

OFFICE OF ORPHAN PRODUCTS DEVELOPMENT¹

FDA's Office of Orphan Products Development summarizes the budget program requirements that justify a \$20,396,034 submission for FY 2010.

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

| | FY 2008 Actual⁵ | FY 2009 Omnibus | FY 2010 Estimate |
|--|---------------------------------------|----------------------------|-----------------------------|
| Program Level | \$16,655,394 | \$18,805,394 | \$20,396,034 |
| Orphan Product Grants ¹ | \$14,035,161 | \$14,035,161 | \$14,315,864 |
| Pediatric Consortia Grants ² | | \$2,000,000 | \$2,000,000 |
| Medical Product Safety and Research ³ | | | \$1,200,000 |
| Program Administration ⁴ | \$2,620,233 | \$2,770,233 | \$2,880,170 |

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

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

³Request for new funds to implement the Food and Drug Administration Amendments Act of 2007 (FDAAA).

⁴The 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. FY 2009 and FY 2010 amounts include a \$150,000 increase to support the Pediatric Consortia Grants.

⁵Includes 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/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

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. The ODA has been very successful – as of April 21, 2009, 339 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 provisions under the Food Drug and Cosmetic Act – more than 48 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.

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.

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 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 60 to 85 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 program 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 that 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 43 products approved by FDA for marketing which received development support from the orphan grants program. Most are listed at <http://www.fda.gov/orphan/grants/magranths.htm>. Highlights of these include treatments for Fabry Disease (approved in 2003), for Mucopolysaccharidosis Type II, also known as Hunter Syndrome (approved 2006), for Cystic Fibrosis patients with *Pseudomonas Aurginosa* (approved 1997), for infant botulism (approved 2003), a titanium expandable rib prosthesis for Thoracic insufficiency syndrome (approved 2004), and Diaphragm Electrical Stimulator for ventilator dependent tetraplegic patients (approved 2008).

In FY 2008, OOPD funded 21 new grants and provide funding for approximately 40 other ongoing grant-funded clinical study projects totaling \$14,035,161. Among the recent new applications recommended for funding are studies for the treatment of neonatal hyperinsulism and for the treatment of cholestasis, a blockage of the bile duct. 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. Another example of a successful orphan product is Elaprase, 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. A more recent example of the success of the orphan grants program was the approval of the NeuRx DPS RA/4 Respiratory Stimulation System in 2008. An Orphan grant to study this device for the treatment of ventilator dependent tetraplegic patients was awarded in 2000. More information is provided in the Humanitarian Use Device (HUD) Designation Activity section below.

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 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 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.

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 1,994 orphan designations issued by OOPD as of April 21, 2009 , 339 have resulted in marketing approval with orphan exclusivity. During FY 2008, OOPD reviewed 192 applications for orphan designation. These include potential treatments for many kinds of cancers, multiple myeloma, sickle cell disease, and pediatric multiple sclerosis. OOPD designated 164 orphan drugs in FY 2008. FDA has approved 13 prior orphan designated drugs for marketing in FY 2008. One example is the approval of Xenazine (tetrabenazine) for the treatment of chorea associated with Huntington's Disease (HD), a devastating neurodegenerative disease that causes progressive movement disorders, cognitive dysfunction and behavioral changes and is ultimately a fatal condition. Chorea is the most common symptom, affecting approximately 90% of HD patients, and is characterized by excessive, involuntary and repetitive movements, which are the most visible and dangerous manifestations of HD and interfere with patients' abilities to perform activities of daily living, including dressing, bathing and caring for themselves. Until this year, patients had no FDA-approved treatments for Huntington's disease. It is estimated that 30,000 Americans are affected by Huntington's disease. This drug was first granted orphan drug designation by the FDA in December 1997. It received marketing approval August 15, 2008.

The number of requests for orphan designation has nearly doubled in the last nine 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 Designation Activity

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).

OOPD conducts activities leading to HUD designation, 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.

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 somewhat like a pre-market approval (PMA) application, but exempt from the effectiveness requirements of sections 514 and 515 of the Safe Medical Devices Act of 1990. In FY 2008, OOPD received 13 HUD applications and designated 9 of these.

A recently approved (June 2008) HDE includes a stimulator device for severe spinal cord injury patients to free the patients temporarily from their ventilator. Christopher Reeve had received the still experimental device in 2003, allowing him to breathe off a ventilator for up to eight hours at a time prior to his death caused by an unrelated bloodstream infection. Spinal cord injuries can affect the muscles of the chest and abdomen, including the diaphragm, which is a lower abdominal muscle essential for breathing. Normally, a person inhales when the diaphragm contracts and the lungs expand with air, and a person exhales when the diaphragm relaxes and the air flows back out of the lungs. The HDE approved implantable device called the NeuRx DPS RA/4 Respiratory Stimulation System electrically stimulates the muscles and nerves that run through the diaphragm. It allows some spinal cord injury patients to breathe for at least four hours a day without a mechanical ventilator. The stimulation device uses four electrodes implanted in the muscle of the diaphragm to stimulate contraction. The device does not cure paralysis of the diaphragm, but does free a patient from a ventilator to enhance their quality of life. There are about 500 ventilator-dependent spinal cord injuries in the U.S., per year.

Pediatric Consortia Grants Activity

The development of pediatric medical devices currently lags five to ten years behind those for adults. 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 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.

The FDA definition of “pediatric” for purposes of device development encompasses devices used from birth to 21 years of age. The FDA’s Center for Devices and Radiologic Health defines “pediatric use” as any use of a medical device in a pediatric population in which there is a

primary pediatric indication or a more general indication where considerable pediatric application is anticipated.

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 will facilitate the development, production, and distribution of pediatric medical devices by:

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

In 2009, an estimated 3 grants will be awarded on a competitive basis up to \$2 million in total (direct plus indirect) costs per year for up to 2 years. It is anticipated that funding for the number of non-competing continuation awards in FY 2010 will be similar to FY 2009.

Medical Product Safety and Research Activity

This is a proposed new activity for FY 2010 in support of the medical product safety and research initiatives in the Food and Drug Administration Amendments Act of 2007 (FDAAA). With the \$1.2 million request for FY 2010, the OOPD plans to support its ongoing activities in the following ways:

1. Encourage additional applications for orphan product grants for research on promising products beneficial to the pediatric community, especially promising pediatric medical device products.
2. Fund additional orphan product grants for research on promising products beneficial to the pediatric community, and
3. Provide additional guidance and training on safety practices and considerations to principal investigators who conduct OOPD-funded research on promising orphan products involving human subjects.

Outreach Activity

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. OOPD provides valuable expertise in regulatory concerns and facilitation with the FDA review divisions.

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 2008. Some of these activities include participation in international governmental conferences, patient support meetings, and meetings addressing rare medical conditions. In FY 2008, OOPD received more than 40 invitations/requests to speak at orphan-drug stakeholders' meetings. OOPD made presentations at over 20 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. Other OOPD accomplishments include:

1. meeting with the Chief Executive Officers of the member companies of PhRMA (the Pharmaceutical Research and Manufacturers of America) to discuss and encourage these companies to commit more effort and resources toward developing products for rare diseases
2. locating a new source of the drug uridine for a 13 year old girl when the current source stopped. This is a life-saving drug to treat Uridine Monophosphate Synthetase Deficiency, a genetic enzyme deficiency that currently affects only 20 surviving patients worldwide
3. partnering with the National Organization for Rare Disorders (NORD), a consortium of rare disease patient organizations, and the NIH, to sponsor an educational conference about rare diseases, which included international groups. This conference coincided with the 25th anniversary of the Orphan Drug Act
4. participating in a conference sponsored by Genetic Alliance, an organization devoted to promoting optimum health care for people suffering from genetic disorders, about the Federal programs and resources available for product developers and patient groups
5. meeting with representatives of the World Health Organization to discuss assistance WHO could provide in facilitating the development of potential products for neglected diseases, typically tropical diseases that are rare in the United States
6. completing the development of a common application format for the approval of orphan products to be used by both the FDA and the European Medicines Agency, FDA's

European counterpart. This agreement was a significant accomplishment that will make it easier for drug sponsors to get their orphan products designated

7. planning a training course on the topic of small clinical trials to be held in FY 2009. The course will consist of experts and will be for FDA and NIH employees who will benefit from a rigorous look at how to apply the newest methodologies for clinical trials to small patient populations
8. meeting with stakeholders in an interagency effort to increase the availability of pediatric medical devices for children with rare diseases or conditions through both the HUD program and the Orphan Grant program.

The following table shows a five-year funding history for the Office of Orphan Product Development's program level resources.

Five Year Funding Table

The following table shows a five-year funding history for the Office of Orphan Products program level, budget authority, and user fee resources.

| Fiscal Year | Program Level |
|--------------------|----------------------|
| FY2006 Actual | \$16,644,270 |
| FY 2007 Actual | \$17,167,256 |
| FY 2008 Actual | \$16,655,394 |
| FY 2009 Omnibus | \$18,805,394 |
| FY 2010 Estimate | \$20,396,034 |

Budget Request

The FY 2010 President's Budget request for the Office of Orphan Products Development is \$20,396,034. The request represents an increase of \$1,590,640 (or almost nine percent) above the FY 2009 Omnibus level. This change represents \$390,640 for pay increases and \$1,200,000 for non-pay increases.

Office of Orphan Product Development
Program Activity Data (PAD)

| PROGRAM WORKLOAD AND OUTPUTS | <u>FY 2008 Actual</u> | <u>FY 2009* Estimate</u> | <u>FY 2010* Estimate</u> |
|---|----------------------------------|-------------------------------------|-------------------------------------|
| GRANTS PROGRAMS | | | |
| New Orphan Product Grants Awarded | 21 | 23 | 23 |
| New Pediatric Consortia Grants | | 3 | 3 |
| ORPHAN DRUG REQUESTS, DESIGNATIONS, AND MARKET APPROVALS | | | |
| Designation Requests | 192 | 220 | 235 |
| Designations | 171 | 180 | 190 |
| Market Approvals | 13 | 18 | 20 |
| | | | |
| HUD REQUESTS AND DESIGNATIONS | | | |
| Designation Requests | 13 | 20 | 22 |
| Designations | 9 | 10 | 11 |

*preliminary estimates based on recent year