OFFICE OF ORPHAN PRODUCTS DEVELOPMENT[1]

Introduction

FDA's Office of Orphan Products Development summarizes the budget program requirements that justify a $16,772,804 request for FY 2008. The Office of Orphan Products Development narrative has four sections:

- summary of FDA's program resources, historical funding and FTE levels
- description of program functions of the Office of Orphan Products Development
- effects of the full year FY 2007 continuing resolution on the Office of Orphan Products Development
- description of the program resources changes, base resource activities, program accomplishments, and program activity data.

The Office of Orphan Products Development (OOPD) funding table shows a three year span of program level resources, budget authority resources, and proposed user fees enacted in FY 2006, displayed in the FY 2007 President's Budget and FY 2007 Continuing Resolution, and proposed in the FY 2008 budget request.

	FY 2006 Enacted[3]	FY 2007 Continuing Resolution	FY 2007 President's Budget	FY 2008 President's Budget	Increase or Decrease
Program Level	$16,644,270	$16,644,270	$16,696,946	$16,772,804	$75,858
Grants [1]	$14,134,100	$14,134,100	$14,134,100	$14,134,100	$0
Program Administration [2]	$2,510,170	$2,510,170	$2,562,846	$2,638,704	$75,858

[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 1 percent Rescission

[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.

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
2004 Actuals	$15,895,400
2005 Actuals	$16,959,000
2006 Enacted	$16,644, 270
2007 Continuing Resolution	$16,644,270
2007 President's Budget	$16,696,946
2008 President's Budget	$16,772,804

Statement of Budget Request

The OOPD is requesting $16,772,804 in program level resources for accomplishing the four functional activities of its mission:

- award and administer grants for clinical research studies of promising new orphan drugs, biologics, medical devices, and medical foods for rare diseases and conditions
- review and designate qualified drugs and biologics as Orphan Products
- review and designate qualified medical devices as Humanitarian Use Devices
- outreach to advance the development of orphan products; this includes determining whether a request for formal research protocol assistance (research on a treatment for a rare disease) qualifies for consideration.

This request for budget authority supports various activities within the Office of Orphan Products Development that contribute to the accomplishment of program outputs, and presents FDA's justification of base resources and selected accomplishments.

Program Description

The Orphan Products Development Program assists the private sector in producing orphan products (drugs, biologics, medical devices, and medical foods) necessary to treat a patient population that otherwise would be considered too small for profitable research, development, and marketing. OOPD has four functional mission activities: orphan product grants, orphan drug designations, humanitarian use device designations, and outreach activities. These are described below:

Orphan Product Grants Activity: 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 lasts for three 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 prior approved grants. OOPD 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.

Orphan Drug Designation Activity: 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. or that affect more than 200,000 persons but who are not expected to recover the costs of developing and marketing a treatment drug. 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. 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.

Humanitarian Use Device (HUD) Designation Activity: The purpose of 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. As defined in 21 CFR 814.3(n), a HUD is a "medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year."

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.

Outreach Activity: OOPD continues its outreach activities to increase the feasibility and level of sponsor interest in orphan products development. 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.

Effects of Full Year FY 2007 Continuing Resolution

The analysis in this justification assumes funding levels for the FY 2007 based on the enactment of the President's FY 2007 budget for the Orphan Products Development Program. If FDA receives the funding level specified in the FY 2007 Continuing Resolution (CR) rather than the FY 2007 President's budget request, this will have a significant impact on FY 2007 performance for the Orphan Products Development Program:

- OOPD will experience a reduction of at least one FTE.
- OOPD will fund one less clinical trial study for a drug device, biologic, and/or medical food of high potential to treat a rare disease.
- Review and approval times for applications for orphan drug status and humanitarian use device status will increase.
- OOPD staff will have less time and ability to perform outreach activities.

If FDA receives the CR rather than the FY 2007 President's budget request, this will have significant impact on FY 2008 performance for the Orphan Products Development Program:

- a decrease in OOPD staff resources will mean less time that grants project officers could spend providing oversight on clinical trials involving human subjects
- continued reductions of activities described under the FY 2007 impacts.

Justification of Base

OOPD is responsible for promoting and advancing the development of products that demonstrate promise for the diagnosis and/or treatment of rare diseases or conditions. To carry out this mission, OOPD administers the orphan product designation processes, provides research study design assistance to sponsors of orphan products, encourages well-controlled clinical studies, and manages a clinical research grants program.

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 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, an HHS priority activity. The table below illustrates how the four functional activities (Orphan Products Grants, Orphan Drug Designations, Humanitarian Use Device Designations, and Outreach) of the OOPD support FDA's strategic goals.

	FDA Strategic Goals		
	Enhance Patient and Consumer Protection and Empower Them With Better Information about Regulated Products	Increase Access to Innovative Products and Technologies to Improve Health	Transform Administrative Systems and Infrastructure to Support FDA Operations
Program Area			
Orphan Product Grants		x	x
Orphan Drug Designations		x	
Humanitarian Use Device Designations		x	
Outreach	x		

Orphan Product Grants Activity

OOPD engages in several grant management activities:

- reviewing of solicited grant applications by OOPD staff to ensure program requirements are met

- coordinating and convening peer review panels to provide technical review of grant proposals to ensure the best scientific proposals are funded

- selecting grant applications for funding
- monitoring the grant-funded products to satisfy regulatory and program requirements
- modernizing the transmission of applications and other review information through full electronic submissions
- improving the OOPD database system to allow for more efficient and effective retrieval of information and other internal management practices.

Orphan Drug Designations Activity

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
- assisting in the development of medical countermeasures through the orphan drug designation process.

OOPD anticipates that the workload associated with the orphan designation requests will continue to increase.

FDA Approves First Treatment for Hunter Syndrome

On July 24, 2006, the Food and Drug Administration (FDA) approved Elaprase (idursulfase), the first product for the treatment of Hunter syndrome (Mucopolysaccharidosis II, or MPS II), a rare inherited disease which can lead to premature death.

Hunter Syndrome, which usually becomes apparent in children one to three years of age, is a disease in which the person's body is defective in producing the chemical iduronate-2-sulfatase, which is needed to adequately breakdown complex sugars produced in the body. Symptoms include growth delay, joint stiffness, and coarsening of facial features. In severe cases, patients experience respiratory and cardiac problems, enlargement of the liver and spleen, neurological deficits, and death.

Elaprase was approved after a clinical trial funded in part with an FDA Orphan Products Grant. Elaprase was designated as an orphan product by FDA. Hunter syndrome is diagnosed in approximately one out of 65,000 to 132,000 births. This is the first product that brings help to a very small group of seriously ill patients who have no other treatment option. Elaprase is manufactured by Shire Human Genetic Therapies, Inc., in Cambridge, MA.

An indirect positive outcome of the Orphan Product Designation Program is the development of medical countermeasures to biological weapons of mass destructions, in support of the President's Project Bioshield initiatives, and the Secretary's emergency response priority activity:

- In 2003, FDA designated as orphan drugs two products for treatment of contamination with radioactive or non-radioactive thallium or cesium. One has since been approved for marketing.

- Since 2003, FDA has designated as orphan drugs two products for the treatment of anthrax.

- In 2004, FDA designated orphan drug status to a Vaccinia Immune Globulin product to treat complications from the smallpox vaccine. This product was subsequently approved for marketing by FDA.

- In 2006, FDA designated orphan drug status to a product for the treatment of smallpox and for post exposure prophylaxis against smallpox.

Humanitarian Use Device (HUD) Designation Activity

OOPD conducts activities leading to HUD designation:

- reviewing applications and designating humanitarian use devices

- facilitating the Humanitarian Device Exemption approval process to help resolve any outstanding issues

- providing expertise to sponsors in approaches to the various types of marketing approvals for medical devices.

FDA Approves First Totally Implanted Permanent Artificial Heart for Humanitarian Uses

The U.S. Food and Drug Administration approved the first totally implanted artificial heart for patients with advanced heart failure involving both pumping chambers of the heart under the Humanitarian Use Device (HUD) provisions of the Food, Drug and Cosmetic Act on September 5, 2006. The AbioCor Implantable Replacement Heart, made by Abiomed, Inc. (Danvers, Mass.), is intended for people who are not eligible for a heart transplant and who are unlikely to live more than a month without intervention. In clinical studies, this product was shown to prolong the life and improve the quality of life for critically ill patients. This device represents a significant advance in artificial heart technology and holds promise for critically ill heart patients who are not candidates for heart transplants due to age or other medical conditions.

The AbioCor system consists of: a two-pound mechanical heart that takes over the pumping function of the diseased heart, which is removed during the implantation procedure; a power transfer coil that powers the system across the skin and recharges the internal battery from the outside; and a controller and an internal battery, which are implanted in the patient's abdomen. The controller monitors and controls the functioning of the device, including the pumping rate of the heart. The internal battery allows the recipient to be free from all external connections for up to one hour. The system also includes two external batteries that allow free movement for up to two hours. During sleep and while batteries are being recharged, the system can be plugged into an electrical outlet.

Source: http://www.fda.gov/bbs/topics/NEWS/2006/NEW01443.html

Outreach Activity

OOPD participates in significant outreach activities:

- 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
- assisting patients and advocacy groups on issues of concern related to rare diseases and orphan products, such as drug shortages.

Selected FY 2006 Accomplishments

OOPD continues to encourage the development of therapies for rare diseases by administering the Orphan Drug Act and other programs that provide incentives to companies willing to develop drugs, biologics, medical devices, and medical foods for rare diseases.

Orphan Product Grants Activity

In FY 2006, OOPD funded 18 new grants and maintain approximately 60 ongoing grant-funded clinical study projects.

In FY 2006, OOPD made improvements to its data systems used to effectively and efficiently review applications for orphan and humanitarian device designations, grant applications, and funded grants:

- linking Business Objects software for data mining
- utilizing the IMPAC II grants management system managed by the National Institutes of Health under the HHS One-Department initiative.

Orphan Drug Designations Activity

Of the 1,657 orphan designations issued by OOPD, as of October 1, 2006, 288 have resulted in marketing approval with orphan exclusivity. During FY 2006, there were 180 applications, representing a 17 percent increase over the average (154 per year) of the prior four years. These include potential treatments for many kinds of cancers, multiple myeloma, sickle cell disease, and anthrax infection. OOPD designated 145 orphan drugs, and approved 17 orphan designated drugs for marketing.

Some of the orphan product approvals in FY 2006 are provided in the following table.

FY 2006 Orphan Product Approvals

Sponsor	Generic Name	Trade Name	Indication
Dialysis Solutions, Inc.	biocarbonate infusate	*Normocarb HF*	Use as a replacement solution in Continuous Renal Replacement Therapy to replace water and to correct electrolytes and acid-base imbalances in adults and children
ImClone Systems Incorporated	Cetuximab	*Erbitux*	For use in combination with radiation therapy, for the treatment of locally or regionally advanced squamous cell carcinoma of the head and neck (SCCHN) and for use as a single agent for the treatment of patients with recurrent or metastatic SCCHN for whom prior platinum-based therapy has failed
Bristol-Myers Squibb Company	Dasatinib	*Sprycel*	Treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia with resistance or intolerance to prior therapy, and with chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib
Novartis Pharmaceuticals Corporation	Deferasirox	*Exjade*	Treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age or older
Farmacon-IL, LLC	Ibuprofen lysine	*NeoProfen*	For closure of a clinically significant patent ductus arteriosus in premature infants weighing between 500 and 1500 g, who are no more than 32 weeks gestational age when usual medical management (e.g., fluid restriction, diuretics, respiratory support, etc.) is ineffective
Shire Human Genetic Therapies, Inc.	idursulfase	*Elaprase*	Indicated for patients with Hunter syndrome (mucopolysaccharidosis II, MPS II). Idursulfase has been shown to improve walking capacity in these patients
Insmed, Incorporated	mecasermin rinfabate	*iPLEX*	Treatment of growth failure in children with severe primary IGF-1 deficiency (Primary IGFD) or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to growth hormone
Jazz Pharmaceuticals	oxybate	*Xyrem*	Treatment of excessive daytime sleepiness in patients with narcolepsy
Astellas Pharma US, Inc.	Tacrolimus	*Prograf*	Prophylaxis of organ rejection in patients receiving allogenic heart transplants

Humanitarian Use Device (HUD) Designations Activity

In FY 2006, OOPD received 15 HUD applications, and designated eight of these, including a monitor for phenylalanine in the blood.

Outreach Activity

OOPD participates in various outreach activities during FY 2006. Some of these activities include participation in international governmental conferences, patient support meetings, and meetings addressing rare medical conditions such as:

- Participated at the International Conference on Rare Diseases and Orphan Drugs in Rome, Italy and and the Genetic Alliance 2006 Annual Conference in Bethesda, Maryland.

- Met with representatives of the European Union, Israel, and Egyptian government and their rare disease groups regarding their orphan product programs.

- Presented information at the United Leukodystrophy Foundation Scientific Symposium in Sycamore, Illinois, and the European Platform for Patients' Organizations, Science and Industry, 6th Workshop on Partnering for Rare Disease Therapy Development, in London.

- Participated at the Families of Spinal Muscular Atrophy, 10th Annual International SMA Research Group in San Diego; the Amyotophic Lateral Sclerosis Association (ALS) workshop in Boston; and the meetings of the National Organization for Rare Diseases.

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

PROGRAM WORKLOAD AND OUTPUTS	FY 2006 Actuals	FY 2007 Continuing Resolution	FY 2007 President's Budget	FY 2008 President's Budget
New Orphan Product Grants Awarded	18	18	17	16
ORPHAN DRUG REQUESTS, DESIGNATIONS, AND MARKET APPROVALS				
Designation Requests	180	180	200	220
Designations	145	145	150	155
Market Approvals	17	17	17	18
HUD REQUESTS AND DESIGNATIONS				
Designation Requests	15	15	25	25
Designations	8	8	10	10