The Dilemma over Orphan Drugs

By

Lisa Horger

In the United States alone, over 25 million people suffer from one of 6000 rare diseases, known as orphan diseases. Although the number of people affected with orphan diseases is collectively high, individually, the incidence of each disease is low. Since such a small portion of the population is affected with each of these rare diseases, the dedication of funds directed toward the research and development of unique therapies to treat these conditions is severely limited. In the recent past, the pharmaceutical industry in the United States has reported annual profits in the billions. However, these same companies have been reluctant to commit resources to efforts aimed at aiding individuals affected by orphan diseases. As a result, the United States government has enacted various laws and acts designed to encourage these companies, by way of incentives, to perform the needed research. Since the passage of these acts, over one thousand new research medications have been granted orphan drug status by the FDA, with an exciting number of them attaining marketing approval in the United States. While these developments provide encouragement and hope for patients affected by some orphan diseases, there are still thousands of diseases and conditions needing attention or continued research. This topic is not without debate however; there are opponents to the laws and acts as well as an ethical dilemma underlying this issue. Two moral obligations, beneficence and justice, are seen by some to be pulling this issue in two different directions.

There are two definitions of the term "orphan disease"; the first being a rare disease that affects fewer than 200,000 Americans at any given time and the second being a disease often overlooked by the developed nations because of a far lower incidence compared to that of developing countries. The orphan disease may, in fact, be quite common in these less developed countries; however, economic depravation prohibits many affected citizens from paying the high costs associated with new medications designed to treat the disease. Faced with making little or no profit from the development of a new drug, pharmaceutical companies often choose to direct their resources elsewhere. This second group of diseases, also known as “neglected diseases”, will not be addressed further in this paper. Orphan diseases which affect fewer than 200,000 Americans are often neglected by drug companies for a similar reason; the companies cannot expect to make a profit on a drug solely designed for such a small population. In the early 1980s, patients and families of patients suffering from these diseases lobbied the United States government for help. These groups helped form and pass the Orphan Drug Act of 1983, as well as established a unique non-profit organization composed of various voluntary health organizations known as
NORD (National Organization for Rare Diseases.) Today, this federation is dedicated to helping people with rare orphan diseases and assisting the organizations that serve them. NORD is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and service.

In the past two decades, NORD has been an instrumental advocate of increased funding for rare-disease research from both the United States government and the pharmaceutical industry. Recent examples of NORD's contributions include advocacy for the passage of another piece of legislature, the Rare Disease Act of 2002, as well as actions leading to the May 2006 announcement by the National Institutes of Health (NIH) of the launch of the first set of clinical studies in its Rare Diseases Clinical Research Network (RDCRN). The RDCRN has been granted five years of funding, totaling $71 million, and is coordinated primarily by two NIH components, the Office of Rare Diseases (ORD) and the National Center for Research Resources (NCRR). This network has established data collection standards for all of the research projects and will allow the collected data to be publicly available so as to aid with future research in the field.

The 1983 Orphan Drug Act was the first piece of United States legislature that made pharmaceutical companies consider committing time, resources, and money to research for these rare diseases. The definition of orphan disease used by the Food and Drug Administration in this act is that it "affects less than 200,000 persons in the United States, or affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug." In exchange for researching and developing treatments for orphan diseases, the Orphan Drug Act provided companies with incentives such as market exclusivity, or a guaranteed period of time without competition beyond the time limits established by regular patent laws to recoup financial investments and earn profits, research grants for small companies with limited resources to cover at least some of the costs of clinical trials, as well as tax credits for big companies to reduce their investment in clinical research.

Although the Orphan Drug Act of 1983 had been very successful and effective at encouraging research, it was felt in 2002 that rare diseases and disorders deserved greater emphasis in the biomedical research field. While Congress granted the NIH substantial increases in funding for research, no appreciable monetary increases were seen in the NIH subsection pertaining to orphan diseases/drugs. The Rare Disease Act of 2002 made an amendment to add the Office of Rare Diseases at the National Institutes of Health. This office is now responsible for acting as the voice and advocate for patients with orphan diseases; encouraging improvements in the field of rare disease research.

Since the passage of the Orphan Drug Act in the United States, several other countries have followed suit and enacted similar legislature. Japan wrote its own Orphan Drug Act in 1993, followed by Australia's Orphan Drug Program in 1997.
The Australian program allows the Australian Therapeutic Goods Administration to use data and information from the United States FDA’s orphan drugs research studies as part of the Australian evaluation process in order to provide its citizens with faster results. As of 2001 the European Union also developed a similar program, administered by the Committee on Orphan Medicinal Products of the European Medicines Agency.\(^7\)

In the 23 years since the Orphan Drug Act went into effect in the United States, there have been over 1100 different orphan drug designations granted by the Office of Orphan Products Development and over 250 orphan drugs have been brought to market. In comparison, during the decade prior to 1983, less than ten of these medications were developed. The implementation of this legislation has provided an obvious incentive to perform much needed rare disease research.\(^1\) An example of such approvals include temozolomide (Temodar), an antineoplastic agent by Schering Corporation that was granted orphan drug status in 1998 and is approved for refractory anaplastic astrocytoma, a type of brain tumor.\(^8\) Another disease state that has seen a number of orphan drug approvals is multiple myeloma, a cancer of the bone marrow resulting in overproduction and improper function of plasma cells affecting approximately 50,000 people in the United States currently. The disease mechanism of multiple myeloma is currently unknown and no cure is available; however, treatments can suppress the disease into temporary remission. One of the newest medications approved as an orphan drug for multiple myeloma is lenalidomide (Revlimid), an immunomodulatory drug, manufactured by Celgene Corporation. It is similar to thalidomide but more potent and with a different side effect profile. The medication has several mechanisms of action; including, enhanced activation of T-cells and natural killer cells, which help kill the cancer cells, and inhibition of inflammatory cytokines such as tumor necrosis factor-alpha and interleukin 1-beta.\(^9\)

One of the most exciting and progressive areas in orphan drug research deals with enzyme replacement therapies (ERT) for various genetic diseases where the patient is either completely deficient for an enzyme or lacking the ability to produce sufficient amounts of the enzyme. One of the diseases for which ERT has been produced is Fabry disease. It is an inherited disorder caused by the deficiency of alpha-galactosidase A, which is needed to break down a glycolipid in the body, globotriaosylceramide. Without alpha-galactosidase A, globotriaosylceramide accumulates in cells throughout the body, leading to renal damage and failure, heart problems, stroke, and bouts of intense burning or tingling pain, usually in the hands or feet. In 2003, Genzyme Corporation was granted orphan drug status for an ERT known as Fabrazyme (agalsidase beta). This drug is not a cure for the disease, as it cannot correct the genetic defect. It is intended to replace the missing enzyme in patients and can reduce globotriaosylceramide in certain cells in the body, thus reducing signs, symptoms, and morbidities associated with Fabry.\(^10\) The following is an account of a mother and son who were diagnosed with the disease at the same time and how enzyme replacement therapy has improved their quality of life.

“Like any mother Karen Hedinger looks forward to seeing her two children, Nicole and Daniel, grow up, go to college and start a career. Those simple joys
seemed to be out of reach only a few years ago, when Karen and Daniel were both diagnosed with Fabry disease.

At age 11, Daniel was already used to long bouts of excruciating pain in his feet, unexplained high fevers and ringing in his ears. Karen herself had suffered from kidney problems and cardiovascular problems all her life. After years of seeing specialists, both Daniel and Karen finally received the enzyme infusion therapy [Fabrazyme (agalsidase beta)] alleviating the pain, and enabling them to live healthier and happier lives.

Despite his physical disabilities from Fabry which prevented him from participating in physical activities, Daniel learned to play the violin and the viola. Showing talent at an early age, Daniel won an award at the New York Viola Society Competition, and has been granted a full scholarship to the Tanglewood Institute, an internationally-renowned program for young people studying music.

"His talent and determination to overcome the pain and handle the extensive hospital visits and treatments give me the inspiration to go on, and also strengthens the knowledge that life is worth living," Karen said. "I have been blessed with a great family and support system, and hopefully our message of hope will inspire someone else dealing with Fabry disease."

Karen now looks forward to traveling more with her husband after he retires. Both have tried to raise awareness about the disease by helping other patients cope with their doubts and fears and steering them towards getting the treatment."

Another successful ERT is used to treat Gaucher disease Type 1, an inherited lipid storage disorder most commonly seen in the Ashkenazi Jewish population. This condition is caused by a deficiency in glucocerebrosidase. This enzyme is responsible for breaking down glucocerebroside, a fatty substance that accumulates in the macrophage cells in body, especially in the spleen, liver, kidneys, and bone marrow. Several modalities to ease the signs and symptoms of these patients were used in the past and may still be needed, including pain medications, surgery for bone and joint problems, and possibly removal of the spleen. However, using the orphan ERT imiglucerase injection (Cerezyme), which was developed in 1994, the progression of the disease can be slowed or even reversed. Cerezyme mimics the action of the naturally occurring enzyme glucocerebrosidase and breaks down the glucocerebrosides that have accumulated in cells. Imiglucerase treatment is a life long therapy because it is not a cure for the genetic defect. This ERT is only effective in treating the systemic or non-central nervous system complications of Gaucher disease, known as the Type 1. Type I Gaucher can affect individuals of any age. Gaucher disease Types 2 and 3 have involvement of the central nervous system and the symptoms generally appear in infancy or early childhood. These patients can present with abnormal eye movements, unsteadiness, swallowing problems, choking or laryngeal spasms (often referred to as breath-holding spells) and seizures, as well as systemic side effects such as hernias,
and stunted growth. These forms of the disease are significantly more debilitating, and in many cases, lead to death within the early years of life. Unfortunately, the ERT Cerezyme has difficulty crossing the blood-brain barrier; therefore, in the Type 2 and Type 3 forms of Gaucher disease, it has had limited affect on the central nervous system, or brain involvement, thus not proving to be beneficial to these patients.\textsuperscript{13}

The most recent ERT approved in the United States is idursulfase (Elaprase). It was developed by Transkaryotic Therapies and sold to Shire Human Genetic Therapies, Inc. It was FDA approved as an orphan drug in July 2006 for Hunter syndrome or Mucopolysaccharidosis II (MPS II), a serious genetic lysosomal storage disorder affecting approximately 2000 individuals worldwide, most of whom are males. Idursulfase is a replacement enzyme for the lysosomal enzyme iduronate-2-sulfatase, which is responsible for cleaving two glycosaminoglycans (complex sugars) in the body. In patients with Hunter syndrome, this enzyme is missing and thus, the patients have accumulation of glycosaminoglycans in various cells, leading to cellular engorgement, enlarged and distended internal organs, tissue destruction, joint stiffness and limited mobility. Accumulation of glycosaminoglycans in the brain leads to delayed development with subsequent mental retardation in many of these patients.\textsuperscript{14} While this medication looks very promising for patients diagnosed with Hunter syndrome, especially when diagnosed early in life, one drawback of the medication is the expense. It is estimated to approximately $300,000 per patient, per year for the therapy.\textsuperscript{15}

Obviously enzyme replacement therapy has proved invaluable for patients afflicted with one of the several disease states mentioned above. Without the implementation of the Orphan Drug Act of 1983, it is unlikely that the pharmaceutical companies would have devoted as much time and money into researching and developing these treatments. There are however thousands of other disease states that still need research to find treatments. For example, besides Hunter syndrome, there are six other major forms of Mucopolysaccharidoses or lysosomal storage disorders. Each of these diseases have various subsects (14 in total) and each is due to a deficiency of one specific enzyme. However, only two of these diseases have any sort of ERT available (Aldurazyme approved in 2003 for MPS I or Hurler syndrome and Naglazyme approved in 2005 for MPS VI or Maroteaux-Lamy syndrome).\textsuperscript{16} Without any sort of treatment available, patients with these disorders may suffer from neurological complications such as pain and impaired motor function, have profound retardation, experience developmental delay, have severe behavioral problems, and have hearing and vision loss. With some types of MPS, communicating hydrocephalus occurs, in which the normal circulation of cerebrospinal fluid becomes blocked over time and causes increased pressure inside the head. This condition often requires surgical insertion of a shunt into the brain to drain fluid. Physical symptoms generally include coarse facial features, such as a flat nasal bridge, thick lips, and enlarged mouth and tongue, as well as short stature with a disproportionately short trunk, thickened skin, enlarged organs, hernias, and excessive body hair growth. Patients often have short, claw-like hands, progressive joint stiffness, and carpal tunnel syndrome which limits their mobility.\textsuperscript{17}
Phenylketonuria (PKU) is another orphan disease which currently has no treatment, but for which several therapeutic approaches are being researched at this time. PKU is an inborn error of metabolism resulting from a deficiency of phenylalanine hydroxylase. This enzyme is responsible for the utilization and breakdown of the amino acid phenylalanine into another amino acid, tyrosine. Without this enzyme, phenylalanine and its metabolic byproducts from other enzyme routes accumulate in the blood and body tissues. In a normal patient, serum levels of phenylalanine are around 1 mg/dl, while in individuals with PKU, levels are usually greater than 30 mg/dl and can reach over 80 mg/dl when not treated. When this occurs it causes mental retardation and brain damage, mental illness, seizures, tremors, and cognitive problems.

All neonates in developed nations undergo newborn screening for this genetic disorder because infants with PKU appear normal at birth, though many have blue or green eyes and fairer hair and skin than other family members. These physical features are due to low levels of tyrosine, which leads to lowered production of the pigment melanin. The incidence of PKU is about 1 in 15,000 births in Caucasians and Asians, with the highest prevalence in Ireland, where 1 in 4,500 births are affected. The incidence in African Americans is far lower.

This disease is treated by restricting dietary intake of phenylalanine. If infants are not treated in this manner and are allowed to ingest breast milk or regular formula, they will develop symptoms including vomiting, irritability, an eczema-like rash, and a mousy odor of their urine. If the ingestion of phenylalanine continues over a longer period of time, they will develop the signs of nervous system function problems mentioned above, such as mental retardation, seizures, and microcephaly, as well as prominent cheek and upper jaw bones with widely spaced teeth, poorly developed tooth enamel, and decreased body growth.

Phenylalanine is found in almost every natural food which makes dietary restriction of this amino acid very challenging and many patients have an extremely difficult time adhering to the diet while maintaining a normal life. Foods that contain high quantities of phenylalanine and must be avoided include: dairy products (including breast milk), meat, fish, poultry, eggs, nuts, dried beans, and peas. Also diet foods, soft drinks, candies, and gum often contain the artificial sweetener aspartame, which is metabolized into phenylalanine and thus must be avoided. Foods such as cereals, starches, fruits, vegetables, and milk substitutes are somewhat lower in phenylalanine and can be consumed in carefully measured and monitored amounts. The best way for patients to be sure they are not ingesting too much phenylalanine and also receiving enough of the other amino acids, is to limit themselves to commercially available medical foods or supplementary formulas, which are available for all age groups. Unfortunately these supplements and foods are very expensive and often unpalatable.

Since there are no ERTs available for PKU yet, recommendations for treatment of adolescents and adults vary. Some recommendations strongly support strict dietary therapy for life, while others are less rigid and suggest that relaxation of the phenylalanine diet after childhood may not be as deleterious as previously thought.
However, a growing number of studies are reporting that increases in dietary phenylalanine even later in life leads to reduced attention span, slow information-processing abilities and motor reaction time, increased muscle tone and tremor, lowered bone mineral content, and mental health disorders. A study involving 125 Irish children with PKU showed that diet relaxation after the age of eight demonstrated a significant reduction in verbal and overall IQ between the ages of eight and fourteen as well as further decreases between the ages of eight and eighteen. The data for this study suggests that continued strict dietary control is very important to maintaining the level of mental functioning, especially in patients with very low residual or no phenylalanine hydroxylase activity. According to the NIH consensus panel that met in 2002 to review information on PKU, “Metabolic control is necessary across the lifespan of individuals with PKU.”

One of the main dilemmas faced by adult females with PKU is pregnancy. Many adults choose not to follow the strictly regimented phenylalanine-restricted diet either because of cost or the limited foods they can consume. While this may cause some health issues for the patient herself, as mentioned above, it can cause very serious and life-threatening effects to the fetus. High levels of phenylalanine in the uterus are toxic and teratogenic; therefore, it is strongly recommended that women with PKU use reliable methods of contraception to prevent unplanned pregnancies. Any woman with PKU who wants to become pregnant needs to comply with the restricted diet for at least several months prior to conception and maintain vigilance throughout the entire pregnancy. She should have phenylalanine levels drawn in the months prior and during pregnancy and levels should be no higher than the range of 2-6 mg/dl. These women also need to make sure that they are receiving enough of the other amino acids by way of supplements.

If the levels of phenylalanine are not controlled and a woman conceives, the risks of the fetus spontaneously aborting, having congenital heart disease, intrauterine and postnatal growth retardation, microcephaly, or mental retardation are high. The Maternal PKU Collaborative Study showed that even with maternal plasma phenylalanine levels in the range of 2-6 mg/dl (the recommended levels for PKU women), 6% of infants are born with microcephaly and 4% with postnatal growth retardation. If maternal plasma phenylalanine levels are at 15 mg/dl or higher, the risk is 85% for microcephaly, 51% for postnatal growth retardation, and 26% for intrauterine growth retardation. The risks of these abnormalities is both dose dependent and time dependent; therefore, optimal phenylalanine concentrations must be strictly maintained throughout the whole pregnancy to reduce the risk of each individual abnormality.

In the case of PKU, enzyme replacement therapy could be extremely beneficial to the patients afflicted with this disease. Most patients with PKU have some degree of mental deterioration by the time they reach adulthood, which is a risk factor for unprotected sexual activity and hence, unplanned pregnancies. This also acts as a risk factor for noncompliance with the recommended restricted diet. These elements lead to many infants born to women with PKU being affected with severe birth defects. If an ERT was available to be used as a lifelong treatment, a number of these birth defects
could potentially be prevented. Additionally, an ERT medication would be a potential safeguard for children with this disease as well. As stated above, most people with PKU experience some degree of mental deterioration by the time they reach adulthood due to occasional dietary noncompliance events. Parents of children with PKU face the challenge of preventing their school age children from doing things like chewing a piece of gum at school or eating prohibited food at a friend’s house. During childhood, each ingestion of phenylalanine furthers the patient’s mental deterioration; therefore an ERT could be protective in these cases of accidental minimal ingestion.

As previously mentioned, there are several avenues of therapy currently being researched for the treatment of PKU. One of the therapies involves using high quantities of certain other amino acids, which are categorized as large neutral amino acids (phenylalanine is one of these) to compete and effectively ‘block’ the common carrier molecule that transports these molecules across the blood-brain barrier. This would then block phenylalanine from entering the brain, even though high levels may be present in the serum. This would benefit noncompliant adults by helping to protect the brain from the acute toxic effects of phenylalanine.\textsuperscript{23,24} Another therapy involves supplementing 6R-BH4 an essential enzyme co-factor, that works with phenylalanine hydroxylase to metabolize phenylalanine. It is hoped that this co-factor will enhance the activity of the existing phenylalanine hydroxylase enzyme, enabling it to metabolize phenylalanine more efficiently. BioMarin Pharmaceuticals has already developed such a product called Phenoptin (sapropterin dihydrochloride), which is a synthetic form of 6R-BH4. It is an oral agent and it currently has been given orphan drug status in the United States and European Union and has been granted Fast Track status in the United States. A third approach to treatment of this disease involves enzyme replacement with phenylalanine ammonia lyase, an enzyme that is able to degrade phenylalanine in the gastrointestinal tract before it is absorbed into the body. BioMarin Pharmaceuticals is also currently investigating this with product called Phenylase (phenylalanine ammonia lyase), which has received orphan drug status in the United States. Currently, both oral and subcutaneous routes of administration are being researched in preclinical models.\textsuperscript{22}

Anytime a certain subset of a population receives some sort of benefit or different treatment than the rest, whether it is a group of patients, or a group of pharmaceutical companies, it is bound to draw hostility and arguments from some. The Orphan Drug Act in the United States as well the similar legislation in the European Union has definitely sparked debate among certain groups. For example, opponents of these laws state that the number of drugs the Orphan Drug Act claims to have helped create is vastly inflated and misleading because many of these medications would have been developed and produced without any assistance.\textsuperscript{27} Another argument is that some of the diseases classified as ‘orphan diseases’ should not be considered rare, such as various types of cancer. This is due to cancer itself being a common disease and the fact that many of the medications designed for one type of cancer can be used to treat other types as well.\textsuperscript{27} While these appear to be rather superficial arguments, there are several others that do have a valid basis.
A recurring issue is the high price of many orphan drugs in the United States. Many believe this is due to the provision of seven years of market exclusivity for these medications; effectively legalized monopolies in the treatment of these specific diseases.\textsuperscript{26,27} However, the rebuttal from pharmaceutical companies is that since the population using these medications is so small, the cost of development and research cannot be reasonably spread among the users, and that this, not market exclusivity, is the reason for such high costs.\textsuperscript{26} Whatever the reason, many enzyme replacement therapies cost approximately $300,000 per year and are required as lifelong therapy. Most patients pay with medical insurance or Medicare, and some companies, such as Genzyme will provide their drug free to those who can't afford it. However, consider the case where a patient’s insurance company will cover 80% of the medication. That family is still responsible for paying $60,000 per year, which is unfeasible for most.\textsuperscript{1}

A related perceived abuse of the Orphan Drug Act involves some of the extraordinarily profitable orphan drugs that have been developed. Recognizing that one of the defining inclusion criteria for being an orphan drug was that “there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will recovered from sales in the United States of such drug,”\textsuperscript{4} drugs such as Retrovir (zidovudine, AZT) and Epogen (epoetin alfa), which have generated billions of dollars in sales and are listed on top-selling drug lists, seem to contradict the definition and have caused many to rethink the policies at hand.\textsuperscript{26,27} An amendment was passed by Congress in 1990 that would have reviewed the sales records of orphan drugs and if it was determined in the fifth year of marketing that the drug was no longer a “drug of limited commercial value,” it would lose the remaining two years of marketing exclusivity.\textsuperscript{5} Pharmaceutical lobby groups have managed to block this change in the United States so far with a veto of the amendment by President Bush; however, the European Union’s Orphan Drug Act has been amended to included such a policy. In normal situations, orphan drugs in Europe receive ten years of market exclusivity, but if any member country requests a review of sales in the sixth year, and the medication is found to be sufficiently profitable, the remaining four years of exclusivity can be withdrawn.\textsuperscript{5,26} This amendment obviously angers many companies since the promise of ten years of market exclusivity was the major incentive for undertaking the research in the first place. The drug companies make a point that by allowing companies to make a considerable profit on some products, it will act as an incentive itself for other companies to partake in this sort of research.\textsuperscript{26}

When the funding and provision of incentives for orphan drug research is analyzed by way of ranking which normative principles apply, two are relevant: distributive justice and beneficence. There are conflicts between these two principles, as well as within justice itself, depending on if justice is approached from a utilitarian point of view or a deontological point of view. Because each orphan disease only afflicts a miniscule portion of the entire population, from a utilitarian perspective, these diseases should only receive a miniscule portion of the total spending on medical research and development. Allocating large amounts of money, time, and resources to these diseases would be considered unethical since it is not helping the majority of
society and may actually even hinder advancements for the larger group. From a deontological or rights based perspective, most industrialized countries have implemented policies that “assure everyone have access to needed services regardless of ability to pay,” and this is often interpreted as “a legal right to health care.”\textsuperscript{2} While this may apply in other countries, such as Italy, where the right to health care is granted in their constitution, this does not apply in the United States, where no such laws exist. In these other countries, this approach would seem to encourage the aiding of research for all subsets of the population, including orphan diseases. Also supporting the case for orphan drug research would be the beneficence, since this research is taking positive steps to help individuals.\textsuperscript{2}

While a tremendous amount of progress has been made in the rare disease field, millions of people in the United States alone are still living with diseases for which no one can provide answers or treatment. For most orphan diseases, there are substantial delays in diagnosis due to a lack of relevant information concerning the disease and difficulty in finding a specialized physician. This leads to many patients living their life without ever having a definitive diagnosis. For the patients who are diagnosed; unfortunately, most cannot be treated because no medicines, therapies, or evidence for clinical practice exist yet. Fortunately, through continued legislation such as the Orphan Drug Act and the work of advocacy groups such as NORD, these patients can have some hope that a treatment will be developed for their disease someday soon.
References

