KGI to Celebrate Rare Disease Day with Orphan Drug Workshop

Keck Graduate Institute (KGI) will celebrate Rare Disease Day on Feb. 28 by hosting its second annual workshop with the U.S. Food and Drug Administration (FDA) for pharmaceutical and biotech companies and academics to learn how to write and file an Orphan Drug designation application.

Hosted by KGI’s Center for Rare Disease Therapies, the goal of the workshop is to simplify and demystify the application process so more companies and individuals will pursue development of drug therapies and medical devices for people who are suffering from rare diseases. Eighteen applications for rare disease therapies were filed after last year’s workshop.

Rare diseases affect nearly 25 million Americans. No treatment is available for most of the 7,000 identified rare diseases, and for those that can be treated the cost to the patient is often prohibitive.

Dr. Tim Coté, director of the FDA’s Office of Orphan Products Development, will conduct the workshop in which participants will be guided by FDA officers through the application process. Meetings will be conducted in private rooms to maintain confidentiality. Participants will be able to submit their proposals in person to the FDA at the end of the two-day workshop. “This is a highly efficient way to get an application done correctly and into the hands of the FDA,” said Ian Phillips, PhD, KGI’s Norris Professor and director of the Center for Rare Disease Therapies.

The workshop coincides with Rare Disease Day, an international effort to raise awareness about the difficulties of combating rare diseases since, for most patients, drugs and treatments are not available.

The Office of Orphan Products Development offers special incentives to companies to develop these products because there often is little profit in developing a drug for a disease that may afflict a small number of people.
The Orphan Drug Act of 1983 defines a rare or orphan disease as one diagnosed in fewer than 200,000 people in the United States. This may seem like a small number relative to the overall U.S. population, but with more than 7,000 different rare diseases, the numbers add up.

In all, 25 million Americans—nearly 1 out of every 10 people in the country—suffer from a rare disease. Their conditions range from the more familiar to those largely unknown, including:

- Cystic fibrosis, a chronic disease of the lungs and digestive system
- Muscular dystrophy, a progressive muscle disease
- Lupus, a chronic inflammatory disease
- Infantile spasm, an early childhood epilepsy
- Spinal cord degeneration
- Inherited metabolic inclusion disease, a condition that can destroy muscle cells
- Uncommon cancers

Treating Rare Diseases—An Economic Challenge

Bringing a new drug or therapy to market requires a significant investment of time and money. In exchange, companies expect to make a profit. But when no more than 200,000 people need a product, companies lack a financial incentive to pursue drug discovery, development and approval. As a result:

- Research is limited. Many companies have discovered compounds or technologies that might be useful in treating rare diseases but haven’t continued their research because of the limited market for any products they might develop.
- Treatments are few. About 1,800 drugs and other therapies have been identified or approved. Yet only 350 are commercially available today. Despite financial incentives created through the Orphan Drug Act of 1983 to encourage pharmaceutical companies to develop new therapies, patients with most of the 7,000 identified rare diseases remain without any treatment at all.
- Cost is an issue. Even when drugs and other therapies are commercially available, their cost can be high. People who might otherwise access treatment simply can’t afford it.

KGI’s Center for Rare Disease Therapies brings attention to the impact and severity of rare diseases in the United States. The center elevates the need for treatment to a problem of national importance that calls for an effective response.
KGI’s Center for Rare Disease Therapies has received a $100,000 grant from the Kenneth T. and Eileen L. Norris Foundation to continue its mission of encouraging the development of more drug therapies for patients with rare diseases.

The Norris Foundation, which supports programs that advance better health and intellectual enlightenment through education, is a generous and long-time supporter of KGI, providing $2.78 million in grants to the institute since it was founded in 1997.

“We’re extremely grateful to the Norris foundation for their generosity,” said Ian Phillips, PhD, the Norris Professor of Applied Life Sciences and director of the Center for Rare Disease Therapies. “It will help us advance on so many fronts. The Norris Foundation’s support of high quality universities reflects the importance of this award and it increases our national standing.” CRDT has received $567,000 from donors, including the Norris Foundation, PhRMA and Sigma Tau since its inception in 2008. The center also raised funds at its FDA industry workshop in February 2010.

Phillips said the grant will fund:

• Internships for KGI students
• Conferences and workshops
• Interaction with patient advocates and companies specializing in rare disease therapies.
• Writing and publishing position papers
• Helping research developing rare-disease therapis.
Dr. Daniel Darvish is two steps closer to finding a cure for the muscle-wasting rare disorder that is gradually robbing him and his brother of their ability to live healthy and productive lives. Darvish was notified recently that both of the orphan drug designation applications he filed in February 2010 at a workshop hosted by KGI’s Center for Rare Disease Therapies had been approved by the U.S. Food and Drug Administration.

“It’s a significant boost to our efforts, both in terms of fund raising and partnering with pharmaceutical companies specializing in clinical development of orphan drug products,” said Darvish, who suffers from Hereditary Inclusion Body Myopathy, or HIBM. The approval cemented a relationship between the Darvishes and KGI to help determine if the drug therapy that was approved is successful. Ian Phillips, KGI’s Norris Professor of Applied Life Sciences and director of the Center for Rare Disease Therapies, said Professors Jim Osborne and Craig Adams, director and assistant director, respectively, of the KGI Center for Biomarker Research, will be starting a study in hopes of finding a biomarker for HIBM. “If Daniel gets the treatment that was designated by the FDA for an orphan drug, he will need a blood test to see that the treatment is working,” Phillips said. The collaboration between KGI and the Darvishes is mentioned in a video that has been shown at HIBM fundraisers across the nation.

Daniel Darvish and his brother, Babak, are both medical doctors who have HIBM, a progressive and muscle-wasting disorder caused by a mutant gene that impairs the body’s ability to produce sialic acid, a vital sugar implicated in muscle and kidney function. Symptoms of the disease usually begin in a person’s twenties and typically lead to total disability in 10 to 15 years. There are only about 500 known cases worldwide. The Darvishes were both in medical school when their symptoms started. Babak Darvish, Daniel’s younger brother, noticed weakness in his fingers that made it difficult to play his guitar and climb stairs. Soon after, Daniel developed similar symptoms.
In 1997, the Darvishes cofounded Advancement of Research for Myopathies (ARM), a non-profit organization dedicated to raising funds for HIBM research. Several years later, they established HIBM Research Group (HRG), a non-profit molecular laboratory dedicated to advancing HIBM research by producing needed biomaterials. Phillips visited HRG before the February workshop, and “was enormously impressed with the fact that [Daniel Darvish] was researching his own disease and trying to come up with a cure.” Phillips added: “Time is a factor for him. It was a huge spiritual uplift that he came to the workshop, submitted his orphan drug designation applications and both were approved.” During the workshop, officials from the FDA met with patient advocates like Darvish as well as pharmaceutical and biotech company representatives to walk them through the orphan drug product designation application process. The purpose was to promote the development of drug therapies for people who are suffering from rare diseases, which is the core mission of KGI’s Center for Rare Disease Therapies.

When asked what he learned from the workshop, Darvish said, “Contrary to popular rumors, it is possible to do it. All you need is a ‘burning desire,’ good scientific rational and information, and a little bit of funding. Now that we have orphan drug status, we will be able to take advantage of these benefits.” The next step will be to apply to the FDA for an Investigational New Drug (IND) and begin early phase clinical trials. “We hope that the trial will begin in one to three years depending on the outcome of animal toxicology studies that will begin soon,” Darvish said.

By Elaine Regus

MBS Student Helps Pharma Company Gain Orphan Drug Designation

Silviya Meletath, a second-year Master of Bioscience (MBS) student, helped win an Orphan Drug Designation from the U.S. Food and Drug Administration (FDA) for BPT Pharmaceuticals in Irvine for a drug that shows promise in treating Pediatric Multiple Sclerosis.

“Receiving the Orphan Drug Designation from the FDA was a terrific milestone for BPT Pharmaceuticals,” said Lynn Foster, BPT Pharmaceuticals’ CEO. “It’s a validation of our approach and also a big boost for our discussions with investors and potential licensing partners.”

“I give Silviya enormous credit for her persistence and skill because it was not easy. Through her, we have achieved one of the original goals of the Center for Rare Disease Therapies—to help companies develop new treatments for rare diseases,” said Ian Phillips, the center’s director.

Silviya Meletath (MBS ’11)
‘Childhood Alzheimer’s’
Patients Benefit from KGI-hosted Workshop

Chris Hempel was notified in May 2010 that the orphan drug designation application she filed in February at a workshop hosted by KGI’s Center for Rare Disease Therapies had been approved by the U.S. Food and Drug Administration. But, the approval is only the beginning of what can be a long process.

Hempel’s 6-year-old twin daughters suffer from Niemann Pick Type C, a rare and fatal genetic cholesterol disease that is often referred to as the “childhood Alzheimer’s” because it causes severe dementia in children. The girls, Addi and Cassi, are among about 150 children living in the United States with Niemann Pick Type C and approximately 500 worldwide.

Ian Phillips, PhD, KGI’s Norris Professor of Applied Life Sciences and director of the Center for Rare Disease Therapies, had heard about Hempel and her twins before the workshop.

“I know she’s so dedicated to finding a cure for her own children. It was incredible news to hear that her application was approved.”
Phillips said Hempel’s success underscores what the center is trying to do: Help patients with rare diseases.

Hempel, who lives in Reno, Nevada, filed her application with the support of Children’s Hospital and Research Center in Oakland, California, for a sugar compound called cyclodextrin, which has shown promise in cats and mice that have the same progressive neurological disease.

“Cyclodextrin has the miraculous ability to pull cholesterol into its core,” Hempel said. “The compound is used frequently to make cholesterol-free products such as salad dressings and butter and is the main ingredient in Febreze air freshener. But when put into the bloodstream or brain, cyclodextrin could be a potentially lifesaving treatment and help save my girls from progressing into a state of complete dementia.”

During the workshop, officials from the FDA met with pharmaceutical and biotech company representatives, academics and patient advocates like Hempel to walk them through the application process for orphan drug product designation. “For me and a lot of people, the FDA can be a very intimidating organization,” Hempel said. “What I learned is they really want to try to help people move things along and get their applications filed.” Hempel said the fact that their application was successful shows that an individual doesn’t need the backing of a pharmaceutical or biotech company to win approval for an orphan drug application.

Currently, she is working on a similar application for the European Medicines Agency, the European equivalent of the FDA, with a mother in the EU whose child also suffers from Niemann Pick Type C.

The Hempels received a compassionate use Investigational New Drug (IND) approval from the FDA last year that allows them to infuse the compound into their daughters’ bloodstream through an IV. They have since determined through research studies that cyclodextrin does not readily cross the blood-brain barrier.

“When put into the bloodstream or brain, cyclodextrin could be a potentially lifesaving treatment and help save my girls from progressing into a state of complete dementia.”

The girls’ physician, Dr. Caroline Hastings at the Children’s Hospital and Research Center, is working on a new IND application that would allow doctors to deliver cyclodextrin directly into the twins’ central nervous systems so it goes directly to their brains.

“Given that we have very little pharmaceutical or biotech support, we’re going to form our own company to move this compound forward,” Hempel said.

Thanks to the FDA approval, the Hempels will receive special tax credits that they can apply to qualified human clinical trial costs and research expenses. They also have the ability to pursue grants from the FDA to help move cyclodextrin through the clinical trial process. The Hempels are working with the company that manufactures Trappsol™, the brand of Cyclodextrin they are using, along with the twins’ doctors and the Oakland hospital to move the compound forward and into broader clinical trials.

By Elaine Regus
Push To Cure Rare Diseases
FDA Officials Go to New Lengths to Encourage Applications for Orphan-Drug Status

Staff members at the Food and Drug Administration are doing something unusual. They are leaving Washington to help drug makers take a crucial step in developing drugs for rare diseases. The staffers help administer the Orphan Drug Act, which provides incentives to create therapies for so-called orphan diseases—those that affect fewer than 200,000 Americans. There are about 7,000 such maladies, most of them serious, that have few or no drugs to treat them, from adenoid cystic carcinoma, a rare head and neck cancer, to Zollinger-Ellison syndrome, which is associated with a tumor that causes the production of high levels of stomach acid. As a result, doctors may end up prescribing drugs developed for other diseases off-label, but not all insurers will cover this kind of use.

Getting an orphan drug designation opens the door to incentives once the FDA approves a medicine for sale in the U.S., including seven years marketing exclusivity and tax breaks. Last year, just 250 requests for orphan-drug designation were filed, and 160 received it. “We’re barely scratching the surface,” says Timothy Coté, director of the FDA’s Office of Orphan Products Development, the workshop’s sponsor. He says there are roughly 350 orphan drugs approved, covering about 150 rare diseases.

Tim Cunniff, vice president of global regulatory affairs at Lundbeck Inc., which has a number of approved orphan drugs, says most companies developing orphan drugs are small. Big companies are starting to get more interested in rare diseases, but the key issue is the high cost of developing a drug and the typically long time it takes to move it from a lab into a clinic as a treatment that gets prescribed. Before starting down this arduous path, a company needs to feel there is a reasonable chance of making a profit.

To help get more applications, Coté’s office put out the word: Help is available, in two workshops with on-the-spot regulatory advice. The first workshop, held last month at Keck Graduate Institute, drew 29 potential sponsors, from major drug companies to academic centers, small biotechs and even some patient advocates. In a follow-up survey, 74% said they had never before filed an application for orphan drug designation.

Ian Phillips, director of KGI’s Center for Rare Disease Therapies, said he knew ensuring confidentiality would be critical, as the drug industry is extremely competitive. So participants’ name badges didn’t include company names. The
rooms where the teams worked to fill out the applications were labeled only by number, such as “Team 1” or “Team 2.” At the introductory meetings, participants were admonished to be friendly at lunches and receptions but not push anyone to reveal more than he or she wanted. “I remember someone introducing himself as ‘Ralph’ at one of the receptions and that’s all I ever found out about him,” Phillips said.

Coté said he wanted participants to understand that the workshop wasn’t providing an alternative pathway to orphan drug designation, just regulatory advice. He said it was very important that the FDA avoid the “perception of favoritism” and even stressed that in the cover letter to an application, the sponsors shouldn’t say they had been at the workshop. Each team met four times over the course of two days with FDA staffers who offered advice on nine critical issues in filling out an application. A key one is providing evidence—preferably either trial data or published reports of animal studies—that a drug exists and holds promise for treating a rare disease. Sometimes statistics on very rare diseases are hard to obtain.

Barbara Fant, president and chief executive of Clinical Research Consultants Inc., attended the workshop to prepare an application for a drug-company client, and said this was her first time filing for an orphan drug designation. An FDA staffer pointed out issues in her application that “would have come back to me as questions and delayed the designation process” if she had filed before the workshop. “I learned some nuances that I didn’t know,” said Fant, who declined to provide details about her client or the drug.

An orphan-drug designation is no guarantee a medicine will ultimately be approved for marketing. A different FDA division reviews safety and efficacy data for approval. Upon further testing, a drug may turn out to be too dangerous or not effective. Companies may decide a product is too expensive to make, change direction, or go out of business. But Phillips and Coté hope that by increasing the pool of applicants for designation, they will increase the chances of getting more approvals.

The resolution of the first workshop suggests the orphan-products office has a ways to go to reach the goal of doubling the number of yearly applications. In the end, 14 of the 29 submitted applications at the end of the two-day workshop, though they can still submit any time, and more could do so in ensuing months. It usually takes the FDA 60 days to determine whether the designation will be given.

“I learned some nuances that I didn’t know,” said Fant.

Coté said he considered the workshop a success but was disappointed that not every group submitted. “It’s not ‘War and Peace,’ he said in a meeting at the close. “The applications are six or seven pages.” Up to 50 more organizations can attend the second workshop, to be held at the University of Minnesota in August. Coté said he was considering a workshop in Europe. Next time, he wants to weed out applicants who can’t file at the end of two days; a number of participants said they couldn’t file the finished product without approval from their companies. The FDA is reaching out aggressively, but resources are still limited. “Don’t come if you’re not going to submit,” he said.

By Amy Dockser Marcus (Wall Street Journal)
Internships

The Center For Rare Disease Therapies has played an important role in supporting student internships in regulatory affairs through generous grants from the Kenneth T. and Eileen L. Norris Foundation. Students got the valuable opportunity to intern at the Food and Drug Administration (Office of Orphan Products Development) and the Pharmaceutical Research and Manufacturers of America to get first-hand information of how the government and the industry functions in bringing safe and effective products to the market. Some of the students who interned at these organizations were:

- Food and Drug Administration (Office of Orphan Products Development)
  - Will Raasch (2008)
  - Sonali Talele and Aditya Kelkar (2009)
  - Daniel Lev, Chandana Thorat (2010)

Publications


Faculty

- M. Ian Phillips PhD, DSc, FAHA - Director, Center for Rare Disease Therapies, KGI
- James Osborne, PhD - Director, Center for Biomarker Research, KGI.
- Craig W. Adams, PhD - Assistant Director, Center for Biomarker Research, KGI.
- Steve Casper, PhD - Health Economics

Supporters

The Kenneth T. and Eileen L. Norris Foundation
Sigma-Tau Pharmaceuticals
Pharmaceutical Research and Manufacturers of America (PhRMA)
The Gross family
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**FDA Workshop**

“Write an Orphan Drug Designation”

**Feb. 28th—March 1, 2011**

Keck Graduate Institute, Claremont, CA
CENTER GOALS
- To serve as an industry incubator for small- to mid-size companies.
- Provide specialized rare disease services related to drugs, biologics and medical devices.
- Leverage collaborations with FDA, NORD and Genetic Alliance to benefit patients with rare diseases.
- To be a national and global resource for expertise, training and information related to rare diseases.