

OFFICE OF ORPHAN PRODUCTS DEVELOPMENT¹

The following table displays funding levels for FY 2010 through FY 2012.

	FY 2010 Enacted	FY2010 Actual	FY2011 CR	FY 2012 Request	+/- FY 2010 Enacted
Program Level ₁	22,109,801	22,785,290	22,183,385	22,260,610	\$150,809
Orphan Product Grants ₂	14,035,060	14,035,060	14,035,060	14,035,060	-
Pediatric Consortia Grants ₃	3,000,000	3,000,000	3,000,000	3,000,000	-
Program Administration ₄	5,074,741	5,750,230	5,148,325	5,225,550	150,809

¹Orphan Product Grants are part of the aggregate amount of budget authority contained in the CDER budget line item of the All Purpose Tables.

²Pediatric Device Consortia Grants are part of the aggregate amount of budget authority contained in the CDRH budget line item of the All Purpose Tables.

³Program Administration is part of the aggregate amount of budget authority contained in the Other Activities budget line item of the All Purpose Tables.

⁴FY 2010 includes a \$1,200,000 increase to implement FDAAA and will support Orphan Product Grants.

The FDA Office of Orphan Products Development operates under the following legal authorities:

Federal Food, Drug and Cosmetic Act (21 U.S.C. 321-399).

Orphan Drug Regulations (21 CFR 316)

Safe Medical Device Act of 1990 (as amended) (21 U.S.C. 351-353, 360, 360c-360j, 371-375, 379, 379e, 381)

Humanitarian Use Device and Humanitarian Device Exemption Regulations: (21 CFR 814 Subpart H)

PHS Act (42 U.S.C. 241). Section 301

Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331 et seq.)

Allocation Method: Direct Federal/Intramural; Grants.

¹ The Office of Orphan Products Development is shown for illustrative purposes and is not contained as a separate line item in the All Purpose Tables.

Program Description and Accomplishments

Public Health Focus: Since its inception in 1982, the public health programs of the Office of Orphan Products Development (OOPD), located in the Office of the Commissioner, have been dedicated to promoting and advancing the development of products (drugs, biologics, medical devices, and medical foods) that demonstrate promise for the diagnosis and/or treatment of rare diseases or conditions. These are products necessary to treat a patient population that otherwise would be considered too small for profitable research, development, and marketing. These programs directly support the HHS priority to accelerate scientific advances in lifesaving cures and quality health outcomes. OOPD administers the major provisions of the Orphan Drug Act (ODA) of 1983 which provide incentives for sponsors to develop products for rare diseases.

Public Health Outcome: The ODA has been very successful – as of September 30, 2010, 353 drugs and biological products for rare diseases have been brought to market since 1983. In contrast, the decade prior to 1983 saw fewer than ten such products come to market. OOPD also administers the designation of humanitarian use device programs under the Food Drug and Cosmetic Act – 50 humanitarian use devices have been approved for very rare diseases and conditions. OOPD interacts with the medical and research communities, professional organizations, academia, and the pharmaceutical industry, as well as rare disease groups. It provides research study design assistance to sponsors of orphan products and encourages well-controlled clinical studies.

Promoting Efficiency: OOPD activities support FDA's strategic public health goals by improving the process of developing promising new product discoveries into safe, effective, and accessible treatments for patients, and by empowering patients and patient groups with vital information and linkages between researchers, patients, and patient advocacy organizations. As more therapies are developed for rare diseases and conditions, and patients and providers become more educated about these therapies, there will be a positive impact on public health. Furthermore, the discovery and innovation of medical products for smaller populations has potentially positive public health implications for personalized health care in the future.

OOPD has five public health sub-programs: orphan product grants which provide funding for clinical research in rare diseases, orphan drug designations, humanitarian use device designations, pediatric device consortia grants, and outreach activities.

Orphan Product Grants Activity

Public Health Focus: OOPD supports new and continuing extramural research projects that test the safety and efficacy of promising new drugs, devices, and medical foods for rare diseases and conditions through human clinical trials. Orphan product grants are a proven method of successfully fostering and encouraging the development

of new safe and effective medical products for rare diseases/conditions. Grants ensure that product development occurs in a timely manner with a very modest investment. In general, OOPD grant funding is for up to three years for Phase 1 trials, and up to four years for Phase 2 and 3 trials. Because grants are for up to four years, at any one time, there are typically 45 to 60 ongoing grant-funded projects. A major portion of the appropriated funds for a given fiscal year go towards continued funding of previously approved grants.

Public Health Outcome: There have been 45 products approved by FDA for marketing which received development support from the orphan grants program. Highlights of these include treatments for Fabry Disease (approved in 2003), Mucopolysaccharidosis Type II, also known as Hunter Syndrome (approved 2006), Cystic Fibrosis patients with *Pseudomonas Aurginosa* (approved 1997), infant botulism (approved 2003), and a titanium expandable rib prosthesis for Thoracic insufficiency syndrome (approved 2004). A more recent example of the success of the orphan grants program was the approval in 2008 of the Diaphragm Electrical Stimulator for ventilator dependent tetraplegic patients. This new device increases patient mobility and reduces the noise and social stigma patients must endure.

In FY 2010, OOPD funded 18 new grants (out of 80 applications) and provided funding for approximately 28 other ongoing clinical study projects. Research projects that recently were awarded new grants include studies for the treatment coral snake venom, pediatric Graves disease, advanced melanoma, cystic fibrosis, pediatric brain tumor imaging, and corneal epithelial defects.

Promoting Efficiency: Funding clinical trials for promising orphan products continues to reap significant public health benefits to society.² Not only have 45 products been approved using data obtained from OPD grants, but hundreds of publications in peer-reviewed journals have resulted from OPD funded studies that have changed the state of medical care for Americans with rare diseases. Grants ensure that product development occurs in a timely manner with a very modest investment.

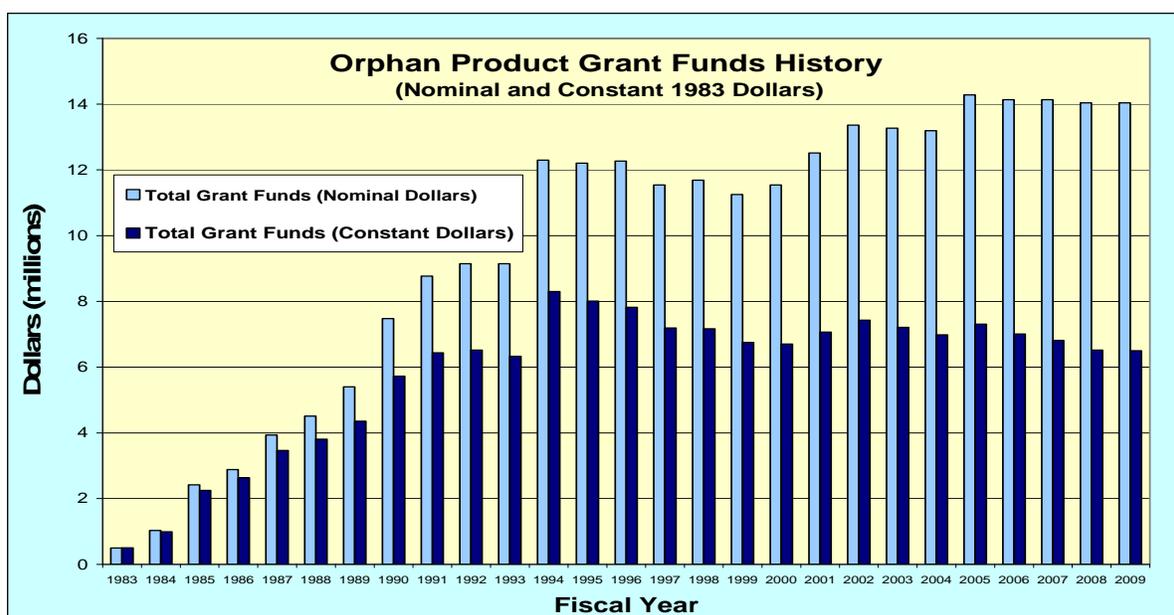
FDA grant funds are covering less and less of the cost for conducting clinical trials. The cost of clinical trials continues to increase far faster than the rate of inflation. For example, pediatric study costs increased eight-fold between 2000 and 2006 as a result of more complexity.³ In addition, the design of clinical trials is even more complicated for rare diseases because there are fewer available patients. FDA plays an integral role in the development of products for rare diseases and conditions in the U.S. Therefore, the appropriation levels for FDA's Orphan Product Grants Program are of increasing

² Johnston SC , Rootenberg JD, Katrak S, Smith WS, Elkins JS. "The impact of an NIH program of clinical trials on public health and costs." *The Lancet*, April 22, 2006, Vol. 367, pp. 1319-1327.

³ Kaitin KI, editor. Pediatric study costs increased 8-fold since 2000 as complexity level grew. *Tufts Center for the Study of Drug Development Impact Report 2007 Mar/Apr*;9(2)

concern to the rare disease community. There are few DHHS clinical grants focused on products for Americans with rare diseases. This public health concern gained greater visibility when the Institute of Medicine (IOM) completed its study on rare diseases. The IOM stated, "Because funding has not kept pace with inflation, the grants program cannot operate at the same level as it did in the 1990s much less at an enhanced level to accelerate the orphan product development."⁴

Because of the increased costs of clinical trials noted above, FDA recently increased the maximum grant award amount and maximum number of grant years. Going into FY 2011 there is a large portfolio of existing clinical studies awarded multi-year grants in prior fiscal years. These approved ongoing studies receive their annual grant award first, and with the remaining appropriated funds, the FDA awards new orphan product grants. With increased award amounts and increased number of award years, and if there are no increases in the amount of grant funds appropriated in FY 2011, the FDA expects that it can only fund up to eight new orphan product grants in FY 2011.



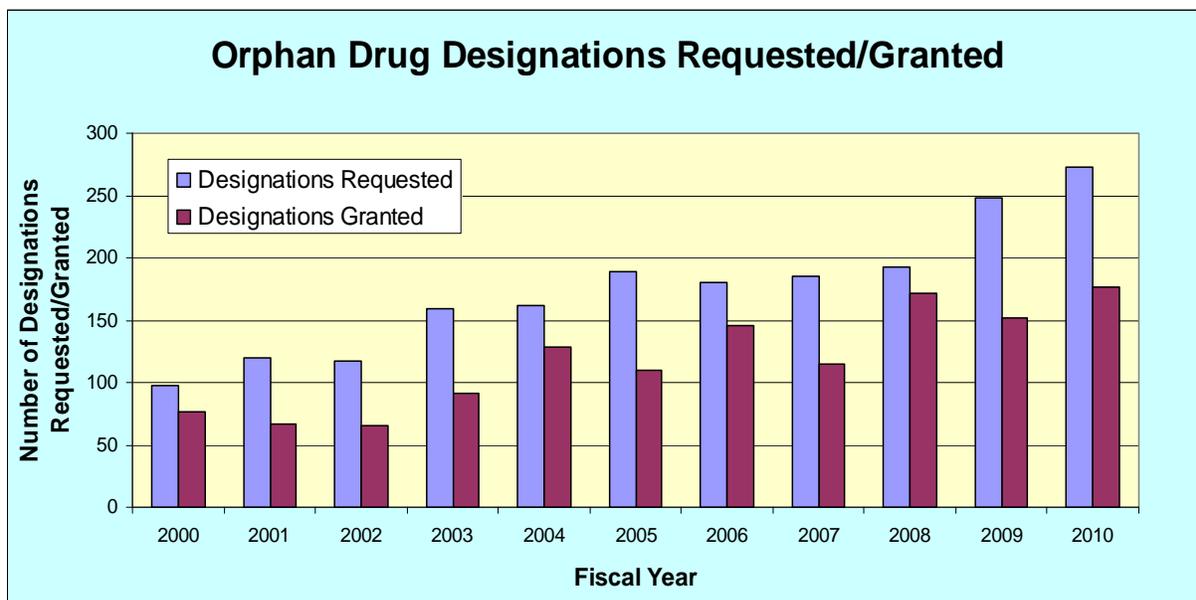
Orphan Drug Designation Activity

Public Health Focus: There are an estimated 7,000 rare diseases, with a public health impact directly affecting more than 25 million people (and many millions of family members more) in the U.S. Between 85 and 90 percent of these are serious or life-threatening. In enacting the ODA in 1983, Congress sought to provide incentives to promote the development of drugs (including antibiotics and biological products) for the treatment of rare diseases. OOPD evaluates applications for orphan drug designations from sponsors who are developing medical products to treat rare diseases or disorders

⁴ Field, M.J. and T.F. Boat, editors. Rare Diseases and Orphan Products: Accelerating Research and Development. *Institute of Medicine*. 2010.

that affect fewer than 200,000 persons in the U.S. Medical products for diseases or disorders that affect more than 200,000 persons may be able to obtain an orphan designation if the sponsor is not expected to recover the costs of developing and marketing the product. After a designation is made, the developer of a designated orphan product is guaranteed seven years market exclusivity for a specific indication following the approval of the product by FDA.

Public Health Outcome: Of the 2,278 orphan designations issued by OOPD, 353 have resulted in marketing approval with orphan exclusivity. During FY 2010, OOPD reviewed 273 applications for orphan designation, the most ever in a single year.. These include potential treatments for many kinds of cancers, multiple myeloma, sickle cell disease, and pediatric ulcerative colitis. OOPD designated 177 orphan drugs in FY 2010.



The number of requests for orphan designation has more than doubled in the last ten years (see chart above). OOPD anticipates that the workload associated with the orphan designation requests will continue to increase in the future. Not only are the requests increasing, but the complexity of the science of potential orphan drugs is increasing. There are many more entrepreneurial ideas and concepts being considered in the areas of pharmaco-genomics and individualized medicine that challenge our reviewers. In FY 2010, 38.5 percent of all the new molecular entities (NME) approved by the FDA were orphan designated drugs and biologics.

FDA approved 11 prior orphan designated drugs for marketing in FY 2010. One recent example is the marketing approval in March 2010 of Viread (tenofovir) for the treatment of HIV infection in combination with other antiretroviral agents in children from 12 to less than 18 years old. This disease affects approximately 50,000 to 100,000 people in the

United States. This drug, which was given orphan status in March 2009, was approved in one year.

Promoting Efficiency: OOPD facilitates the designation and development of orphan drugs by reviewing applications and designating orphan drugs; acting as an intermediary between sponsors and FDA medical product review divisions in the drug development process to help resolve any outstanding problems, discrepancies, or misunderstandings in the regulatory review process; providing expertise in clinical trial design and outcome review; and assisting in the development of medical countermeasures through the orphan drug designation process.

Humanitarian Use Device Designation Activity

Public Health Focus: The purpose of the Humanitarian Use Device (HUD) program is to encourage the discovery and use of devices intended to benefit patients in the treatment or diagnosis of diseases or conditions that affect or are manifested in fewer than 4,000 individuals in the United States per year.

A device manufacturer's research and development costs could exceed its market returns for diseases or conditions affecting small patient populations. FDA, therefore, developed and published a regulation to carry out provisions of the Safe Medical Devices Act of 1990 to provide an incentive for the development of devices for use in the treatment or diagnosis of diseases affecting these populations. This regulation became effective on October 24, 1996. A HUD designation from OOPD is required for a device prior to applying for a Humanitarian Device Exemption (HDE) from the Center for Devices and Radiological Health (CDRH).

Public Health Outcome: An HDE for a specific device allows the sponsor to bring the device to market for the small patient population after demonstrating the safety and probable benefit of the device. It is a marketing approval that is exempt from the full effectiveness requirements of sections 514 and 515 of the Safe Medical Devices Act of 1990. In FY 2010, OOPD received 28 HUD applications and designate 14 of these.

An HDE approved in January 2010 is a transcatheter pulmonary valve for the treatment of pediatric and adult patients with congenital malformation of the pulmonary heart valve. The heart valve is implanted through a catheter, which can prevent or delay the need for open heart surgery. This option is thus a much less invasive procedure to treat heart conditions.

Promoting Efficiency: OOPD conducts activities leading to HUD designations, including: reviewing applications and designating humanitarian use devices; facilitating the HDE approval process to help resolve any outstanding issues; and providing expertise to sponsors in approaches to the various types of marketing approvals for medical devices.

Performance Measures

The following table lists the performance measures associated with this subprogram.

Measure	Most Recent Result	FY 2011 Target	FY 2012 Target	FY 2012 +/- FY 2011
Increase the total number of decisions on applications for promising orphan drug and humanitarian use device designations. Baseline period is FY 2008 Target period is FY 2009 - 2013	FY 2009: 269 FY 2010:301	312	335	+23

Pediatric Consortia Grants Activity

Public Health Focus: The development of pediatric medical devices currently lags five to ten years behind those for adults due to the lack of commercial incentives for pediatric medical device development. Children differ from adults in terms of their size, growth, development, and body chemistry, adding to the challenges of pediatric device development. There currently exists a great public health need for medical devices designed specifically with children in mind. Such needs include the de novo development of pediatric medical devices, as well as the specific adaptation of existing adult devices for children. Thus, as part of the 2007 FDAAA legislation, Congress passed the Pediatric Medical Device Safety and Improvement Act of 2007. Section 305 of this Act mandates demonstration grants for improving pediatric device availability, to be administered for the creation of pediatric device development consortia. The demonstration grants are not limited to addressing diseases or conditions that are considered to be rare.

Public Health Outcome: So far, four Pediatric Device Consortia have been established under this program; collectively they have helped facilitate the early development of over 80 potential medical devices for children." The four consortia are as follows:

- The Pediatric Cardiovascular Device Consortium, based out of Boston Children's Hospital,
- The UCSF Pediatric Device Consortium, based out of the University of California at San Francisco (<http://www.pediatricdeviceconsortium.org/>),
- The Michigan Pediatric Device (M-PED) Consortium, in partnership with the Pediatric Medical Devices Institute, of Roanoke, VA, based out of the University of Michigan (<http://peddev.org/>),
- The MISTRAL (Multidisciplinary Initiative for Surgical Technology Research Advanced Laboratory) Collaborative based out of SRI International in Stanford, California (<http://mistralpediatric.org/>).

Promoting Efficiency: The goal of FDA's Pediatric Consortia Grant Program is to support the development of nonprofit consortia designed to stimulate projects which will promote pediatric device development. The consortia facilitate the development, production, and distribution of pediatric medical devices by:

- encouraging innovation and connecting qualified individuals with pediatric device ideas with potential manufacturers
- mentoring and managing pediatric device projects through the development process, including product identification, prototype design, device development, and marketing
- connecting innovators and physicians to existing Federal and non-Federal resources
- assessing the scientific and medical merit of proposed pediatric device projects
- providing assistance and advice as needed on business development, personnel training, prototype development, and post-marketing needs.

Performance Measures

The following table lists the performance measures associated with this subprogram.

Measure	Most Recent Result	FY 2011 Target	FY 2012 Target	FY 2012 +/- FY 2011
Increase the number of medical devices facilitated in development by the new Pediatric Device Initiative (program funded through 2011)	FY 2009: N/A FY 2101: 80	90 under development	100 under development	+10

Outreach Activity

Public Health Focus: OOPD participates in significant outreach activities by providing information on approved therapies for rare diseases for the patient community and advocacy groups; speaking at meetings and conferences on the FDA approval processes, the Orphan Products Grants Program, and the science of developing therapeutic products for rare diseases/conditions; and assisting patients and advocacy groups on issues of concern related to rare diseases and orphan products, such as drug shortages.

Public Health Outcome: OOPD participated in various public health outreach activities during FY 2010. Some of these activities include participation in international governmental conferences, patient support meetings, and meetings addressing rare medical conditions. In FY 2010, OOPD received more than 75 invitations/requests to speak/participate at orphan-drug stakeholders' meetings. OOPD made presentations at nearly 50 of these meetings. The presentations ranged in scope from explaining to a

small patient advocacy group with less than 250 patients in this country how orphan drugs and humanitarian devices could be developed with ODA incentives and HDE provisions to international meetings that discuss global issues. The attendance at these meetings ranged from 30 professionals to over 500 patients and families. At these meetings, the missions of OOPD and FDA were prominently explained and displayed, and the questions and concerns from stakeholders were satisfactorily addressed.

Examples of public health related OOPD outreach activities in FY 2010 include:

- Co-sponsored an extramural training course in Maryland on the important aspects of designing and analyzing clinical trials in small populations
- Co-sponsored 2 workshops (California and Minnesota) for drug sponsors on preparing an application for requesting an orphan drug designation,
- Presented at the 6th International Conference on Rare Disease and Orphan Drugs in Buenos Aires,
- Presented at the Neglected Disease Forum in Washington, D.C., sponsored by the Tufts Center for the Study of Drug Development
- Presented at the 11th Annual Rett Syndrome Symposium in Leesburg, Virginia.

Promoting Efficiency: OOPD continues its public health outreach activities to increase the feasibility and level of sponsor interest in orphan products development through the orphan grants program, orphan designations programs, and HUD program. Companies and others interested in commercializing new products for rare diseases and conditions often seek the advice of OOPD staff. The complexity of the science of potential orphan drugs is increasing. There are many more entrepreneurial ideas and concepts being considered in the areas of pharmaco-genomics and individualized medicine that are challenging and potentially useful to patients with rare diseases. OOPD frequently meets with companies that have expressed an interest in commercializing new products for rare diseases to encourage them to go forward with development and to advise them on possible approaches to follow while gathering information that will lead to the approval of their product. The design of clinical trials is more complicated for rare diseases because there are fewer available patients. OOPD provides valuable expertise in regulatory concerns and facilitation with the FDA review divisions.

Five Year Funding Table

The following table displays funding levels from FY 2007 through FY 2011 for the Office of Orphan Products.

Fiscal Year	Program Level
2007 Actual	\$17,167,256
2008 Actual	\$17,691,161
2009 Actual	\$19,840,060
2010 Actual	\$22,785,290
2011 CR	\$22,183,385

Budget Overview and Supported Activities

Summary of the Budget Request

The FY 2012 President's Budget request for the Office of Orphan Products Development is \$22,183,385. The request represents an increase of \$ 150,809 above the FY 2010 enacted. This change represents the total FY 2012 inflation increase

Office of Orphan Product Development Program Activity Data (PAD)

PROGRAM WORKLOAD AND OUTPUTS	<u>FY 2009</u> <u>Actual</u>	<u>FY 2010</u> <u>Actual</u>	<u>FY</u> <u>2011*</u> <u>Estimate</u>	<u>FY 2012</u> <u>Estimate</u>
GRANTS PROGRAMS				
New Orphan Product Grants Awarded	22	18	8	8
Total Pediatric Consortia Grants (new and continuations)	3	4	4	4
ORPHAN DRUG REQUESTS, DESIGNATIONS, AND MARKET APPROVALS				
Designation Requests	248	273	290	310
Designations	153	177	218	230
Market Approvals	19	11	22	24
HUD REQUESTS AND DESIGNATIONS				
Designation Requests	18	28	22	25
Designations	11	14	11	12

*preliminary estimates based on recent year