The Orphan Drug Act of 1983

There are more than 5,000 rare disorders (a point prevalence of 200,000 patients or less in the United States) that collectively afflict more than 20 million Americans. This means that 1 out of every 14 people in the United States has a rare disorder. While this represents a sizable collective market, unfortunately the development of pharmaceutical products to treat each of these individual disorders has not been a major focus of pharmaceutical companies. Driven in large part by the activities of Abbey Myers and the National Organization of Rare Disorders (NORD), the Orphan Drug Act was signed into law on January 4, 1983. This legislation gives financial incentives and assistance to pharmaceutical and biotech companies engaged in orphan drug research and development. Since the Orphan Drug Act was passed, approximately 200 orphan drugs and biological products have been brought to the market. The success of this legislation is due in large part to the Orphan Drug Act’s creation of the Office of Orphan Products Development. This office, headed by Dr. Marlene Haffner, works as an official ombudsman for orphan drug products.

The intent of the Orphan Drug Act is to stimulate the research, development, and approval of products that treat rare diseases. This mission is accomplished through several mechanisms:

· Sponsors are granted seven years of marketing exclusivity after approval of its orphan drug product

· Sponsors also are granted tax incentives for clinical research

· The FDA’s Office of Orphan Products Development coordinates research study design assistance for sponsors of drugs for rare diseases. This assures that products are not delayed due to inadequate study design. (Note: Orphan drugs are held to the same high standards as are other drugs)

· Grant funding is available to defray costs of qualified clinical testing expenses incurred in connection with the development of orphan products.

In the last decade a merger trend emerged among the large global pharmaceutical companies consolidating such companies as Sandoz and CIBA and Pharmacia and UpJohn. These large global companies are driven by the exigencies of global market share and blockbuster products. One effect of these mergers has been the raising of the requisite return on investment and the minimum sales required justifying product development. As a result orphan products are becoming even less attractive to big pharmaceutical companies. However, small to medium sized biotech and biopharmaceutical companies are becoming more and more active in researching and developing orphan products. The incentives offered by the Orphan Drug Act and the availability of grants provide these companies with the resources and assistance necessary to support orphan research and development activities. Companies such as Orphan Pharmaceuticals, U.S.A., Inc., Genzyme, Sigma Tau, SciClone, and Transkaryotic Therapies are making major corporate commitments to meeting the unmet medical needs of those afflicted with orphan diseases.

The existence of the Orphan Drug Act, NORD, and the FDA Office of Orphan Products Development will make developing and distributing hPTH (1-34) not only feasible but their contributions will help obtain a more rapid approval. The financial incentives and assistance available through the Orphan Drug Act will significantly reduce the price of these product as compared to similar drugs not enjoying orphan designation.

Synthetic Human Parathyroid Hormone (1-34)

The FDA’s Office of Orphan Products Development works closely with the National Institutes of Health’s Office of Rare Diseases headed by Dr. Steven Groft, to support NIH research and development of orphan products. Small Business Innovation Research Grants are also available through various sections of the NIH such as the National Institute of Child Health and Human Development (NICHD) for extramural research and development. The NIH plays an important role in developing orphan products. One example of this is the NICHD’s Developmental Endocrinology Branch’s sponsorship of the work of Dr. Karen Winer in successfully studying the potential of Synthetic Human Parathyroid Hormone (1-34) in maintaining normal serum calcium without hypercalciuria in patients with Hypoparathyroidism.
Dr. Winer extended her research to include a study of an optimal dosing regimen as well as longer-term efficacy of the therapy on bone density and renal complications. This study is ongoing.

Dr. Winer has written, “Hypoparathyroidism is one of the hormonal insufficiency states that is usually not treated by replacing the missing hormone. Current therapy for Hypoparathyroidism, with Calcitriol or other vitamin D analogs normalizes serum calcium but does not have the renal calcium-retaining effect needed to normalize urine calcium levels. As a result, patients treated with vitamin D therapy have a tendency to develop hypercalciuria – a condition that may lead to nephrocalcinosis, nephrolithiasis or renal insufficiency.” These analogs often have other side effects such as weakness, dry mouth, and depression. The present hopeful proposition is that Synthetic Human Parathyroid Hormone (1-34) will be more physiological and better tolerated than the vitamin D analogs. Dr. Winer’s research currently supports this proposition.

_Exactly what is meant by Synthetic Human Parathyroid Hormone (1-34)?_ The parathyroid hormone produced in humans is a peptide or chain of amino acids that forms a protein or macromolecule of amino acids. Parathyroid hormone is a protein that exists normally as an eighty-four amino acid peptide [hPTH (1-84)] in humans. The active end of the peptide is actually the first 34 amino acids in the peptide chain.

Attempts to produce hPTH (1-81) in genetically modified yeast (Saccharomyces cerevisiae) have met with limited success due to a break down of the amino chain forming the peptide during the process of extracting the hormone from the yeast. This results in a less pure form of the hormone bearing potential harmful impurities. Therefore, the logical method for manufacturing a pharmaceutical grade product is to manufacture it synthetically by linking the amino acids, one after the other until the chain of 34 amino acids forms the active site of the human parathyroid hormone. The manufacturing process for hPTH (1-34) is a slow, tedious process requiring frequent quality control measures such as high performance liquid chromatography assessments at each step along the way to assure purity. The process is both time consuming and expensive. The finished, highly purified peptide product is lyophilized (freeze-dried) and ready to be reconstituted in a sterile 5% mannitol solution for subcutaneous injection.

_Researching and developing a product such as hPTH (1-34) would be cost prohibitive for a small to medium sized biopharmaceutical company. The cost would certainly exceed the capabilities of a small company like Orphan Pharmaceuticals, U.S.A., Inc. However, Orphan Pharmaceuticals, U.S.A., Inc. does have the regulatory, distribution and marketing expertise to complete the clinical work, execute the regulatory processes, and obtain third-party payer reimbursement. Clearly it will require a joint effort to provide the hPTH (1-34) in a timely, efficient, and cost effective manner to those patients in need of the product._

Orphan Pharmaceuticals U.S.A., Inc.

The story of Orphan Pharmaceuticals, U.S.A., Inc. (OPUS) is the story of hopes vs. realities and the filling of the very specific and special medical needs of a small population of adults and children seeking life preserving therapeutics for rare diseases. Many of these diseases are not immediately recognizable to even the most astute physicians, thus the role of OPUS, Inc must include creating awareness of such diseases and their diagnosis. Unfortunately, the realities are that all too few companies are willing to invest in low volume, low return research programs. Thus the needs of the few are lost to corporate profit/loss statements. OPUS on the other hand, is a company built on the hope and premise of providing options where there are no options, for providing a therapy where there is no therapy, for looking beyond the financial bottom line to the bottom line of the quality of life of those in need.

Orphan Pharmaceuticals, U.S.A., Inc. is a well established company founded in 1991 by Milton H. Ellis, W. Darrell Moseley, and Lars-Uno Larsson and is one of the key companies in a global consortium of Orphan Pharmaceutical companies throughout the United States, Europe, Japan, Australia, and Canada. Strategically located in Nashville, Tennessee the company is active throughout North and South America. Orphan Pharmaceuticals, U.S.A., Inc. mission is to provide patients, healthcare personnel, and the pharmaceutical industry with an independent global network specializing in the marketing and distribution of Orphan Products for the treatment of rare disorders. Globally our consortium has a solid track record with multiple licensing agreements, a comprehensive global patient advocacy network, and significant success in drug development and approvals.
OPUS is modeled after their affiliate Swedish Orphan AB a pioneer company formed to market orphan drugs in Scandinavia. Founded in 1988 in Stockholm, Sweden by Lars-Uno Larsson, a former executive of a large multinational pharmaceutical company, Swedish Orphan AB has established a very credible reputation for itself and our companies throughout the world. In fact, for his efforts in the area of Orphan Products Mr. Larsson was recently recognized by the Board of National Organization of Rare Disorders who presented him with the 1998 NORD International Humanitarian Award. On May 8, 2000 Milton Ellis was similarly honored by NORD for his work in developing the first ever treatment, Orfadin, for Hereditary Tyrosinemia Type I, an inborn error in liver metabolism that is usually fatal within one year of birth unless a suitable liver transplant can be found. There are only 40 Hereditary Tyrosinemia patients in the United States and 200 patients worldwide.

Last summer Lars Uno Larsson was contacted by the family of Halla Ruth Halldorsdottir in Iceland desperate to obtain hPTH (1-34) for their child. They informed him that there was a Dr. Karen Winer at the NIH who had an ongoing clinical trial studying hPTH (1-34) and could we seek her out and ask for her help in obtaining the product. After one telephone conversation with Dr. Winer, we were made aware of the needs of many Hypoparathyroidism patients and the potential for hPTH (1-34) to help these patients. This led to a remarkable effort and demonstration of unselfish teamwork as many individuals and groups combined efforts over a busy 12 month span of time to make hPTH (1-34) available, if only on a limited basis.

OPUS first met with Dr. Winer and Dr. Gilman Grave, the chairman of the NICHD and Dr. George Grimes, Head of the NIH Developmental Pharmacy. At this meeting OPUS proposed a plan to get the product made in Sweden to supply the needs of Halla Ruth and other European patients. In addition, OPUS proposed a plan for Orphan Pharmaceuticals U.S.A. Inc. to enter into a formal relationship with the NIH in order to complete the necessary studies and apply for marketing approval. Several meetings and telephone conferences have taken place since that initial meeting.

As for the ongoing effort in the United States, Dr. Winer has incredible data sets and has done a wonderful job in organizing and conducting her studies. She has been supportive of OPUS’ efforts and willing to contribute in every way. Currently, they’re many things ongoing in parallel. We are producing limited amounts of the product in Sweden with the Swedish company. Our regulatory experts are using Dr. Winer’s latest data to prepare a package to present to FDA at meeting that will determine exactly what we must do in addition to Dr. Winer’s studies to get the hPTH (1-34) on the market. An application for Orphan Designation is being filed with the FDA, and a Clinical Research and Development Agreement is being drafted that will be the formal basis of collaboration with the NIH. Manufacturing and formulation issues are being addressed with various companies in an effort to provide the product at a reasonable price.

We expect to make some significant strides this summer, and we will keep everyone updated on the progress. In the interim, it is always helpful for us to hear from patients and their families. The better we understand the problems and unmet medical needs present with this disorder, the better we can work towards addressing these issues. You can learn more about OPUS by going to our Webb site http://www.orphanusa.com and you can contact us through our Webb site or by e-mail at boall918@aol.com. Information on the prevalence of the disorder, key physicians with expertise in the field, and quality of life issues are examples of the kinds of information that would be helpful if shared with OPUS.

In closing there is a great deal of hard work to be done to get hPTH (1-34) approved by the FDA. OPUS has strong allies in the Dr. Winer and the NIH, in Dr. Haffner and the FDA, in Abbey Meyers and NORD, and now in the readership of the Hypoparathyroidism Newsletter. Hypoparathyroidism is a serious disorder for which hPTH (1-34) may prove to be a significant therapeutic advance. OPUS takes its commitment to making hPTH (1-34) available very seriously. This point is driven home to me each time I talk with physicians and patients about this rare disorder. I am often reminded of the words of the Greek poet Aeschylus who wrote “in our sleep, pain which cannot forget falls drop by drop upon the heart until, in our despair, against our will, comes wisdom through the awful grace of God.” It is our hope and prayer that through our shared collective wisdom we can make this product a reality.