Journal of Pharmacokinetics and Pharmacodynamics (2019) 46:387–393
https://doi.org/10.1007/s10928-019-09645-4

ORIGINAL PAPER

FDA's Office of Orphan Products Development: providing incentives to promote the development of products for rare diseases

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Received: 15 February 2019 / Accepted: 18 June 2019 / Published online: 5 July 2019

Abstract
There are nearly 30 million Americans that suffer from at least one of the more than 7000 rare diseases identified to date. Therapies for treating, preventing, or diagnosing rare diseases have been limited due to various reasons. Incentives are provided to sponsors in an effort to promote the development of therapies for rare diseases and to encourage the availability of therapeutically superior drugs or biologics. This paper will discuss the mission of the Office of Orphan Products Development within the Food and Drug Administration (FDA), the specific programs within the office and the relation to incentives provided, achievements of the programs, and continued challenges in rare disease product development.

Keywords Orphan Drug Act · Rare disease · Orphan-drug designation · Incentives · Orphan grants

Introduction

Nearly 30 million Americans suffer from at least one of the more than 7000 rare diseases identified to date [1]. Historically, therapies for treating, preventing, or diagnosing rare diseases have been limited. Possible reasons behind the paucity of available therapies for this underserved population include the small patient populations affected by each individual rare disease coupled with the high cost of drug development and a lack of incentives to offset these developmental costs. In 1983 Congress enacted the Orphan Drug Act (ODA) to motivate the development of therapies for rare diseases. In the ODA, a rare disease or condition is generally defined as a disease or condition that affects $< 200{,}000$ persons in the United States [2]. The main purpose of the ODA was to promote the development of therapies for rare diseases and to encourage the availability of therapeutically superior drugs or biologics by providing financial incentives to sponsors [3]. The Office of Orphan Products Development (OOPD) within the Food and Drug Administration (FDA) was created to help advance the evaluation and development of products (drugs, biologics, devices, or medical foods) that demonstrate promise for the diagnosis, prevention and/or treatment of rare diseases or conditions. OOPD has several programs that aid in this effort including: three designation programs: (1) the Orphan Drug Designation Program, (2) the Rare Pediatric Disease Designation Program and (3) the Humanitarian Use Device Program; and three grant programs: (1) the Clinical Trial Grants Program, (2) the Natural History Grants Program and (3) the Pediatric Device Consortia Grants Program. Each of these programs will be further described below.

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Designation programs

Orphan drug designation program

Orphan-drug designations are granted under the Orphan Drug Designation Program, which receives about 500 orphan-drug designation requests per year. Sponsors who obtain orphan-drug designation are eligible to receive financial incentives including tax credits for qualifying clinical studies, a waiver of the approximate $2 million prescription drug user fee associated with a marketing

application and could be eligible for 7 years of marketing exclusivity upon marketing approval of their orphan designated drug or biologic. This "orphan exclusivity" prohibits the FDA from approving a "same drug" or biologic as defined under 21 Code of Federal Regulations (CFR) 316.3(b)(14) for the same indication for a period of 7 years from the date of the marketing approval of the orphan designated drug or biologic. To be considered for orphan-drug designation, sponsors must submit a designation request to OOPD that includes the information requested in the CFR for Orphan Drugs (see 21 CFR Part 316.20(b)). Sponsors may submit a request for orphan-drug designation to the OOPD at any time during the development process for their drug or biologic so long as it is before the submission of a marketing application for that same drug or biologic for the same rare disease or condition. While orphan-drug designation may be requested for a same drug or biologic for the same use as a previously approved drug or biologic, additional criteria must be met prior to determining whether designation can be granted. In the case of a "same drug," the sponsor requesting orphan-drug designation must provide a plausible hypothesis for clinical superiority for their drug or biologic over the already approved same drug or biologic.

The two most heavily analyzed elements that sponsors must address in their orphan-drug designation request include the population estimate and the scientific rationale. For all designation requests, the population estimate provided by the sponsor must be current as to the time of submission of the orphan-drug designation request. Referenced texts, journals, the internet (government and patient support group websites) may all be helpful in determining the population estimate for a disease or condition. A sponsor is expected to make a good faith effort in finding the most recent population estimate data that refers to a United States population. If the data are old, the sponsor should explain why the data are still pertinent and, if from a foreign source, why data with the country's population could also be representative of the United States population. When prevalence is not readily available, it may be calculated by taking the incidence of a disease and multiplying that by the average duration of the disease. Orphan-drug designation may be requested for a disease that affects fewer than 200,000 persons in the United States, however, the Orphan Drug regulation also allows sponsors to seek orphan-drug designation for a subset of a non-rare disease or condition (i.e., population estimate of disease $\geq$ 200,000; referred to as an orphan subset) if they are able to provide a characteristic or feature of their drug or biologic (e.g., based on the mechanism of action, toxicity profile or prior clinical experience) that supports restricting the use of the therapy to only that orphan subset with a population of less than 200,000 [4]. In other words, sponsors must make it clear to the FDA that the use of the drug or biologic outside of the orphan subset would never occur due to a characteristic or feature of their drug or biologic. This is often a challenging hurdle to surpass and as a result, orphan subsets are not commonly granted. The other element that is heavily analyzed in the designation request is the scientific rationale. To designate a product as an orphan drug, the scientific rationale portion of the designation request must include enough information to establish a medically plausible basis for expecting the drug or biologic to be effective in the rare disease. While the scientific rationale is best supported by human data, in the absence of human data, the request for designation may be satisfactorily supported with preclinical data using the drug or biologic in a relevant animal model for the human disease. When there is no relevant animal model of the disease, and in the absence of human data, the scientific rationale may be supported with a combination of alternative data that includes the pathogenesis of the disease, a clear description of the drug or biologic and its mechanism of action specific to the disease and supporting in vitro data.

Since the inception of the ODA in 1983, more than 6000 orphan-drug designations requests have been received by OOPD and more than 4500 requests have been granted. Figure 1 shows the number of original orphan-drug designation requests received versus the number of requests granted orphan status by year. Approximately 50% of all drug-designation applications are for oncology products, which is followed by neurology, hematology and gastroenterology uses.

Rare pediatric disease designation program

In an effort to further the development of drugs and biologics for the prevention and treatment of rare pediatric diseases, OOPD in conjunction with the Office of Pediatric Therapeutics (OPT) oversees a Rare Pediatric Disease Designation Program. Once a request for rare pediatric disease designation is submitted to OOPD, the determination of whether or not the disease is rare as per the ODA is made by OOPD. The OPT will then determine if the disease is a rare pediatric disease based on the definition in the law (see below). Sponsors who are granted marketing approval for a drug or biologic for a rare pediatric disease can qualify for a voucher that can be used to obtain a priority review of another future marketing application for a different product. The review divisions determine if the drug or biologic for the prevention or treatment of a rare pediatric disease is eligible to receive this voucher.

The definition of a rare pediatric disease has evolved since its original inception into Section 529 of the Food, Drug and Cosmetic Act (FD&C Act). In 2016, the

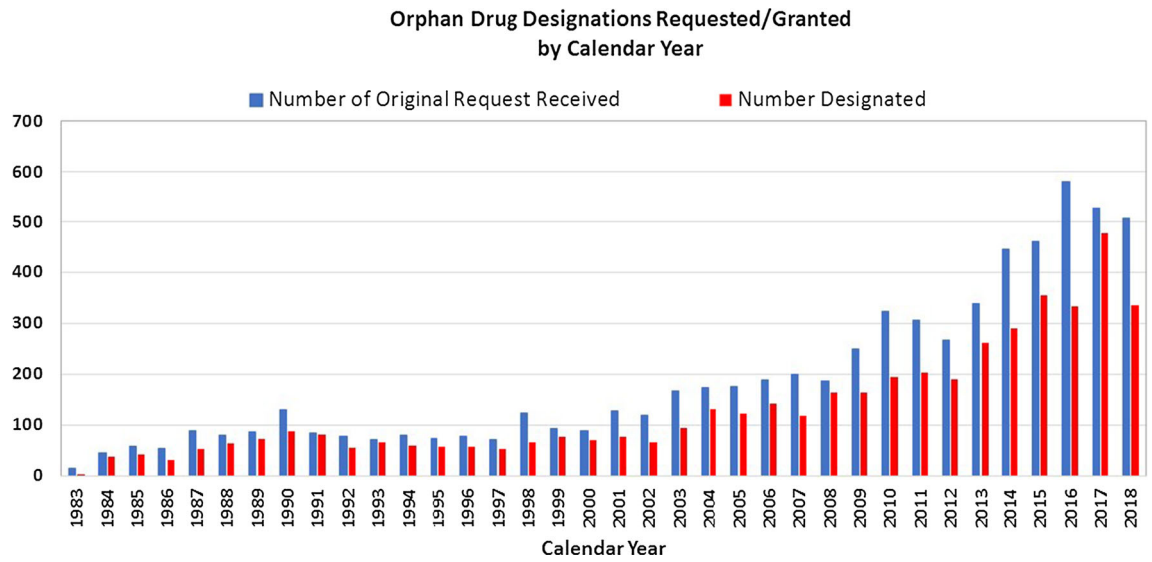

Fig. 1 Orphan drug designation requests versus number granted by year

Advancing Hope Act (https://www.gpo.gov/fdsys/pkg/BILLS-114s1878enr/pdf/BILLS-114s1878enr.pdf) amended the definition such that in order to be considered to be a rare pediatric disease, the sponsor must make the case that the disease is a serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years, including age groups often called neonates, infants, children, and adolescents, and that disease is a rare disease or condition.

As of December 2018, 216 rare pediatric disease designation requests have been received and 164 rare pediatric disease designation requests have been granted. There have been ten vouchers awarded as of December 31, 2018.

Humanitarian use device program

The third designation program within OOPD is the Humanitarian Use Device (HUD) Designation Program, which is part of the Humanitarian Device Exemption (HDE) Program established in 1990 through the passage of the Safe Medical Devices Act. In order for a medical device to qualify for the HUD Designation Program, the disease or condition that the device treats or diagnoses must affect or be manifested in not more than 8000 individuals in the United States per year (i.e., annual incidence).

To obtain HUD designation, sponsors must submit an application that contains the information requested under 21 CFR Part 814.102. Similar to orphan-drug designation, sponsors may make the case for an orphan subset. The review process for a HUD designation request is completed within 45 calendar days from the date of receipt of the application by OOPD. Obtaining HUD designation allows the sponsor to pursue an alternative pathway for obtaining marketing approval for medical devices, referred to as the HDE Program. While an HDE application is similar to a Premarket Approval (PMA) application, in that sponsors who file an HDE application must still show that there is a reasonable assurance of safety with their device, the HDE application pathway is not subjected to the effectiveness requirements of the PMA pathway. Rather, sponsors who go through the HDE pathway have to show that there is a probable benefit from the use of their device in the disease that is the subject of the HDE application and that this probable benefit outweighs the risks of injury or illness from the use of the device. HDEs are also subject to some profit and use restrictions. Once a device has obtained HUD designation, the sponsor is then eligible to submit an HDE marketing application. While obtaining HUD designation from OOPD is a requirement prior to the submission of an HDE marketing application, possessing HUD designation by itself is not a guarantee for approving an HDE application.

As of November 2018, 410 HUD requests have been received and 266 HUD requests have been granted HUD designation. There have been 74 HDE approvals.

Grants programs

The Orphan Products Grants Program began in 1983 following the ODA to ensure funding for research that is needed for the development of products for rare diseases. The goal of the program is to identify and promote the development of orphan products by providing funds to help offset clinical trial costs where investors may lack interest

until data was obtained on the safety and/or efficacy of a product for a rare disease. The program started out with only ~ $500,000 and funded just 8 grants that initial year. Over time, the success of this program and the need for financial resources became more evident leading to a budget increase of ~ $17.7 million per year which is in part used to support clinical trials (~ $15.7 M) that will test the safety and efficacy of products for a rare disease with the intent of using the data toward marketing approval. These grants are open to any domestic or foreign, public or private, for-profit or nonprofit entities that are studying a disease that meets the definition of a rare disease under the ODA (i.e., affecting fewer than 200,000 in the United States). OOPD funded grants ensure that product development occurs in a timely manner with a very modest investment. OOPD typically receives about 100 applications a year and has funded over 600 new studies. Figure 2 shows the total number of clinical trial grant applications submitted to the program versus the number of new awards that were funded by fiscal year. The rapid increase in the cost of clinical trials in recent years has precluded an increase in the number of new OOPD grants. At any one time, there are typically 60 to 85 ongoing grant-funded projects. Similar to orphan-drug designations, OOPD grant applications submitted to the office tend to be primarily focused on the oncology indications, including general oncology, hematology-oncology and neuro-oncology. This is followed by neurology and endocrine/metabolism specialties [5].

The 2014 public workshop on Complex Issues in Developing Drugs for Rare Diseases as well as through conversations with stakeholders including patient advocacy groups, FDA, and National Institutes of Health's (NIH), confirmed the need for better well-defined natural history data. To address this issue, in 2016, FDA launched a $2 Million Natural History Grants Program. The purpose of a natural history study is to describe the course of a disease over time, as well as to identify demographic, genetic, environmental, and other variables that correlate with its development and outcomes. These studies can facilitate a better understanding of the rare disease to help design more efficient clinical trials by defining the target population, developing clinical outcome measures and biomarkers. There was an overwhelmingly large response from the rare disease community for this program as seen by the numerous application submissions as well as through discussions with stakeholders which echoed the need for these studies and funding for them. FDA was able to fund six grants through the 2016 pilot (two with the collaboration and support of the NIH National Center for Advancing Translational Sciences (NCATS)). These awards include studies for Friedreich's ataxia, sickle cell anemia, Angelman syndrome, and myotonic dystrophy.

Although there are over 7000 rare diseases that affect nearly 30 million Americans, most do not have approved treatments. The Orphan Products Grants Program has been supporting clinical trial research since 1983 and has facilitated the marketing approval of over 60 products for rare diseases including: ivacaftor for cystic fibrosis subjects with G551D mutations, L-glutamine for sickle cell anemia, C1 esterase inhibitor (recombinant) for hereditary angioedema (HAE), ibalizumab for multidrug resistant HIV-1, and cheatham platinum stent system prevention for treatment of aortic wall injury associated with aortic coarctation.

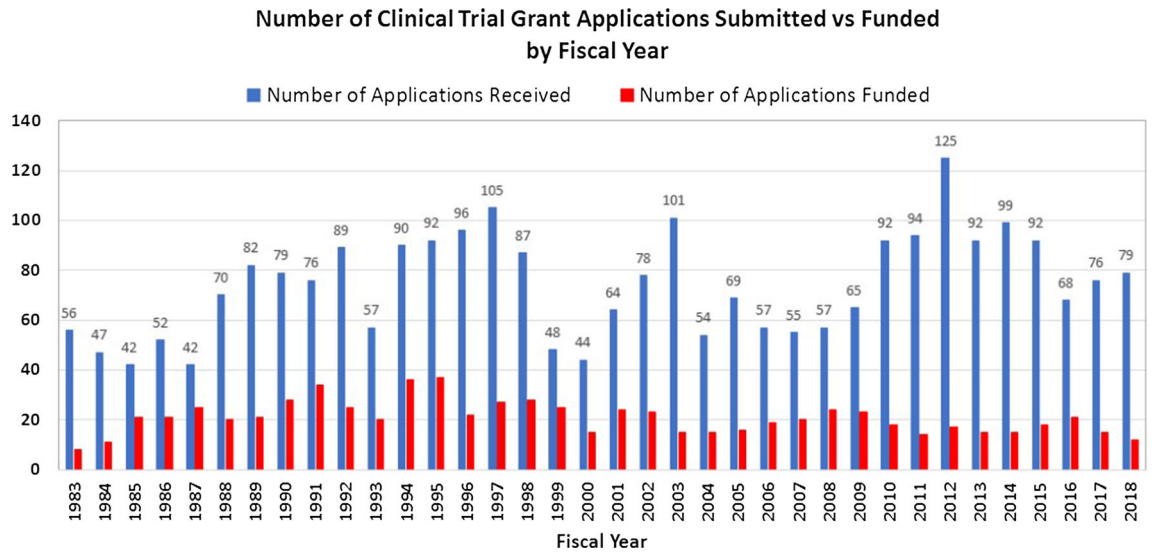

Fig. 2 Number of clinical trial grant applications submitted versus funded by fiscal year

Despite the successes of the Orphan Products Grants Program, there still remains a significant unmet need to develop therapies for patients living with rare diseases. Therefore, through two new OOPD Request for Applications (RFA) in 2018 (one for Clinical Trials grants and one for Natural History grants), OOPD is focusing its efforts to move new therapies along in drug development in safe yet efficient means by encouraging innovative study designs for rare diseases with an unmet medical need. For clinical trials grants, FDA is encouraging methods such as adaptive and seamless trial designs, modeling and simulations, and basket and umbrella trials. Adaptive trials allow for planned modifications to one or more aspects of the design based on data collected from the study's subjects while the trial is ongoing; seamless trial designs compress the phases of a trial into one continuous trial; and basket, umbrella and platform trials allow for testing of multiple drugs and/or multiple diseases using a common infrastructure. These types of studies will be given priority during the review process. Consideration should be given to the use of real world data as well, which has the potential to allow for more efficient design and conduct of clinical trials in the health care setting to answer questions previously thought infeasible. In addition, applications that propose simulations and modeling used toward the study of safety and effectiveness of a product are encouraged. For example, modeling and simulation allow for organization of diverse data sets, optimization of product dosing based on individual physiology and genetics, as well as, aid in the prediction of product safety which can help to design a more efficient trial design (dosing, number of patients, outcomes, length of trial, etc.) and provide a vital tool to help evaluate new treatments in rare diseases where patient populations are inherently difficult to study because of their small size. Many of these approaches are appropriate in the early stages of product development and may hold significant promise for the advancement of therapeutic treatments for rare diseases. Early engagement with FDA review divisions to discuss the use of these innovative tools is recommended prior to submitting a grant application to OOPD. Similarly, priority will also be given to efficient natural history studies where the study has a potential to exert a broad impact in advancing multiple rare diseases sharing a similar pathophysiology as well as use simulations and modeling in conjunction with the natural history study. Innovative methods for data collection as well as data dissemination which can serve as a model for future studies is also highly encouraged. Using these efficient approaches in these two grant programs, FDA expects to address critical knowledge gaps, to remove major barrier(s) to progress in the field, to exert a significant and broad impact on a specific rare disease or multiple rare diseases with similar pathophysiology, and to inform current or future product development including the design of clinical trial(s) and to ultimately inform the development of medical products that meet patient needs and increase the number of treatments for rare diseases with an unmet medical need.

Another grant program that is administered by OOPD is the $6 million per year Pediatric Device Consortia Grant Program, which was initiated in 2009 to fund consortia which provide expert advice and support services to innovators of children's devices. These services include business and regulatory consulting, as well as device testing capabilities. This program recently had a call for applications and has funded five consortia including the Philadelphia Pediatric Medical Device Consortium, National Capital Consortium for Pediatric Device Innovation 2.0, Southwest National Pediatric Device Consortium, University of California San Francisco-Stanford Pediatric Device Consortium, and the West Coast Consortium for Technology and Innovation in Pediatrics. $1 Million will be used for the Real World Evidence (RWE) Demonstration Project, in which three of the consortia will conduct RWE projects in the pediatric space that develop, verify and operationalize methods of evidence generation, data use, and scalability across the health care systems, device types and manufacturers. The FDA intends to use the information gathered through this project to further efforts to incorporate RWE into the agency's work.

Continued challenges in rare disease drug and device development

Despite the numerous marketing approvals for rare disease therapies and strides made in rare disease research, there is still a significant unmet need to further the development of products in the orphan space as many of these conditions still have no approved treatments due to the several challenges that remain with developing products for rare diseases. For example, there is limited knowledge regarding many rare diseases as compared to common diseases. There remains a lack of natural history data resulting in unanswered questions regarding the rare disease itself (e.g., mechanistic basis for the disease), and diversity within a rare disease (e.g., differences in phenotypes, genotypes and clinical presentations) [6]. This lack of information may make it difficult to choose an appropriate study endpoint, study population, or create additional challenges in ensuring that the most optimal study design is used. Clinical expertise may also be limited which affects the ability of patients to find help and diseases with limited number of patients make it difficult to enroll into trials. Therefore, there is great need for more efficient and well-designed trials for rare diseases to move products along in regulatory

development. However, recruiting an adequate number of patients for certain diseases due to the limited affected population size and the ability to find clinical sites may be challenging. Additionally, a sponsor studying a product for a rare disease, must still demonstrate that the product is safe and effective in treating, preventing or diagnosing the rare disease or condition through well-controlled studies [6]. For any marketing approval, including for a rare disease, there must be a substantial amount of evidence that the drug or biologic will have the effect that it claims on the disease at hand [6]. While programs such as the Orphan Drug Designation Program may provide financial incentives to help continue the development of products for a rare disease, simply because a sponsor holds orphan-drug designation does not alter the standard regulatory requirements and processes for obtaining marketing approval of the drug or biologic [7].

Another major challenge is the cost of drug development for a small patient population and limited research dollars available. While the ODA has promoted the development of therapies for rare disease and conditions by providing sponsors with financial incentives which may help to offset some of the development costs, and orphan grants may indeed act as seed money to attract further investors, the development of treatments for rare diseases can still be as expensive as therapies for non-rare diseases. These barriers may be especially discouraging for smaller pharmaceutical companies with limited resources.

Additionally, the complexity of science is increasing with advances in pharmacogenomics and precision medicine which can affect certain diseases that may have once qualified for rare disease status and orphan-drug designation and now, may no longer qualify and vice versa. One example of an evolving view on diseases and conditions is ovarian cancer. While the entire prevalence of ovarian cancer alone currently exceeds the 200,000 prevalence threshold for orphan-drug designation, OOPD had at one time granted orphan status for drugs and biologics for only ovarian cancer as this disease was considered to be a distinct disease or condition with a prevalence under the 200,000 threshold. This thinking has since evolved to where now, the disease or condition is a combination of ovarian, fallopian tube and primary peritoneal cancer. At the time that the thinking of what the disease is had changed, the combined prevalence of all ovarian, fallopian tube, and primary peritoneal cancer exceeded 200,000 and sponsors were no longer eligible for orphan-drug designation if they came in with a designation request for only one of these cancers. The rationale behind why FDA combined these three diseases is based on their shared origin, and also on the way these diseases would be studied for marketing approval. Specifically, the rarity of fallopian tube and primary peritoneal cancers would likely not render the study of either disease on its own and these populations would likely have to be combined with the ovarian cancer population in clinical studies. Therefore, even when the prevalence of ovarian cancer alone was under 200,000, once the thinking on the disease evolved to include all three cancers, ovarian cancer no longer qualified for orphan status. The evolution of what a disease or condition is puts the onus on the sponsor to keep abreast of FDA's thinking on diseases and conditions as this would directly impact not only their eligibility for orphan-drug designation, but also the use for which their drug or biologic is being developed.

The FDA has tried to address the challenges in developing products in the orphan space. The Agency understands that some aspects of drug development for common diseases differ from and may not be possible for rare diseases and recognizes the challenges sponsors face when developing therapies to address rare diseases. Due to certain challenges, such as limited patient population size, FDA works with stakeholders to consider creative and flexible approaches to product development as appropriate. To better navigate the development of the drug or biologic for a rare disease, the FDA encourages sponsors to meet with the Agency early on in their development process through meetings such as the pre-IND, Critical Path Innovations, and INTERACT meetings so that the appropriate clinical trial design based on the patient population and disease may be identified [6]. Sponsors are also encouraged to maintain frequent communication with the Agency throughout their development process [6]. With respect to orphan-drug designations, the Agency encourages sponsors to submit their request early in the drug or biologic development process (providing that all the elements of a designation request can be adequately addressed). By obtaining orphan-drug designation earlier on in their development process, sponsors may become eligible at an earlier timeframe for tax credits for qualifying clinical trials. Additionally, companies holding orphan-drug designation have publicly noted the orphan status of their drug or biologic and have been able to gain additional attention from outside sources. Sponsors may find this visibility to be beneficial in their drug development process. Orphan products are also eligible for various expedited pathways, and guidance documents that help explain the Agency's current positions on various topics pertaining to rare diseases are available to assist sponsors in their development of products for rare diseases.

The number of requests for orphan-drug designation has been quickly rising and the complexity of the science with advances in pharmacogenomics and precision medicine has been increasing. The FDA has tried to address some of the challenges associated with rare disease therapy development. With respect to the orphan-drug designation

program, the FDA has examined where it can make the designation processes more efficient so that timely review of designation requests can take place. The overall objective is to provide more certainty to sponsors and to reduce the time and costs associated with orphan drug development. As a result, despite not having a statutory requirement, OOPD has committed itself to reviewing 100 percent of all new orphan-drug designation requests within 90 days of their receipt. The FDA has also employed measures to increase efficiency and innovation in the clinical trial and natural history grants programs and has implemented novel approaches such as simulations and modeling trials and looking at real world evidence data in a rigorous way through the pediatric device consortia grants program.

Conclusion

Prior to the enactment of the ODA, between 1973 and 1983 there were fewer than ten drugs approved by the FDA for the treatment of a rare disease [8]. Since the inception of the ODA, more than 700 orphan drug or biologic approvals for rare diseases have been granted [9]. Additionally, the number of sponsor requests per year for orphan-drug designation and the interest expressed in the grant programs, continues to increase. While challenges associated with rare disease drug development continue, there is clear interest surrounding the development of therapies for rare diseases and conditions, demonstrating clear successes of the ODA. In addition to the programs under the purview of OOPD, the FDA has multiple other offices devoted to rare diseases product development and patient advocacy. By continuing to address the various challenges associated with the development of therapies for rare diseases and conditions, the FDA remains a strong advocate and valuable resource for sponsors seeking to further the development of products for the underserved rare disease community.

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