Are Orphan Product Program Funds Underused by Nuclear Medicine Researchers?

In an era of fiscal constraints, with more good ideas than ever chasing the precious dollars set aside for scientific research, it is unusual to find a funding source that would like to see more investigators come forward and ask for money.

"I just don't get enough grant applications," said Neil Abel, deputy director for the Office of Orphan Product Development for the Food and Drug Administration (FDA), Rockville, Maryland, and part-time reviewing pharmacist at the IND branch of the FDA's Center for Biological Evaluation and Research. "We've had three or four requests for grants for nuclear medicine-type products. I would have expected a lot more."

Despite budget-cutting elsewhere, lack of funding is not a problem for orphan projects. In March the United States House of Representatives and Senate voted to extend the Orphan Drug Act through fiscal year 1990, authorizing $12 million for fiscal year 1989 and $14 million for fiscal year 1990. Tax credits for companies investing in orphan product research were also extended through 1990. The reason for the increases, according to the lawmakers who testified at the time, was the success of the program in encouraging the development of products for rare conditions.

Competition Valuable

While the FDA has received sufficient grant requests to utilize its funds each year, Mr. Abel noted that competition for research support has positive effects: "The more grant proposals you get, the better the chance you have of getting good studies." He also believes many nuclear medicine researchers are working on projects that could be recast in such a way as to be eligible for orphan grant funds. "I'm happy to talk to researchers about how to reword their request to include it in the program," Mr. Abel added.

Orphan drugs are drugs, antibiotics or biological products for the diagnosis, treatment or prevention of a rare disease or condition. The Orphan Drug Act, an amendment to the Food, Drug and Cosmetic Act that became law in 1983, led to the grants program. The Act also established the governing Orphan Products Board within the Department of Health and Human Services, which is chaired by the Assistant Secretary for Health (see *Newsline*, June 1986, pp. 743–744 and Feb. 1987, p. 154).

The Orphan Drug Act was originally conceived to encourage research into diseases that afflict so few people that no commercial concern could make enough profit on its products after absorbing research and development costs. Although each orphan disease may represent a small number of cases, collectively more than 8 million Americans have orphan diseases, according to recent congressional testimony by Senator Howard Metzenbaum (D-OH).

There are at least 5,000 conditions that qualify. These include Gilles de la Tourette's syndrome, Huntington's disease, neurofibromatosis, and, perhaps surprisingly, AIDS. In fact, the AIDS drug zidovudine (AZT) was developed under the orphan drug grant program. While the number of AIDS cases will increase, Mr. Abel explained that so far there have been approximately 50,000 cases of AIDS recorded with about half still alive, making it a rare disease under the program's definition.

The handful of investigators in nuclear medicine who have received support under the program speak well of the experience. "I found the [FDA] people extremely cooperative and helpful. In this time of difficult research funding, it's a source people aren't aware of or haven't tried," said Brahm Shapiro, MD, PhD, professor of internal medicine at the University of Michigan Medical Center in Ann Arbor. If researchers haven't been applying, he said, "it hasn't been for lack of cooperation or interest at the FDA; they've been very supportive throughout."

MIBG Grant

Dr. Shapiro obtained a three-year grant to study tracers for pheochromocytoma, a rare tumor of the adrenal medulla or sympathetic paraganglia that causes hypertension and other problems. "It may be very hard to find by conventional imaging techniques," Dr. Shapiro pointed out. His grant enabled him to study how effective metaiodobenylguanidine (MIBG) is as a diagnostic agent for this condition. The results were so positive that a commercial supplier is seeking to market it, and will undoubtedly be using some of his data in the approval process.

Amendments to the law in 1984 defined a rare disease or condition as one that either (1) affects fewer than 200,000 persons in the United States or (2) affects more than 200,000 persons, but for which there is no reasonable expectation that the cost of developing and marketing the drug will be recovered from sales in the US within seven years. Because nuclear medicine technology has been applied to

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so many relatively common conditions, such as heart disease and cancer, there may be a perception that research proposals in the field fail to meet the orphan criteria. But Mr. Abel believes nuclear medicine may be an especially fruitful area for orphan grants. "Most of the products in nuclear medicine are orphans almost by definition," Mr. Abel said. "A lot of them are not used that frequently" with a few obvious exceptions, such as bone scan radiopharmaceuticals. "There are a lot of tracers for unusual or not very visible diseases," Dr. Shapiro noted.

'Widespread Use'

Diseases need not be virtually unheard of to qualify. S. Ted Treves, MD, chief of the division of nuclear medicine at Children's Hospital in Boston and professor of radiology at Harvard Medical School, obtained a grant to use an osmium-191/iridium-191m generator for radionuclide angiocardiography, which would be used in the study of cardiovascular disease in children. "The product has the potential for widespread use, but studies had to be carried out to demonstrate that," Dr. Treves said. He hopes his results will prove so attractive to industry that some manufacturer will decide to market the product.

Since 1983 amendments to the Orphan Drug Act have expanded its grant component to include medical devices and foods, as well as drugs, and preclinical, as well as clinical, testing. The program offers co-funding arrangements for investigators receiving partial support from another source.

In its most recent reappropriation in March, Congress voted to retain the seven-year market exclusivity status now granted to the first manufacturer to get FDA approval of an orphan product. Representative Henry Waxman (D-CA), one of the sponsors of the original bill, had wanted to modify the exclusivity provision to prevent companies from using it to block competition because he believed one company was overcharging for human growth hormone to treat Turner's syndrome. That product, which costs more than $10,000 a year per person, would appear to be profitable without the protection of the Orphan Products Act. But because the exclusivity provision provides an important incentive for the production of drugs that otherwise would not be developed, Rep. Waxman dropped his plan to get the measure passed, but warned that he would revive it later if companies abuse the exclusivity privilege.

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Word of Mouth

In the five years of the program, more than 200 orphan products have been designated and 24 orphan products were approved for marketing. This represents more than five times as many drugs under development since the Act as during the 10 years before, according to Rep. Waxman's testimony during reauthorization.

Better promotion might lead to even more orphan products, as word of mouth seems to be one of the program's chief publicity mechanisms. Dr. Shapiro found out about the Orphan Products Program from a hospital pharmacist who had heard of it. He had been working on the tracer and the disease before the FDA funding became available. "We were sort of bemoaning the fact that here's a fantastic tracer, but the condition for which it is so good is such that no company will be bothered to go through the rigamarole needed to take it to market," Dr. Shapiro said.

James Sisson, MD, a professor of internal medicine in the division of nuclear medicine at the University of Michigan, received his grant for work with iodine-131 cholesterol and adrenal tumors. He said the paucity of applications may simply mean that researchers "just haven't put enough thought into it" to put forward a proposal.

NIH Forms

The orphan products application process would seem familiar to anyone acquainted with the National Institutes of Health (NIH) grant application procedure, Mr. Abel said, as both agencies use the same form. "The reviews are reasonably rigorous but very fair," Dr. Sisson said. Under a rating system in which 100 is a perfect proposal and 500 is unacceptable, Dr. Sisson has found that the orphan program funds proposals in the 160's whereas NIH proposals tend to require a rating of 140 or less. Mr. Abel notes, however, that such cutoff points vary from year to year with the quality of the submissions.

Researchers agree that the orphan product program is worth considering, especially when the administrators of other sources of funding are unenthusiastic about a project. "For weird and wonderful tumors that are rare, who [else] is interested?" asked Dr. Shapiro. Not commercial concerns, he said, "unless there's a big payola at the end of the line."

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