COMPOUNDING FOR Investigational Studies:

The Experience of Ken Hughes, RPh

Background

Ken Hughes, RPh, the owner of Greenpark Pharmacy in Houston, Texas, is a specialist in sterile-preparations compounding and a member of the United States Pharmacopeial Convention's (USP) Expert Committee on Pharmacy Compounding-Sterile Preparations. As such, he reviews and assists in the creation of USP policy guidelines for sterile preparations compounding in US pharmacies. For years, he has also compounded specialized dosage forms of investigational new drugs (which are designated only by number) for use in clinical trials funded by the US government and private industry and has collaborated with individual physicians whose patients benefit from modified forms of established therapies.

In Hughes' compounding-only pharmacy, located near the Texas Medical Center in Houston, preparing unusual formulations is the norm. For physician clients, Greenpark Pharmacy staff compound an average of 40 prescriptions daily in addition to the preparation of special dosage forms of investigational drugs. Hughes' success in providing researchers with what they need to perform clinical trials has earned him a well-justified reputation as a pharmaceutical problem solver. Investigators from the National Institutes of Health (NIH), the Veterans Administration (VA), nearby Baylor College of Medicine and a host of private industries and individuals contact him directly with requests for new combinations and forms of drugs to be used in clinical investigations.

Hughes has always been interested in the challenge of improving patient care, and he began to compound investigational treatments in 1992. One of the first formulations he was asked to prepare was in response to a request from a local urologist who was independently evaluating the effectiveness of prostaglandin, phentolamine and papaverine as a penile injection to treat impotence. He asked Hughes to formulate an appropriate concentration of that preparation as a sterile injection. Ten years later, that medication is one of the most frequently compounded prescriptions that he and his pharmacy staff prepare each day. Now referred to as *Trimix*, it is not stable long enough to be commercially made, but it is more effective for certain types of patients than anything currently available for treating impotence. He prepares Trimix in quantities of about 50 to 60 vials per week in various strengths and has several standard formulations that are requested by different clinics, hospitals and physicians in private practice. They also compound it at the request of several physicians for cancer patients who suffer from chemotherapy-induced impotence.

"Three or four years after I first compounded Trimix, an alprostadil urethral suppository for the treatment of impotence became commercially available, and the sales of Trimix decreased," said Hughes. "Over time, though, the effectiveness of the combination of drugs in Trimix has been proven. For many patients, it has a better profile of adverse effects than that of other injectable medications; and it can be used by diabetic patients who cannot take oral medications for the treatment of impotence."

NIH

The first clinical trial for which Hughes supplied investigational drugs was a study conducted by the NIH that involved a sterile solution of butyric acid administered by intravenous (IV) infusion for the treatment of thalassemia. Greenpark

Pharmacy prepared about twenty-four 1000-mL bottles per week for approximately 2 years for participants in that trial. As in many investigational studies, Hughes was not notified of the outcome; but he continues to provide several NIH researchers with the unique formulations they need for investigational drug trials.

Stehlin Foundation

As Hughes' interest in investigational studies increased, so did his reputation as a reliable compounder of customized drug preparations for clinical use. In 1994, the University of Houston College of Pharmacy suggested his name to Houston's Stehlin Foundation for Cancer Research, which had funded a study on the camptothecin family of chemicals for the treatment of pancreatic cancer. Greenpark Pharmacy prepared the drugs used in the initial phase of that trial. The Stehlin Foundation supplied the pharmacy with several different types of camptothecin derivatives that were compounded, in different strengths, into capsule form for administration to study subjects. Every week they compounded thousands of capsules for use in that study. Over the next 3 to 4 years, the requests from Stehlin for camptothecin compounds became so great that the demand exceeded the quantities that the pharmacy could supply. Hughes still compounds for the Stehlin Foundation, but an independent pharmaceutical company was established by the Foundation to meet its demand for camptothecin products.

Baylor College of Medicine

Hughes' interest and participation in investigational drug studies continued, and several years ago he embarked on the first of many projects for Baylor College of Medicine. "The dosage forms required for that study could not be produced by the drug company that funded the trial or by Baylor," Hughes said. Since that first project, he has compounded many other challenging formulations for trials conducted by Baylor College of Medicine, including oral enteric-coated gelatin capsules containing a lyophilized liposomal influenza vaccine; an oral dosage form of placebo, azithromycin and levofloxacin, each of which was evaluated in a three-way blinded study of an effective treatment for "traveler's diarrhea"; and a sterile eyedrop for the treatment of ocular infections caused by *Acanthamoeba*.

VA Hospital, Houston

Hughes has also established an enduring collaboration with the VA hospital in Houston. The first order that he and his staff prepared for the VA had some unusual features.

"We were asked to compound butyric acid, which is a short-chain fatty acid, into rectal suppositories used in a trial testing effective treatment for diverticulitis," he said. "We began to compound the medications during regular business hours as usual, but the smell of the butyric acid soon became a problem; a single drop smells like potent vomit. The obstetricians and gynecologists in the building began to complain that their pregnant patients couldn't tolerate the odor and would frequently vomit in the elevator as it rose to the upper levels of the building. When I was looking for a solution to correct that problem, I discovered that I was a valuable tenant: my unusual request to drill a hole through the wall of the office building and install a vent to the outside was granted! In addition to venting the vapors, we compounded the suppositories after hours in the evening. That combined approach resolved the problem."

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VA Research and Development Service

Hughes recently provided the final batch of medications for use in an ongoing three-way blinded crossover drug study (sponsored by the VA Research and Development Service in Washington, DC) of the effectiveness of amitriptyline versus gabapentin in decreasing central neuropathic pain in patients with a spinal-cord injury. Diana H. Rintala, PhD, associate professor in the Department of Physical Medicine and Rehabilitation at Baylor College of Medicine, and Sally Ann Holmes, MD, spinal-cord-care-line executive at the Houston VA Medical Center, are the co-principal investigators for that trial. According to Rintala, spinal-cord injury is a major concern at the VA; and many people with such an injury have very severe neuropathic pain at or below the level of injury that is extremely difficult to treat. "Physicians have prescribed gabapentin or amitriptyline for those patients, but no trial to date has compared the effectiveness of

How To Identify Clinical Trials That Require Compounded Drugs or Placebos

Investigational studies are a preliminary requirement for the release of drug products in the US market, and compounding pharmacists can play a key role in providing researchers with the combinations, dosages and dosage forms required to conduct drug trials. An increasing number of compounding pharmacists are realizing the value of providing that service. In most clinical studies that evaluate new therapies for human and veterinary diseases, the use of a placebo is required. However, the US pharmaceutical industry is not equipped to prepare small quantities of placebos that cannot be visually distinguished from the active drugs against which they are evaluated. Although some placebo batches are prepared in smaller pilot-plant operations, more and more compounding pharmacists are providing inert tablets, capsules, injectables, creams, ointments and gels for investigational drug studies. The active drugs evaluated in clinical trials must also often be modified from their manufactured dosage and form. A compounding pharmacist can provide these customized medications and may also assist in developing a formulation, eg, for IV, intramuscular or subcutaneous administration if an injection is required, as specified by the trial requirements.

those drugs," she said. As of June 2003, the study, which has a goal of enrolling 54 patients, consisted of 22 men (some of whom are veterans) and 1 woman, all of whom live within 100 miles of the VA hospital in Houston, to facilitate treatment and follow-up. After having completed only one medication phase, 5 of the 22 patients withdrew from the study because of personal problems or a comorbid condition.

Participants in the trial, initiated in November 2001, receive capsules that are identical in appearance and that contain one of three drugs: amitriptyline, gabapentin, or diphenhydramine (placebo). The order in which subjects receive each drug is randomized, and the trial is implemented in several phases: treatment that is tapered up to a maximum dosage during a 4-week period, 4 weeks of maintenance at the maximum dosage, 1 week during which the dosage is tapered down, and 1 week of washout. At the end of the washout, administration of the second of the three drugs is initiated, and the same protocol is followed in each patient for all three drugs tested. At the conclusion of each subject's 30-week participation in the trial, his or her response to therapy is evaluated, and the results of those evaluations (12 of which have been prepared so far) are released to that patient and to his or her physician. "It appears thus far that for most patients, one or both active drugs are more effective than the placebo in reducing pain intensity rated by each patient on a scale of 0 to 10 and on a visual analog scale," said Rintala. "Some patients have reported more pain relief from amitriptyline; others have benefited more from gabapentin. Two patients reported no relief from any of the drugs. The most severe adverse effects (drowsiness and dry mouth) were noted after treatment with amitriptyline, but those symptoms occurred to a lesser degree from treatment with gabapentin or placebo.

"The VA does not compound drugs for research, and Ken has been extremely helpful in enabling us to meet the specifications for drugs used in the trial," said Rintala. "He has formulated all 70,000-plus purple capsules to appear identical and has packaged them in blister packs so that each patient can keep track of the capsules that he or she is to take and of the time when he or she is to take them. That encourages compliance with the study protocol."

Compounding for Other Investigations

Clinical trials are not the only investigations in which Greenpark Pharmacy participates. "We do special

compounding all the time," said Hughes, "not always for an investigational study, but often for an investigational *use* of a drug." One of the more exotic challenges the staff faced was to devise a treatment for a beekeeper whose hands and eyes were afflicted with a fungus common in honeybees. They obtained the commercial chemical sprayed on honeybees to cure them and compounded it into a sterile ophthalmic antifungal eyedrop in the concentration specified by the ophthalmologist. The treatment was successful.

Documentation and Quality Control

Pharmacists interested in compounding drugs for investigational studies should be aware that extensive record keeping is required, and intensive quality-control programs must be in place. The pharmacy that supplies the compounds must be fully equipped for the preparation of the investigational drug (sometimes in large volume) according to the exact specifications of the trial, and each step of the compounding process must be documented and available for review. To ensure the accuracy of the documentation that must be amassed for investigational drug studies, Hughes uses PK Software (Professional Compounding Centers of America, Houston, Texas) to track formulations. He must provide documentation about every step of the compounding process, including the lot numbers of chemicals and information about the compounding methods used. Spectrophotometry and chromatography testing for drug concentration and sterility and testing for the presence of pyrogens are performed at independent laboratories.

Conclusion

For pharmacists willing to withstand the rigorous requirements of compounding for clinical trials, personal and professional satisfaction more than compensate for the challenges.

Pharmacists interested in compounding for investigational drug studies can obtain information about current and future studies from the research administration departments of universities, government institutions and private companies that conduct clinical trials.

For additional information, contact Ken Hughes, RPh, Greenpark Pharmacy, 7515 S. Main, No. 150, Houston, TX 77030 ■