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Orphan Drugs: Understanding the FDA Approval Process

Gauri Srivastava
IQVIA, Inc.

Ashley Winslow
Orphan Disease Center, Perelman School of Medicine, University of Pennsylvania

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Summary

- In the U.S., a rare disease is one that affects fewer than 200,000 patients. There are more than 7,000 rare diseases today but relatively few specific therapies for them, mainly because the manufacturers cannot recoup their drug development costs.
- Orphan drug status allows sponsors to apply for incentives such as the Orphan Drug Tax Credit (ODTC), marketing exclusivity for seven years for the first orphan drug for a given rare disease, and an attractive drug-pricing scheme, amongst other benefits.
- Orphan drug trials are generally single arm (no placebo arm), nonrandomized, and open label. Safety Phase 1 trials are not usually required, and Phases 2 and 3 can be combined when the patient population is very low.
- Sponsors of an orphan drug can make use of expedited Food and Drug Administration (FDA) programs such as the Fast Track, Breakthrough Therapy, and Priority Review designations, as well as the Accelerated Approval pathway and unique grant funding opportunities, such as the Orphan Products Clinical Trials Grant program.
- The FDA facilitates patient-focused drug development (PFDD) meetings, wherein they collect patient experience data from the patients, their family members, their caregivers, and disease foundations. These data can help the orphan drug developers for a given rare disease in determining clinical endpoints and the route of therapy administration for their clinical trials.

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Gauri Srivastava, MS¹ and Ashley Winslow, PhD²



Topic Relevance by Timeline

Summary

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Introduction

During the 1990s, the pharmaceutical industry flourished due to the discoveries and introduction of small molecule “blockbuster” drugs, or drugs that bring pharmaceutical companies high annual

¹ IQVIA, Inc.

² Orphan Disease Center, Perelman School of Medicine, University of Pennsylvania

sales, into the market. When these drugs went off-patent in the 2000s, there was a rise in the generics industry. Since pharmaceutical companies struggle to come up with new drugs, and their previous discoveries are available as cheaper generics, many companies have started developing drugs for rare diseases, known as orphan drugs. These so-called “niche busters” constitute the fastest-growing area of drug development, with 14 orphan drugs approved between October and December 2017 (Pariser; Sharma et al.; Office of the Commissioner, “FDA-TRACK: Agency-Wide Program Performance”).

Orphan drugs are medicines or vaccines intended to treat, prevent, or diagnose a rare disease. In the United States, the FDA defines a rare disease as a disease or a condition that affects fewer than 200,000 patients in the country. More than 7,000 rare diseases are estimated to exist today, affecting approximately 6% to 8% of the world population (Melnikova; Mwamburi et al.).

There is a scarcity of treatments for rare diseases, with fewer than one in ten rare disease patients receiving disease-specific treatment. Drug development for rare diseases is often limited by the large cost of investing in an original pharmaceutical agent with poor profit potential, given the small patient size per rare disease indication. Other obstacles include limited understanding of the disease, difficulty in identifying patients for trial recruitment, and trouble in identifying clinical centres with expertise in the disease to run the trials (Melnikova).

Nonetheless, 39% of the novel drugs approved by the FDA Center for Drug Evaluation and Research (CDER) in 2017 were orphan drugs, mainly due to the provisions of the Orphan Drug Act of 1983 (“2017 New Drug Therapy Approvals”). An increase in this trend is expected in the future. It is therefore important to understand the critical regulations and the policy initiatives for orphan drugs that exist in our country, which are explained in this chapter.

IND Process

The first formal step for a sponsor who is ready to initiate clinical studies for a promising drug is to file for an Investigational New Drug (IND) application. A pre-IND meeting with the FDA is strongly advised. The IND application includes available information about the drug—data from preclinical, animal, and other studies indicating that it is reasonable to begin human trials (Center for Drug Evaluation and Research, “Investigational New Drug (IND) Application”) (see the chapter on “FDA Drug Regulation: Investigational New Drug Applications”).

Early communication with the FDA is essential for the progress of a drug’s approval process. The CDER reviews most orphan drug applications, and the Office of Orphan Products Development (OOPD) promotes orphan drug development and provides grants for the same. It is advised to contact these organizations regularly (Institute of Medicine (US) Committee on Accelerating Rare Diseases Research and Orphan Product Development; West).

The ideal time to begin communicating with the FDA is prior to filing an IND application (Pariser). Timely review of IND submissions by the FDA, along with their feedback to sponsors, can result in greater efficiency of the drug development process. At the sponsor's request, the FDA will, if possible, provide advice on specific IND matters (Center for Drug Evaluation and Research, "Best Practices for Communication Between IND Sponsors and FDA During Drug Development").

The officials whom the sponsors should contact are usually the regulatory project managers (RPMs) in the CDER review divisions or the Center for Biologics Evaluation and Research (CBER) review offices (collectively called "review division RPMs"). The review division RPMs and specific functional area RPMs are referred to as "FDA RPMs."

FDA RPMs communicate via written correspondence, email, fax, or telephone. They are the primary contacts for facilitating the timely resolution of technical, scientific, and regulatory questions, conflicts, or communication challenges between sponsors and the review teams. It is advised to communicate via a telephone call for any time-sensitive issue and later to follow up with a written communication (e.g., email, submission, or letter), so that there is a documentation of the decisions, agreements, or action terms that arose during the interaction (Center for Drug Evaluation and Research, "Best Practices for Communication Between IND Sponsors and FDA During Drug Development"). The FDA website lists the contact representatives and telephone numbers of different departments involved in different stages of the orphan drug development process. The Office of New Drugs (OND) and the CDER together provide guidance under the Rare Diseases Program. If the sponsor is unsure about whom to call or is not quite ready for clinical trials but has some questions, they can contact either the associate director for rare diseases or the regulatory scientist (Center for Drug Evaluation and Research, "Rare Diseases Program").

Formal meetings at critical points in the drug development process are useful for resolving questions and issues regarding drug development plans, the evidence required to demonstrate the effectiveness of the orphan drug, drug safety, clinical trial design, and product quality. These meetings help to minimize wasteful expenditures of time and resources, speeding up the drug development and evaluation process (Center for Drug Evaluation and Research, "Best Practices for Communication Between IND Sponsors and FDA During Drug Development").

Orphan Drug Designation

The Orphan Drug Act (ODA) grants a special status to a drug or a biologic product that is intended to treat a rare condition or disease, upon the request of the sponsor. This status is referred to as "orphan designation" or "orphan status" (Office of the Commissioner, "Designating an Orphan Drug or Biologic").

Before the sponsor can apply for drug approval under the Orphan Drug Act and before the sponsors are eligible for incentives like the Orphan Products Grant, they must apply and receive the orphan

designation from the FDA (Institute of Medicine (US) Committee on Accelerating Rare Diseases Research and Orphan Product Development).

The sponsor can submit the application for the designation anytime in the drug development process before the submission of a marketing application for the drug of the same rare disease (“Electronic Code of Federal Regulations”). However, it is recommended that the application be done before the IND studies as it helps to design the trials when the requirements regarding clinical endpoints are known beforehand.

The request for designation must be submitted to the OOPD with the information required in CFR 316.20 and 316.21 (Office of the Commissioner, “Designating an Orphan Drug or Biologic”). Formal, preclinical study data are not required, since the FDA wants evidence of efficacy and the “scientific rationale” for the use of the drug. The applicant does not need to have animal toxicology data; only the results of efficacy studies conducted in an animal model for the human disease are needed (“Electronic Code of Federal Regulations”). The applicant may provide clinical data, animal studies, or in vitro data, but if sufficient information exists in published literature, that may suffice (Antos).

The sponsor must submit documentation of the estimated prevalence of the disease or condition for which the drug is being developed, together with a list of the sources for the estimate, in order to prove that the drug would be administered in the U.S. to fewer than 200,000 patients. “Prevalence” is the number of persons in the U.S. who have been diagnosed with the disease at the time of the submission of the request for designation. If the drug is to treat a disease that affects a larger number of people, it may still be designated as an orphan if it is expected that the costs of research and development of the drug for a particular medical indication cannot be recovered by sales in the U.S. This is rare, and the sponsors must submit supporting data related to the cost of their development activities (“Electronic Code of Federal Regulations”).

More than one sponsor may receive orphan drug designation of the same drug for the same rare disease or condition, but each sponsor seeking orphan drug designation must file a complete request for designation (“Electronic Code of Federal Regulations”). However, only the sponsor who receives the first FDA approval can receive orphan drug marketing exclusivity (discussed later). A manufacturer may obtain multiple orphan designations and approvals for different indications for the same product (Institute of Medicine (US) Committee on Accelerating Rare Diseases Research and Orphan Product Development).

Regulation of Biologics

Biologics are an important part of the orphan drug development, as certain rare diseases require therapies based on biologics, such as monoclonal antibodies, vaccines, and blood-based clotting factors, among others. Hence, it is important to understand the regulation of biologics by the FDA

(see the chapter on “Intellectual Property Protection for Biologics”). Generally, biologic drugs are held to the same standard of efficacy and safety as nonbiologic drugs.

In 2003, the FDA transferred responsibility for review and approval of most therapeutic biologics from CBER to CDER. Nonetheless, the CBER continues to oversee vaccines, antitoxins, antivenoms, venoms, allergenic products, blood, and blood products. Depending on the category of the product being developed, the sponsor can approach the corresponding organization (Institute of Medicine (US) Committee on Accelerating Rare Diseases Research and Orphan Product Development).

Although the U.S. was the first country to introduce orphan drug legislation in 1983, Japan, Australia, and the EU followed suit soon after. However there are certain differences in how orphan drugs are handled in each of them. Sponsors are required to file for an orphan drug designation in all of these countries (Table 1). While there is no national plan for orphan drugs and rare diseases in the U.S., Japan, and Australia, there is one in place in the EU. All these countries allow independent marketing authorization, with Japan and the EU providing up to ten years of marketing exclusivity as opposed to seven years in the U.S. Australia does not allow marketing exclusivity to the manufacturers. In terms of pricing, Australia and Japan have a fixed pricing model, whereas different countries in the EU have different policies ranging from fixed pricing to free pricing and also reference-based pricing (Gammie et al.).

New Drug Application/Biologics License Application

Approval of all drugs must be based on substantial evidence of efficacy in preventing or treating the specific condition, along with evidence of safety for that use. The FDA expects sponsors to have an in-depth understanding of the disease and its natural history, which is not usually available for rare conditions. The FDA does not require that natural history studies be conducted, but when knowledge about the disease is insufficient to guide clinical development, a well-designed natural history study may help in designing an efficient drug development program (Center for Drug Evaluation and Research, “Rare Diseases: Common Issues in Drug Development Guidance for Industry”).

A New Drug Application (NDA) or a Biologics License Application (BLA) is submitted for approval of the drug to be launched in the market, and it contains the results from the human clinical trials. An NDA is for the market approval of small molecule drugs, whereas a BLA is for the approval of biologics. The required substantial evidence of efficacy and safety is based on the results of two or more (for common diseases) and sometimes only one (for rare diseases) adequate and well-controlled (A&WC) investigations designed and conducted such that they are able to “distinguish the effect of a drug from other influences, such as spontaneous change in the course of a disease, placebo effect, or biased observation” (21 CFR 314.126, 2018).

Table 1. Orphan Drug Benefits in Some Other Major Countries

(Adapted from (Gammie et al.)).

Country	Orphan Drug Designation	Marketing Exclusivity	Financial Incentives	Nonfinancial Incentives	Pricing
Australia	Yes	No	Fee reduction for marketing authorization approval	Pre-licensing access, regulatory assistance	Fixed
Canada	No	No	Tax incentives, fee reduction for marketing authorization	Pre-licensing access, scientific advice, protocol assistance, regulatory assistance	Reference pricing
Japan	Yes	10 years	Financial subsidies, tax credits, user fee waivers	Priority review, fast track approval, free protocol assistance	Fixed = cost + 10%
EU5 (France, Germany, Italy, Spain, U.K.)	Yes	10 years	Reduced rebates in Spain and tax exemptions in France	Pre-licensing access in all EU5 countries, protocol assistance and scientific advice in France and Italy	Free pricing in Germany, reference pricing in Italy, fixed pricing in Spain and the U.K, and price negotiations in France

Rare disease interventional trials differ from those in non-rare conditions, with notable differences in enrollment, design, blinding, and randomization. For clinical trials of rare diseases, there is frequently no requirement for a placebo arm and a safety Phase 1 study in healthy volunteers. For diseases with a very small population, the FDA accepts trials where Phase 2 and Phase 3 are condensed together to test for efficacy as well as safety in the patients. A study done in 2014 shows that the majority of the rare disease clinical trials between 2006 and 2012 enrolled fewer participants, were more likely to be single arm, nonrandomized, and open label when compared to the non-rare disease clinical trials (Bell and Tudur Smith).

Orphan Products Clinical Trials Grants Program and Other Resources

Originally called the Orphan Products Grants, these grants are provided by the FDA for clinical studies on safety and/or effectiveness that will either result in or substantially contribute to market approval of these products for rare diseases. These grants are funded by the FDA's Office of Orphan Products Development (OOPD). The application for these grants must include a clear documentation of the estimated prevalence of the orphan disease/condition—showing that it is intended to treat a disease with fewer than 200,000 patients in the U.S.—and an explanation of how the proposed clinical study will provide the essential data needed for product development. It is not necessary for a drug or biologic product to hold orphan drug designation to be eligible for the grant program.

The OOPD receives about 100 applications per year and has funded over 700 studies so far. In general, the OOPD grant funding lasts between three and four years. Phase 1 studies are eligible for up to \$250,000 per year for up to three years. Phase 2 and 3 studies are eligible for up to \$500,000 per year for up to four years (Office of the Commissioner, "Orphan Products Clinical Trials Grants Program").

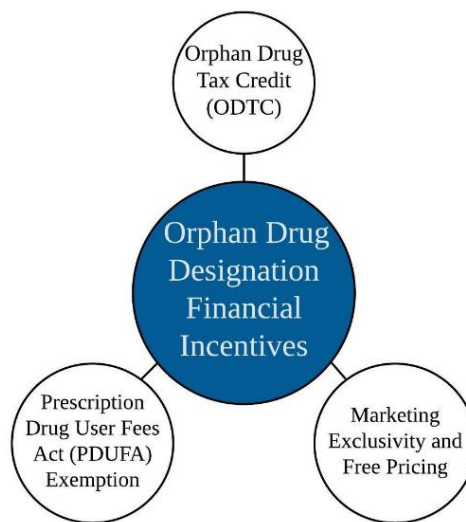
The National Organization for Rare Disorders' (NORD) Research Grant Program provides seed grants to academic scientists in the U.S. or outside, for translational or clinical studies related to the development of potential new diagnostics or treatments for rare diseases. Out of each grant awarded between \$30,000 and \$50,000, NORD uses \$5,000 to cover the administrative expenses and direct costs of initiating a request for proposals (RFP). A search for researchers who have published journal articles about a specific disease in the last two to five years is conducted in order to reach the most expert scientists. Each research proposal is reviewed by NORD's Medical Advisory Committee, which recommends funding for the highest-scored proposals. After the grant is awarded, NORD monitors the progress of the research, processing biannual reports to NORD's Medical Advisory Committee ("Research Grant Program").

The NIH's National Center for Advancing Translational Sciences (NCATS) collaborates with the National Human Genome Research Institute (NHGRI) to support the Genetic and Rare Diseases Information Center (GARD). GARD was established to help the researchers working in this space by providing fundamental information and resources to formalize their study protocols. GARD information specialists can provide custom literature searches, GARD's rare disease list, and a contact network of advocacy organization. These organizations may collaborate in the research and assist the sponsors in the recruitment of a team. They can also direct the researchers to NIH programs that support rare disease research, such as the Rare Diseases Clinical Research Network (RDCRN), Therapeutics for Rare and Neglected Diseases (TRND), and the Bridging Interventional Development Gaps program (BrIDGs) (NCATS NIH). These programs are funded by the

NCATS to assist researchers with developing clinical trials or therapeutic agents. There are foundations for specific diseases listed on the GARD website that provide funding resources to researchers working on that particular condition. For example, the Prader-Willi Syndrome Association (PWSA) offers one- to two-year grants for a maximum of \$100,000 for projects aimed at discovering and developing treatments, cures, and technologies benefiting those with Prader-Willi syndrome (Genetic and Rare Diseases Information Center (GARD) and National Center for Advancing Transnational Sciences).

Key Financial Incentives of Orphan Drug Designation

Figure 1. Financial Incentives of Orphan Drug Designation.



Orphan drug tax credit (ODTC)

The developers of an orphan drug get a tax credit for 50% of qualified clinical trials cost plus seven years of market exclusivity. Since the credit's inception in 1983, the FDA has approved more than 500 such drugs, as opposed to only 10 prior to it. However, congressional Republicans proposed to repeal the orphan drug tax credit as part of a U.S. tax reform package (Cunningham), and the senate bill proposed to decrease it to 27.5% (Dickey). The tax credit has been a huge financial incentive for the orphan drug manufacturers, and the credit's uncertain future spurred a large-scale "Save Orphan Drugs" movement against the repealment of the tax credit. The National Organization for Rare Disorders (NORD) strongly advocated that the ODTC be strengthened, or at the very least maintained at 27.5% and not reduced any further (Jensen). However, as of this writing, the ODTC has been reduced to 25% (Wechsler).

Prescription Drug User Fee Act (PDUFA) exemption

The FDA has the authority to assess and collect user fees for certain drug and biologics license applications. Pharmaceutical companies pay fees for certain new human drug applications, biologics applications, and supplements submitted to the agency for review. This fee is around \$2.2

million in value (Antos). Review of an application by the FDA cannot begin until the fee has been submitted.

A human drug NDA/BLA application for an orphan drug is not subject to an application fee unless the human drug application includes an indication other than the rare condition. Form FDA 3397, the PDUFA user fee cover sheet, is designed to provide the minimum necessary information to determine whether a fee is required for review of an application (Center for Drug Evaluation and Research, “PDUFA User Fee Cover Sheet”). If an application qualifies for an orphan exemption, the applicant does not need to send the FDA a written request. The applicant should simply notify the FDA that they are claiming the orphan exemption when they complete and submit FDA Form 3397. This form should be included with the application or supplement, and a brief statement claiming the orphan exception should be included in the cover letter (Center for Drug Evaluation and Research, “User Fee Waivers, Reductions, and Refunds for Drug and Biological Products”).

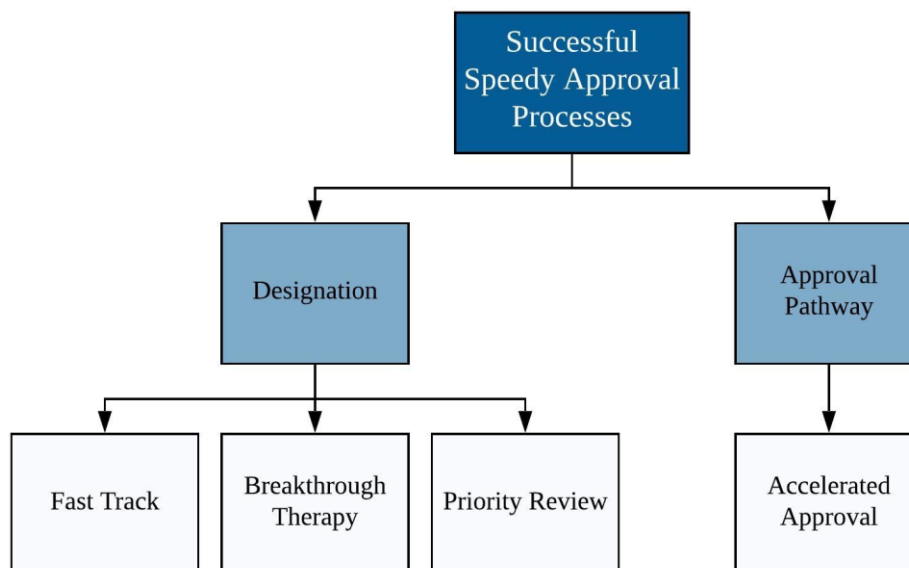
Marketing exclusivity and free pricing

Marketing exclusivity is given to orphan drug developers in order to provide several years to recover their drug development costs. The FDA’s orphan drug exclusivity (ODE) period runs for seven years from the time of approval of the NDA or BLA. During the marketing exclusivity period, the FDA cannot approve a generic drug abbreviated new drug application (ANDA) for the same drug or brand name drug (full NDA or BLA application) for the same rare disease indication (Seoane-Vazquez et al.; Lal). However, the same drug can receive approval for a different disease indication, and no limits are currently put in place on the number of drugs that may be selected for the same rare disease profile.

Pricing of the orphan drugs is unique in that it is designed to retrieve the costs of R&D from a small number of patients, compared to the pricing model of other drugs, where pricing is often based on the capacity of the customer to pay. Given this, the marketing exclusivity, and the lack of therapeutic alternatives, orphan drugs are relatively expensive. Spark Therapeutics’ Luxturna costs \$850,000 for a one-time gene therapy treatment for a rare, inherited retinal disease that can lead to blindness (Tirrell). One of the reasons for this is that patients with rare diseases often have a high willingness to pay, given the limited therapeutic alternatives and the life-threatening or chronically debilitating nature of many rare diseases. Pricing is also influenced by the change in quality of life in a more cost-effective approach. In other words, a drug that could provide a cure will be priced higher than a drug that provides just symptomatic relief or treatment. Therefore, third-party payers (insurance companies) are generally forced to pay the manufacturer’s high price. In addition, the free pricing scheme in the U.S. allows the manufacturer to set the price at their discretion. In comparison, in different European countries, pricing is controlled by a single-payer system and cost referencing with other nations (Gammie et al.).

Eligibility for Expedited Approval Processes

Figure 2. Four Successful Rapid Approval Processes Allocated by the FDA.



Out of the CDER new molecular entity (NME) approvals between 2008 and 2016, a significantly higher number of orphan drugs used expedited clinical development programs compared to the non-rare disease drugs (Moscicki). If the drug is eligible, the sponsor can make use of any of the four rapid-approval processes allocated by the FDA (Figure 2):

Fast Track (designation)

This designation facilitates the development and speeds up the FDA review process of drugs that would treat serious conditions and fill an unmet medical need. To be eligible as a drug that treats a serious condition, the drug must positively impact such factors as survival, day-to-day functioning, or the likelihood that the condition, if left untreated, will progress from a less severe condition to a more serious one. Filling an unmet need means that no current therapy is available for the condition or that the proposed therapy is potentially better than available therapies (see the chapter “Identifying Unmet Needs: Problems that Need Solutions”). If there are available therapies, a Fast Track drug must show some advantage over available therapy, such as evidence of superior effectiveness, improved effectiveness on serious outcomes, or lesser side effects (Office of the Commissioner, “Fast Track”).

The sponsor can initiate the request for Fast Track designation anytime during the drug development process. The FDA will review and make a decision within 60 days from the request. The type of data required are usually preliminary nonclinical and mechanistic or clinical data (Krulowitz). Ideally, the sponsor should submit the application no later than the pre-BLA or the

pre-NDA meeting (Center for Drug Evaluation and Research, “Expedited Programs for Serious Conditions—Drugs and Biologics”).

The benefits of Fast Track designation include more frequent meetings and written communication with the FDA, and rolling review. Rolling review refers to the ability of the FDA to begin review of the BLA or NDA as sections are completed, rather than waiting for the finalized NDA or BLA to begin the review (Office of the Commissioner, “Fast Track”).

Breakthrough Therapy (designation)

This program is similar to the Fast Track program in providing quick review of drugs that are intended to treat a serious condition and are better than any available therapy. The most important difference between the two is the type of data that needs to be submitted to get a Breakthrough Therapy designation, which is preliminary clinical evidence indicating that the drug may demonstrate substantial improvement over available therapy on (a) clinically significant endpoint(s). Substantial improvement is judged on the basis of the magnitude of the treatment effects and the importance of the observed clinical outcome. A clinically significant endpoint is one that measures an effect on irreversible morbidity or mortality (IMM) or on symptoms that represent serious consequences of the disease. It can also refer to findings that suggest an effect on IMM or serious symptoms (Office of the Commissioner, “Breakthrough Therapy”).

Ideally, a Breakthrough Therapy designation request should be received by the FDA from the sponsor no later than the end-of-Phase-2 meetings. The FDA responds to the request within 60 days of the receipt of request (Office of the Commissioner, “Breakthrough Therapy”).

Along with the benefits of a Fast Track designation, Breakthrough Therapy drug sponsors are also given intensive guidance on an efficient drug development program and have the involvement of FDA senior managers. It is fairly common for a drug on the fast track to be granted Breakthrough Therapy designation during the drug development process (Krulewitz; Office of the Commissioner, “Breakthrough Therapy”).

Accelerated Approval (approval pathway)

Instituted in 1992 by the FDA, Accelerated Approval regulations allow drugs for serious conditions that fill an unmet medical need to be approved based on a surrogate endpoint. This endpoint should be a marker like a laboratory measure or a radiographic image, but is not itself a clinical benefit. Studies demonstrating this must be A&WC (Office of the Commissioner, “Accelerated Approval”).

The sponsor should discuss the possibility of accelerated approval with the review division during development, supporting, for example, the use of the planned endpoint as a basis for approval and

discussing the confirmatory trials, which should usually be already underway at the time of approval (Center for Drug Evaluation and Research, “Expedited Programs for Serious Conditions—Drugs and Biologics”).

It is important to note here that the sponsor is required to conduct additional clinical trials after the approval (Phase 4 or post-market surveillance) of the drug to confirm the clinical benefit. Until the clinical benefit is confirmed, the label mentions that the use of the drug has not shown clinical benefit yet. Moreover, failure to do these Phase 4 clinical trials can result in removal of the drug from the market (Krulewitz).

Priority Review (designation)

In 1992, under the PDUFA, the FDA agreed to a Priority Review designation of any drug for which the agency would take action within six months to review the application, as opposed to ten months otherwise. The sponsor must submit an application (original or efficacy supplement) for a drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. Other eligibility criteria can be seen on the FDA website (Office of the Commissioner, “Priority Review”).

The sponsor must submit the request for the original BLA or NDA, or the efficacy supplement. The FDA responds within 60 days after the submission of request (Center for Drug Evaluation and Research, “Expedited Programs for Serious Conditions—Drugs and Biologics”).

Seeking Expert Guidance

Partnering with clinical and/or regulatory experts who have relevant experience could help guide the developers of an orphan drug to approval, potentially saving the developer significant resources in time and money (West). Candidate partners could be large pharmaceutical companies and certain nonprofit organizations and foundations. The most important areas to look for when considering a partnership with a pharmaceutical company are the partnering company’s commitment to the rare disease community, their ability to find innovative methods for patient group identification, their ability to navigate patient access to rare disease therapies, and their intention to give sustained support to the patients and their caregivers (Ascher et al.).

Patient experience data (PED) are collected by diverse stakeholders (including patients, family members, caregivers, disease research foundations, researchers, and drug manufacturers) and are intended to provide information about a patient’s experience with a disease, including its impact and the patient’s preference for or against its treatment (“Public Workshop on Patient-Focused Drug Development: Developing and Submitting Proposed Draft Guidance Relating to Patient Experience Data”). Patient-focused drug development (PFDD) meetings are one of the helpful community engagement mechanisms designed by the FDA. PFDD is a systematic approach to help ensure that patients’ experiences, perspectives, needs, and priorities are captured and meaningfully

incorporated into drug development and evaluation. Although pharmaceutical companies are not involved in such meetings, the makers of orphan drugs can benefit significantly by reviewing the PED collected in such meetings. The 21st Century Cures Act of 2016 states that the FDA will conduct public workshops to draft guidance documents related to the PFDD meetings (*FDA Plan for Issuance of Patient-Focused Drug Development Guidance*). The most recent workshop was held on March 19, 2018, and the meeting slides and recordings are available online (Office of the Commissioner, “Public Workshop on Patient-Focused Drug Development: Developing and Submitting Proposed Draft Guidance Relating to Patient Experience Data”).

Conclusion

Orphan drugs target rare diseases that affect fewer than 200,000 patients in the U.S. The Orphan Drug Act was signed in 1983 and provided for various incentives for orphan drug development. Since then, the orphan drug industry has been growing at a very fast rate. Researchers working on orphan drugs must learn about these incentives and others that are offered by nonprofit organizations and groups. Patients and their caregivers are coming together to generate data that will help drug developers come up with new therapies for rare diseases. Although the drug approval process remains the same for all drugs, exceptions are made in cases of rare disease drugs. Not only do orphan drug trials require smaller number of patient populations and condensed phase studies but they also are eligible for tax credits and grants. Additionally, the U.S. free pricing of drugs and patients’ higher willingness to pay for rare disease therapies make orphan drug development less expensive and allow for recovering the R&D costs during the seven years of marketing exclusivity. Pharmaceutical companies increasingly want to invest in these therapies and look for ways to partner with researchers and small biotech startups.

Practical Guides/Worksheets

FDA Orphan Drug Designation Checklist: For Sponsor Seeking Orphan Designation

(“CFR—Code of Federal Regulations Title 21”)

This checklist is to make sure that the sponsor has submitted all the required information to the FDA for obtaining the orphan drug designation for their proposed drug.

1. Have you included the description of the rare disease/condition for which the drug is being or will be investigated, the proposed use of the drug, and the reasons why such therapy is needed?
Yes No
2. Have you discussed in the request, the scientific rationale to establish a medically plausible basis for the use of the drug for the rare disease?
Yes No

3. Have you included all copies of pertinent unpublished and published papers that provide evidence of the medical plausibility of the treatment?
 Yes N/A
4. Is the number of people affected with the disease or condition for which the drug is being developed is fewer than 200,000 persons in the U.S.?
 Yes No
- OR
- Is there no reasonable expectation that the sales of the drug will be sufficient to offset the costs of developing the drug for the U.S. market and the costs of making the drug available in the United States?
 Yes No
5. Is the estimated prevalence of the disease together with a list of sources (including dates of information provided and literature citations) included in the documentation?
 Yes No
6. If the drug is a vaccine or a drug intended for diagnosis or prevention of a rare disease/condition, is the estimated number of people to whom the drug will be administered annually listed?
 Yes N/A
7. If your drug is the same drug as an already approved drug and seeks orphan drug designation for the same rare disease, have you justified that the proposed variation may be clinically superior to the first drug?
 Yes N/A

Resources

1. Orphan Disease Center
 - a. The Orphan Disease Center (ODC) at Penn, led by Dr. Jim Wilson, provides a unique set of programs that add value to every drug development stage, from building the initial knowledge base to enabling therapeutic development. Through their grants, the Programs of Excellence, international patient registries, Jump Start programs, and a number of new initiatives, the ODC seeks to drive therapeutic development for rare diseases. The ODC offers 50+ grant opportunities in 30+ diseases annually to researchers. Key functions of the ODC include—but are not limited to—uniting investigators and clinicians within Penn, CHOP, and internationally who are committed to treating and curing orphan conditions, creating resources for the rare disease community, and providing means for pharmaceutical and biotech companies to partner with researchers. The ODC’s Million Dollar Bike Ride pilot grant program opened in the summer of 2018.
 - b. <http://www.orphandiseasecenter.med.upenn.edu/>.
2. Orphan Products Natural History Grants Program

- a. The Orphan Products Natural History Grants Program by the OOPD supports studies that advance rare disease medical product development. The searchable database for these grants will be available soon.
 - b. <https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/OrphanProductsNaturalHistoryGrantsProgram/default.htm>.
3. Genetic and Rare Diseases Information Center (GARD)
 - a. The detailed guides for researchers on “Finding Research Participants” and “Where to find statistics for Rare Diseases” will be available soon on the NIH’s GARD webpage.
 - b. <https://rarediseases.info.nih.gov/about-gard/pages/23/about-gard>.
 4. Search database of Orphan Drug designations and approvals
 - a. If a product receives orphan drug designation, certain information about the orphan designated product (sponsor’s name, address, and contact information, as well as the name of the drug, orphan designated use, and the date of designation) is updated monthly on the searchable database on the FDA’s website.
 - b. <https://www.accessdata.fda.gov/scripts/opdlisting/opd/>.
 5. FDA Track Updates
 - a. Sponsors could subscribe to the FDA track updates to keep track of drugs being accepted for the expedited programs.
 - b. <https://www.fda.gov/AboutFDA/Transparency/track/default.htm>.

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