Insight into Orphan Drug Formulations and Regulations

Alcami

Jack James
Senior Scientist, Formulations Development

Elsie Melsopp
Director, Formulations Development

Andrea Young
Supervisor, Regulatory Affairs

The US Orphan Drug Act of 1983 characterizes an orphan disease as a rare medical condition that affects a population of fewer than 200,000 people. Rare diseases are caused from various reasons— most notably by genetics. However, the National Institutes of Health (NIH) states, "many rare diseases, including infections, some rare cancers, and some autoimmune diseases, are not inherited. While researchers are learning more each year, the exact cause of many rare diseases is still unknown" (NIH, 2017).

The term orphan disease resulted from pharmaceutical companies not having the resources to design and scale up formulations to treat these diseases due to the lack of financial support for such highly specialized programs. The Orphan Drug Act (ODA) allows for the necessary financial backing of pharmaceutical companies to develop treatments for rare diseases (NIH, 2017), giving special status to a drug or biological product (drug) upon request of a sponsor. This status is referred to as orphan designation or orphan status.

Worldwide Orphan & Prescription Drug Sales (2010-2024)

Source: EvaluatePharma® May 2018

	Worldwide sales ($bn)														
Year	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
Orphan drug sales	69	77	82	88	94	100	112	125	138	151	169	192	216	240	262
Growth per year		+11.7%	+6.7%	+7.7%	+6.8%	+6.3%	+12.5%	+11.3%	+9.9%	+9.6%	+11.9%	+13.4%	+12.9%	+10.8%	+9.2%
Orphan sales as a % of Rx	10.0%	10.5%	11.4%	12.1%	12.5%	13.5%	14.6%	15.9%	16.6%	17.3%	18.3%	19.2%	20.2%	21.1%	21.7%
Non-orphan drug sales	618	656	638	639	657	642	655	663	692	720	756	805	852	893	941
Growth per year		+6.2%	-2.7%	+0.1%	+2.8%	-2.2%	+2.0%	+1.1%	+4.4%	+4.1%	+5.1%	+6.4%	+5.9%	+4.8%	+5.3%
Prescription (Rx) (excluding generics)	627	667	653	657	675	665	688	708	746	782	831	897	965	1,024	1,090
Growth per year		+6.3%	-2.0%	+0.6%	+2.8%	-1.5%	+3.4%	+2.9%	+5.3%	+4.9%	+6.3%	+8.0%	+7.5%	+6.2%	+6.4%

WW Orphan Drug Market CAGR 18-24 +11.3%
WW Non-Orphan Drug Market CAGR 18-24 +5.3%
WW Prescription (Rx) Excluding Generics CAGR 18-24 +6.5%

Note: Industry sales based on Top 500 pharmaceutical and biotech companies.

Sales to 2016 based on company reported sales data. Sales for 2017 based on available company reported sales data. Sales forecasts to 2024 based on a consensus of leading equity analysts' estimates for company product sales and segmental sales.

All sales analysis based on EvaluatePharma®'s 'Orphan Drugs' sub-set of products, as defined in the Overview section.

The US Food and Drug Administration (FDA) is working alongside the NIH to strengthen efforts to deliver the results of the research and development of rare disease treatments to the market and ultimately to the patient. Almost half of those affected by rare diseases are children and are responsible for 35 percent of deaths in the first year of life (Global Genes, 2018). With minimal research and few subject matter experts, oftentimes little is documented for scientists to draw information from when developing and scaling up an orphan designation product formulation.

"The FDA Office of Orphan Products Development (OOPD) mission is to advance the evaluation and development of products (drugs, biologics, devices, or medical foods) that demonstrate promise for the diagnosis and/or treatment of rare diseases or conditions. In fulfilling that task, OOPD evaluates

scientific and clinical data submissions from sponsors to identify and designate products as promising for rare diseases and to further advance scientific development of such promising medical products. The office also works on rare disease issues with the medical and research communities, professional organizations, academia, governmental agencies, industry, and rare disease patient groups (FDA, 2018)."

Formulations

Designing an orphan drug formulation is typically limited by the number of resources available from the sponsor. Special attention is given to the role of precise concepts and methods in experiments to generate the necessary data without redundancy or waste, yet thorough enough to be robust. Oftentimes a small budget is set so the development process must be efficient and cost-effective. The amount of available active pharmaceutical ingredient, or API, is often very limited, so once again the formulation must be developed using minimal numbers of experimental batches at small scale. Timelines tend to be condensed as well for orphan drugs. The formulation development often needs to proceed rapidly to meet the needed timelines and financial restrictions of the client.

Working with APIs that have unfriendly physical and chemical properties is challenging especially when time, financial resources, and API availability are often in short supply. The various problems that may be encountered with the API in orphan drugs are similar to those often encountered in non-orphan drugs such as stability problems, poor solubility, poor flow, and compression tablet properties. However, the problems and obstacles have to be solved quickly in orphan drugs without exhausting the supply of API and the innovator, researcher, or company's financial resources. It is crucial to have a knowledgeable formulation staff that has extensive experience in solving the various problems that arise from difficult API properties. It is also crucial for developers to understand the value of allowing formulations enough time for early development work to support a higher chance of success. It is important to resist the temptation to take the easiest, quickest path that could lead to problems later on.

Late stage development and scale up can be problematic due to the limited experimentation and development required by the narrow window of time and the lack of early-stage resources for upfront development. The strategy for early-stage development process must include a robust formulation and process to minimize surprises at the later stage of development. Problems solved early in the development phases is much easier than later in development.

Regulatory

When reviewing rare disease designations one must also consider FDA's designation of breakthrough therapies: drugs intended to treat a serious condition when preliminary clinical data shows that the drug may demonstrate significant improvement over available treatments. Sixty percent of the 87 breakthrough therapy drugs approved since 2013 are indicated for rare diseases. The FDA grants priority review to drugs that treat a serious condition.

The number of orphan drug approvals has increased in recent years as a result of novel agents and new

indications. The majority of orphan drug products were initially approved to treat rare diseases and do not see growth in the non-rare sector. Approximately 12 percent of drug products were initially approved for a non-orphan designation and subsequently approved for orphan status. Since 1983, over 600 drugs and biologics have been developed and marketed for rare diseases. In contrast, between 1973 and 1983 there were fewer than ten products advanced for rare indications.

A sponsor seeking orphan designation for a drug must submit a request for designation to OOPD with the information required in 21 CFR 316.20 and 316.21. Each designation request must stand on its own merit. Sponsors requesting designation of the same drug for the same rare disease or condition as a previously designated product must submit their own data and information in support of their designation request. The granting of an orphan designation request does not alter the standard regulatory requirements and process for obtaining marketing approval. Safety and efficacy of a drug must be established through adequate and well-controlled studies.

The agency realizes that some aspects of the drug development process are not feasible for rare diseases. Therefore some flexibility is granted in the application of regulations when discussing orphan drugs. However, there are several aspects of drug development that can impact the process potentially leading to more efficient development and more productive meetings with the FDA:

- Adequate description and understanding of the disease's natural history– a natural history study can provide information about the disease, guide the clinical studies, and aid the designing of an efficient drug development program.

- Proficient understanding of the pathophysiology of the disease and the drug's proposed mechanism of action is a valuable channel to assess drug development. Among other things this information can be used to define study endpoints, determine when to treat patients as the disease progresses, and identify new biomarkers.

- Nonclinical pharmacotoxicology considerations for the proposed clinical investigation or investigations— supporting the safety aspect of the drug and also providing additional information regarding the drug's mechanisms of action. The data obtained will support early-stage clinical study design including the following: selecting the dose level and regimen and route of administration. FDA acknowledges that for most rare diseases an animal disease model does not exist. FDA encourages early Pre-Investigational New Drug (IND) meetings to discuss non-clinical development pathways.

- Reliable endpoints and outcome assessment— for many rare diseases a well-characterized efficacy endpoint relevant to the disease is not available. Assessment tools should be developed or modified early in the process to allow adequate time to develop and evaluate the tools to be used in clinical studies.

- Standards of evidence to establish safety and effectiveness. The requirement that a drug has substantial evidence to have its claimed effect is not waived for orphan drugs. Studies need to be able to "distinguish the effect of a drug from other influences, such as spontaneous changes in the course of a disease, placebo effect or biased observation (FDA, 2018)." Regulations govern the essential elements that determine if a study was adequate and well-controlled. The FDA encourages early and frequent communication throughout the development process to identify appropriate clinical trial designs for the patient population and the disease being studied.

- Drug manufacturing considerations during drug development— Chemistry, Manufacturing, and Controls (CMC) development plans should be discussed openly, frequently, and begin early in the process to decrease developmental or approval delays related to manufacturing. Consideration should be given to changes in manufacturing and whether bridging studies might be required.

On June 29, 2017, the FDA unveiled a strategic plan, known as the Orphan Drug Modernization Plan, to completely eliminate the agency's existing orphan designation backlog and to continue increased timely responses to all new requests for designation with firm deadlines. Dr. Scott Gottlieb commissioner of the FDA, created a blog post on September 12, 2017 in which he stated that review of all orphan drug designation requests older than 120 days was completed on August 28, 2017. He further stated that new policies are being implemented to support meeting 90-day review timelines to prevent backlogs. The article also cited several incentives that go along with orphan designation:

- Tax credits of 50 percent for expenses incurred during clinical research and testing

- Waive prescription drug user fees unless an indication for a non-rare disease or condition is designated

- FDA grants seven years of marketing exclusivity upon approval

The blog post also noted that some sponsors are using orphan drug designations as a way to circumvent other public health goals established by Congress. The FDA will issue guidance documents and other policies to address these issues with sponsors adhering to the appropriate regulations.

Case Study

Alcami was faced with a scenario where a client had a project that needed full development and product readiness with an extremely short supply of the API. The scale up batch was small because of the low volume of product demands of their orphan drug. Alcami supported this product with supply constraints, and successfully developed a capsule formulation for two dosage strengths. The formulations group performed studies at a micro-laboratory scale using a scientifically based approach

to identify a lead prototype. The results provided a formulation amenable to two dosage strengths by applying a proportional dosing weight method.

Taking into consideration that small batches present a challenge in proving robustness of the processing equipment, the Alcami project team in collaboration with client team members prepared a failure mode, effects, and criticality analysis (FMECA) of the formulation and process. The team was able to identify and prioritize studies that would provide necessary product and process understanding needed to develop a control strategy— securing reproducibility of the product and meeting its intended safety, efficacy, stability, and performance profile regardless of the manufacturing scale.

The Quality by Design (QbD) studies were designed concisely to minimize the use of the API and evaluate the critical product parameters that could affect the product quality attributes of the drug product, per FDA's QbD guidance. Currently, the product is in late-stage development with the New Drug Application (NDA) filing expected in the fourth quarter of 2018.

About Alcami

Alcami's formulations team has experience in developing a vast number of compounds in various oral solid dosage forms as well as parenteral dosage forms– giving insight into developing formulations quickly, with a high chance of success with minimal experimentation. The manufacturing areas also have a broad range of experience in providing clinical supply materials over a number of years at the pilot scale— fitting nicely with the size of orphan drug development and manufacture.

Alcami has the facilities, equipment, flexibility, and expertise to manufacture the customized small and moderate-sized batches required for orphan drugs— supporting client projects in over 35 countries around the world. All of Alcami's facilities are in good standing with all regulatory authorities including DEA, EPA, OSHA, with successful regulatory inspections from the FDA, TGA, PMDA, MHRA, Health Canada, MPA, IMB, and more. Our experts provide guidance on the latest industry guidelines and the best approach tailored to each client's specific needs.

Technical Contributors

Jack James is a 20 year veteran of Alcami's formulation development laboratory primarily developing solid oral dosage forms. Jack has considerable experience in formulating both immediate release and sustained release products with patents granted and pending in both areas. He has worked with a vast number of drug substances and is familiar with a large variety of process and manufacturing procedures. He obtained his Chemistry Degree from the University of California at San Diego.

Dr. Elsie Melsopp serves as the director of the solids formulations group at Alcami in Wilmington, NC. She has a Bachelor of Science in Pharmacy from the University of Puerto Rico and earned her PhD in Pharmaceutical Sciences from the University of Connecticut. She has 25 years of experience in pharmaceutical product development and manufacturing, including oral liquids and solid dosage forms from pre-toxicological development to product validation. She has six scientific publications and is co-inventor of two patents (approval pending).

Andrea Young is the Supervisor of Regulatory Compliance at Alcami. She has over 18 years of experience in the pharmaceutical industry and has spent nine years providing both internal and external support for regulatory related matters. She also has considerable experience in Quality. Andrea has a Bachelor of Science degree in Biology from St. Bonaventure University, and an MBA from the University of North Carolina Wilmington.

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