7
Orphan Drug Designation Requests/Designations Granted/Orphan Drug Approvals			
New Orphan Drug Designation Requests	521	550	550
Drug Designations Granted	339	350	350
FDA Orphan Drug Marketing Approvals	90	90	90
HUD Requests and Designations			
New HUD Designation Requests	17	27	27
HUD Designations	17	20	20
Rare Pediatric Disease Priority Review Voucher Requests and Designations			
New RPD Requests	53	65	65
RPD Designations	52	55	55