OFFICE OF ORPHAN PRODUCTS DEVELOPMENT[1]

FDA's Office of Orphan Products Development summarizes the budget program requirements that justify a $16,655,394 request for FY 2009.

The following table shows a three-year funding history for the Office of the Orphan Products Development

	FY 2007 Actual	FY 2008 Enacted[3]	FY 2009 Estimate	Increase or Decrease
Program Level	$17,167,256	$16,655,394	$16,655,394	0
Grants [1]	$14,134,100	$14,035,161	$14,035,161	0
Program Administration [2]	$3,033,156	$2,620,233	$2,620,233	0

[1]The Grants piece is part of the aggregate amount of budget authority contained in the CDER budget line item of the All Purpose Tables.
[2]The Program Administration piece is part of the aggregate amount of budget authority contained in the Other Activities budget line item of the All Purpose Tables.
[3]Includes 0.7 percent Rescission.

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; 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

Since its inception in 1982, the Office of Orphan Products Development (OOPD), located in the Office of the Commissioner, has 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. OOPD administers the major provisions of the Orphan Drug Act (ODA) which provide incentives for sponsors to develop products for rare diseases. ODA has been very successful - more than 300 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 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.

OOPD activities support FDA's strategic goals by improving the efficiency of translation of new 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 four functional mission activities: orphan product grants which provide funding for clinical research in rare diseases, orphan drug designations, humanitarian use device designations, and outreach activities.

<u>Orphan Product Grants Activity</u>
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.

Because grants are for up to three years, at any one time, there are typically 50 to75 ongoing grant-funded projects. A major portion of the appropriated funds for a given fiscal year go towards continued funding of prior approved grants.

OOPD engages in several grant management activities. OOPD staff review solicited grant applications to ensure program requirements are met, and coordinate and convene peer review panels to provide technical review of grant proposals to ensure the best scientific proposals are funded. OOPD selects grant applications for funding, and conducts site visits to grantees to ensure extramural funded studies, which involve human subjects, are consistent with grant

agreement terms and minimize FDA's exposure to risk of violations in human subjects protection requirements. OOPD monitors the grant-funded products to satisfy regulatory and program requirements. OOPD is modernizing the transmission of applications and other review information through full electronic submissions, and improving the OOPD database system to allow for more efficient and effective retrieval of information and other internal management practices.

There have been over 40 products approved by FDA for marketing which had development support from the orphan grants program. All are listed on at http://www.fda.gov/orphan/grants/magrants.htm. Highlights of these include treatments for Fabry Disease (approved in 2006), for severe Crohn's Disease (approved 1998), for Cystic Fibrosis patients with Pseudomonas Aurginosa (approved 1997), a titanium expandable rib prothesis for Thoracic insufficiency syndrome (approved 2004), and neurostimulator implantable electrodes for Quadra-paraplegia with loss of hand function (approved 1997).

In FY 2007, OOPD funded 19 new grants and maintained funding for approximately 40 other ongoing grant-funded clinical study projects totaling $14,134,100. In addition, the OOPD completed peer review and scoring for the 59 FY 2007 applications that passed the OOPD's program review criteria. In September, 2007 the OOPD's review recommendation received approval from the final level national level board review. OOPD has begun funding for the top scoring FY 2007 applications with FY 2008 CR funds for clinical studies of the most promising treatments for rare diseases. Through FY 2008, as OOPD confirms the requisite certifications and evaluations for funding, OOPD will complete its recommendation for funding the best ongoing and new clinical studies for rare disease diagnosis and treatment. Among the recent new applications recommended for funding are studies for the treatment of infantile Hemangiomas and for the treatment of Advanced Non Small Cell Lung Cancer.

A recent example of the success of the orphan grants program was the approval of the first product for the treatment of Hunter syndrome, a rare inborn disease of metabolism characterized by deficiency of the enzyme iduronate-2-sulfatase. Symptoms of Hunter syndrome, which usually become apparent at the age of one to three years, include growth delay, joint stiffness and coarsening of facial features. More advanced features include respiratory and cardiac problems, enlargement of liver and spleen, and neurologic deficits. The condition is diagnosed in approximately one out of 65,000 to 132,000 births. Elaprase is a new molecular entity that received Orphan designation on November 28, 2001. An Orphan grant to study Elaprase in the treatment of this disease was awarded in 2004. Elaprase was approved for marketing by FDA in 2006 after a randomized, double-blind, placebo-controlled study of 96 patients with Hunter syndrome showed that the treated participants had an improved capacity for walking.

Orphan Drug Designation Activity

There are an estimated 6,000 rare diseases, affecting more than 25 million people in the U.S., between 85 and 90 percent of which are serious or life-threatening. In enacting the Orphan Drug Act 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 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 sponsors 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.

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

Of the 1,780 orphan designations issued by OOPD as of September 30, 2007, 315 have resulted in marketing approval with orphan exclusivity. During FY 2007, there were 184 applications for orphan designation. These include potential treatments for many kinds of cancers, multiple myeloma, sickle cell disease, pediatric multiple sclerosis and cyanide poisoning. OOPD designated 115 orphan drugs, and FDA approved 21 prior orphan designated drugs for marketing in FY 2007. One example is the approval of the first drug of its kind that slows the effects of phenylketonuria (PKU disease), a genetic disorder that causes mental retardation, smaller brain size, delayed speech and other neurological problems and occurs in one out of every 15,000 live births in the United States. This drug was first granted orphan drug designation by the FDA in January 2004. It received marketing approval December 13, 2007. Now, for the first time, there is a medical intervention to help patients and their families slow the devastating neurological effects of this disease.

The number of requests for orphan designation have nearly doubled in the last 8 years on average. 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 pharmacogenomics and individualized medicine that challenge our reviewers.

Humanitarian Use Device (HUD) Designation Activity

The purpose of the Humanitarian Use Device 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 Humanitarian Use Device (HUD) designation from OOPD is required for a device prior to applying for a Humanitarian Device Exemption (HDE) from CDRH.

OOPD conducts activities leading to HUD designation, including: reviewing applications and designating humanitarian use devices; facilitating the Humanitarian Device Exemption 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.

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 similar to a pre-market approval (PMA) application, but exempt from the effectiveness requirements of sections 514 and 515 of the Act. In FY 2007, OOPD received 17 HUD applications, and designated 6 of these.

A Humanitarian Use Device approval, the Karl Storz Fetoscope received special honors this year from the National Organization for Rare Disorders, which citied the device's contribution to treating life-threatening rare disease in fetuses. The device, the Karl Storz Fetoscopy Instrument Set, is used in the treatment of twin-to-twin transfusion syndrome (TTTS). This disease is a rare and life-threatening condition in which there is an imbalance in the amniotic fluid of some identical twins. The imbalance is caused by an uneven flow of blood between the twins through shared blood vessels that are present when the twins share one placenta. The fetoscope is a telescopic camera used to view a fetus. After it identifies the shared blood vessels, a laser is used to destroy the problem blood vessels with heat and normalize the flow of blood between the twins.

<u>Outreach Activity</u>

OOPD continues its 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 pharmacogenomics 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. Because of this, OOPD staff members provide valuable expertise in clinical trial design and outcome review.

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.

OOPD participated in various outreach activities during FY 2007. Some of these activities include participation in international governmental conferences, patient support meetings, and

meetings addressing rare medical conditions. In FY 2007**,** OOPD received nearly 50 invitations/requests to speak at orphan-drug stakeholders' meetings this year. OOPD made presentations at over 30 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 could be developed with orphan Drug Act incentives, to providing regulatory recommendations for a pending orphan-drug legislation in Canada. The meetings ranged in number form 30 professionals to over 500 patients and families. At these meetings, the missions of OOPD and FDA were prominently explained/ displayed, and the questions/concerns from stakeholders were satisfactorily addressed.

An OOPD representative attended the 2006 Annual Family and Professional Conference (June 21-23, 2007) organized by the Families of Spinal Muscular Atrophy in Schaumberg, Illinois. He presented two talks at the conference: the first on the OOPD Orphan Products Grant program to clinical investigators, pharmaceutical industry representatives, and other professionals; the second on regulatory issues involving orphan drugs to the family members of those afflicted by spinal muscular atrophy (SMA). After the presentations, several investigators and pharmaceutical company representatives expressed their strong interest in applying for grants to conduct clinical investigations of new drugs for SMA. In addition, the family members expressed their appreciation for an opportunity to frankly discuss with OOPD issues concerning orphan drug development.

FIVE YEAR FUNDING TABLE

The historical funding and FTE levels table shows a five year history of program level funding, budget authority funding, user fee funding, and program level FTE.

Fiscal Year	Program Level
2005 Actual	$16,959,000
2006 Actual	$16,644,270
2007 Actual	$17,167,256
2008 Enacted	$16,655,394
2009 Estimate	$16,655,394

Budget Request

The FY 2009 President’s Budget requests $16,655,394 in program level funding for the Orphan Products Development Program. The OOPD extramural grants request is $14,035,161.

Office of Orphan Product Development (OOPD)
Program Activity Data (PAD)

PROGRAM WORKLOAD AND OUTPUTS	FY 2006 Actuals	FY 2007 Actuals	FY 2008 President's Budget	FY 2009 President's Budget*
New Orphan Product Grants Awarded	18	20	17	17*
ORPHAN DRUG REQUESTS, DESIGNATIONS, AND MARKET APPROVALS				
Designation Requests	180	184	200	220*
Designations	145	115	150	155*
Market Approvals	17	21	17	18*
HUD REQUESTS AND DESIGNATIONS				
Designation Requests	15	17	25	25*
Designations	8	6	10	10*

*preliminary estimates based on recent years